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Recent advances in liver transplantation for cancer: The future of transplant oncology

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Summary

Liver transplantation is widely indicated as a curative treatment for selected patients with hepatocellular carcinoma. However, with recent therapeutic advances, as well as efforts to increase the donor pool, liver transplantation has been carefully expanded to patients with other primary or secondary malignancies in the liver. Cholangiocarcinoma, colorectal and neuroendocrine liver metastases, and hepatic epithelioid haemangioendothelioma are amongst the most relevant new indications. In this review we discuss the fundamental concepts of this ambitious undertaking, as well as the newest indications for liver transplantation, with a special focus on future perspectives within the recently established concept of *transplant oncology*.

Keywords: Liver transplant; Oncology; Hepatocellular Carcinoma; Cholangiocarcinoma; Colorectal Liver Metastasis; Neuroendocrine Tumours; Hepatic Epithelioid Hemangioendothelioma.

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Introduction

Annually, hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) are diagnosed in 841,000 people and are responsible for 782,000 deaths worldwide.[1] Colorectal cancer is diagnosed in 1.8 million people every year and it is estimated that ~50% of these patients will develop colorectal liver metastasis (CRLM).[1,2] For patients with liver cancer, the surgical removal of the tumour offers the best chance of cure. Unfortunately, only a minor proportion of these patients are candidates for liver resection (LR) mostly because of decompensated liver disease. Liver transplantation (LT) offers a chance of cure given that it removes the tumour with the widest margin, as well as removing the pro-carcinogenic hepatic microenvironment.

Transplantation as treatment for unresectable liver cancer has been explored since the early development of LT.[3] The initial experiences with LT for liver cancer were, however, disappointing.[4–6] The landscape of LT for cancer changed in 1996, when a strict selection criteria for patients was published.[7] Since then, with better patient selection and refinements to operative and postoperative care, LT has become an effective treatment for several hepatic malignancies. Together with other important advances in hepatology and oncology (*e.g.* new chemotherapies for gastrointestinal cancer; direct-acting antivirals [DAA] for hepatitis C) a new field in medicine has risen: *transplant oncology*.[8] In this review, we aim to explore the current indications for LT as a treatment for hepatic malignancies, with a special focus on future perspectives within the concept of *transplant oncology*.

Hepatocellular carcinoma

The treatment of HCC has become multidisciplinary, involving hepatobiliary and transplantation surgery, hepatology, interventional radiology, radiation and medical oncology. Among all possible strategies to treat HCC, LT offers the best chance of cure.[9] Unfortunately, the number of available grafts is insufficient for all potential candidates. For this reason, LT is reserved for patients who will benefit most. Efforts should focus on strategies to better select patients and to increase the number of available grafts.

LT for HCC: improvement of patient selection

Selection criteria worldwide

Patient selection is the mainstay of LT for cancer. After the Milan criteria were published, LT became the standard of care for patients with unresectable HCC who fit within its bounds.[7] The success of the Milan criteria has led to increased interest in expanding the criteria for LT.[10] Several "expanded criteria" have been proposed over the last 10 years (Table 1).[11]

Impact of serum alpha-fetoprotein

Serum alpha-fetoprotein (AFP) is an important biomarker in HCC. The 5-year disease-free survival (DFS) for patients with a serum AFP >1,000 ng/ml has been reported as 53% in comparison with 80% in patients with AFP ≤1,000 ng/ml.[12] Toso *et al.* demonstrated that patients beyond Milan

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criteria and with AFP ≤400 ng/ml can achieve satisfactory post-LT outcomes.[13] The hazard ratio (HR) of HCC recurrence for patients with total tumour volume (TTV) ≤115 cm^3 and serum AFP <400 ng/ml was 2.0 (95% CI 1.7–2.4), when compared to patients with TTV >115 cm^3 and serum AFP >400 ng/ml.[14,15] The "AFP model" uses a scoring system to classify patients by their risk of recurrence based on largest tumour diameter, number of lesions and serum AFP. Patients who have ≤2 points have a lower probability of recurrence and are within the criteria. Among these patients, the 5-year recurrence rate was 14% *vs.* 48% for those beyond the AFP criteria.[15] The Metroticket 2.0 system applies serum AFP, tumour size and tumour number to determine the risk of HCC-related death after LT (applying competing-risk analysis). The c-statistic of the model was 0.72, which was superior to previous criteria.[16] Halazun *et al.* recently published a model incorporating the concept of AFP response during waiting time. The AFP response was defined as the difference between the highest value and the final pre-LT serum AFP. They showed that dynamic changes in AFP during waiting time are valuable tools to identify patients beyond Milan criteria who could have good outcomes after LT.[17]

Surrogates of tumour biology

Surrogates of tumour biology have been studied with the aim of improving the selection criteria for HCC. Tumoural differentiation has been proposed as a selection criteria for LT.[18,19] Sapisochin *et al.* prospectively demonstrated that in the absence of macroscopic vascular invasion, extrahepatic disease, cancer-related symptoms and poor differentiation (the Extended Toronto Criteria) patients can undergo LT with satisfactory results regardless of tumour size and number (Table 1).[20] Kaido *et al.* have shown the utility of associating the levels of serum des-γ-carboxy prothrombin (DCP) to size and number of tumours.[21] The Kyoto criteria select patients with a DCP ≤400 mAU/ml, a largest tumour diameter ≤5 cm and ≤10 lesions (Table 1). Recently, the 5-5-500 criteria (tumour size ≤5 cm, tumour number ≤5, and AFP ≤500 ng/ml) was associated with a 5-year recurrence rate of 7.3% in patients treated with LDLT.[22] The use of ^{18}F-fluorodeoxyglucose positron-emission tomography/CT (^{18}FDG-PET/CT) has been correlated with HCC recurrence and increasingly used as a tool for patient selection.[23,24] Further research is still needed to be able to incorporate PET/CT widely into clinical practice.

Key points

Liver transplantation is widely indicated as a curative treatment for selected patients with hepatocellular carcinoma.

Increasing the donor pool, liver transplantation has been carefully expanded to patients with other primary or secondary malignancies in the liver.

Cholangiocarcinoma, colorectal and neuroendocrine liver metastases, and hepatic epithelioid haemangioendothelioma are amongst the most relevant new indications.

Table 1. Liver transplantation criteria for patients with hepatocellular carcinoma.

Criteria	Definition	Recurrence-free survival	Post-transplantation survival	Innovation
Milan criteria (MC)[7]	Single tumour ≤5 cm or 3 tumours all ≤3 cm	92% at 4 years	85% at 4 years	First criteria widely accepted
UCSF criteria[153]	Single tumour ≤6.5 cm or 3 tumours all ≤4.5 cm with TTD ≤8 cm	90.9% at 5 years	80.9% at 5 years	Extended MC criteria limits
Up-to-7 criteria[154]	The sum of the maximum tumour diameter and number <7	Beyond MC but within Up-to-7: 64.1% at 5 years	Beyond MC but within Up-to-7: 71.2% at 5 years	Extended MC limits
TTV[13]	TTV ≤115 cm^3 Serum AFP ≤400 ng/ml	Beyond MC but within TTV/AFP: 68% at 4 years	Beyond MC but within TTV/AFP: 74.6% at 4 years	Added surrogates for tumoural biology
Extended Toronto criteria (ETC)[20]	No limit in size and number No vascular invasion No extrahepatic disease No cancer-related symptoms Biopsy of largest tumour not poorly differentiated	Cumulative risk of recurrence for patients beyond MC but within ETC: 30% at 5 years	Beyond MC but within ETC: 68% at 5 years	Added surrogates for tumoural biology Extended MC limits.
Kyoto criteria[21]	Number of lesions ≤10 tumours Size biggest lesion ≤5 cm DCP ≤400 mAU/ml	Cumulative risk of recurrence of patients beyond MC but within Kyoto: 30% at 5 years	Beyond MC but within Kyoto: 65% at 5 years	Added serum biomarker to the criteria (DCP)
5-5-500[22]	Size biggest tumour size ≤5 cm Number of lesions ≤5 Serum AFP ≤500 ng/ml	71.4% at 5 years	74.8% at 5 years	Identified patients with worse prognosis within MC.

AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin; TTD, total tumour diameter; TTV, total tumour volume; UCSF, University of California at San Francisco.

Time on the waitlist has been considered a surrogate of tumour biology.[25] Recently, the United Network for Organ Sharing (UNOS) implemented a 6-month mandatory observation period prior to granting MELD exception points.[26] However, given the high heterogeneity in referral times amongst centres worldwide it is difficult to extrapolate a threshold to all jurisdictions. Firl *et al.* validated the hazard associated with LT in HCC (HALT-HCC) and demonstrated a significant heterogeneity by site and year, reflecting practice trends over the last decade..[27]

Response to locoregional therapies

Response to locoregional therapies (LRT) such as ablation, transarterial chemoembolisation (TACE), selective internal radiation therapy and stereotactic body radiation therapy correlates with tumour biology.[28–30] Complete pathological response in the explant has been associated with a higher overall survival (OS) and DFS.[30] In patients within the Milan criteria, poor response to LRT was associated with HCC-dependent transplant failure. Lai *et al.* have shown that patients with progressive disease despite LRT had a higher risk of dropout or post-transplant HCC recurrence (subdistribution HR 5.62, 95% CI 4.10–7.69).[31] Additionally, Mehta *et al.* demonstrated significantly improved post-LT outcomes when restricting LT to patients with a reduction in AFP from >1,000 to <500 ng/ml after LRT.[32] In the near future, the assessment of tumour response on pre-LT imaging can be improved with artificial intelligence methods (*e.g.* radiomics).[33–35]

Primary vs. salvage LT

The optimal approach for patients who have failed on prior curative treatments for HCC is controversial. In retrospective series, salvage LT and secondary LR had similar outcomes.[36,37] However, the risk of recurrence after salvage LT may be lower than secondary resection.[38,39] The decision to treat with secondary resection or salvage LT remains controversial and depends on the availability of organs within each jurisdiction.

Genetic advances in HCC

Profiling the genomic and biological patterns of tumours and correlating them with clinical outcomes is key to better understanding HCC biology.[40] There are a wide range of HCC biomarkers currently under investigation, mostly in phases I and II studies. MacParland *et al.* using single-cell RNA techniques have shown that there are at least 2 different types of immune cells in the liver, and this may be key for HCC-directed therapies.[41] Different authors have published a wide range of possible biomarkers in HCC diagnosis and surveillance, such as osteopontin,[42] GALAD score and BALAD-2,[43] midkine,[44] DCP, lectin-bound alpha-fetoprotein (or AFP-L3),[45] Dickkopf-1, glypcan-3, HCCR, alpha-L-fucosidase,[46,47] golgi protein-73, squamous-cell carcinoma antigen (or SCC-IgM),[48,49] micro-RNA, kininogen,[50,51] metabolomics, proteomics,[52,53] circulating tumour cells and cell-free DNA,[54] polo-like kinase genes, PD-1 (programmed cell death protein 1) and TIM-3 (T-cell immunoglobulin and mucin-domain containing-3).[55,56] Most of this research has not been done in the transplant population. Table 2 summarises the main biomarkers under research.

Genomic expression does not always reflect an immunologically active phenotype in patients with HCC. Thus, a tumour biopsy may not provide all the information necessary for therapeutic decision making. The association of these tumour genetic findings with adjacent normal liver assessment, serum circulating tumour DNA (ctDNA) and the phenotypic expression in metabolites or serum proteins, could potentially identify a more aggressive tumour behaviour, changing the therapeutic indication and selection for transplantation. At this point, this is all hypothetical and further research is needed and ongoing in this area.

LT for HCC: Increasing the donor pool

To support the expansion of LT for patients with HCC without compromising patients without HCC, there is a need to increase the number of available grafts. There is controversial data on the impact that the different types of grafts can have on the outcomes of patients transplanted with HCC.

Use of marginal grafts

The use of marginal grafts (*i.e.* older donors, donors after cardiac death (DCD), split livers, steatotic grafts or hepatitis C virus (HCV)-infected grafts) is one of the options to increase the donor pool. Marginal grafts have been of particular interest for patients with HCC given that they usually have better liver function than patients listed with decompensated cirrhosis. The use of non-ideal grafts (*i.e.* “liver that nobody wants”) in patients with HCC has been investigated, showing that acceptable outcomes can be achieved.[57] However, this strategy must be approached with caution to avoid putting patients in good general condition at higher risk of post-transplant complications. Initial studies with the use of DCD grafts raised questions about the increased risk of tumoural recurrence due to the potential oncogenic effect of ischaemia-reperfusion injury.[58,59] This concern was not confirmed by subsequent studies.[60–62] Likewise, the use of grafts from older donors was seen as a risk factor for post-LT HCC recurrence[63] and currently donor age is not by itself a limitation for donation in many centres worldwide.[64,65] The use of HCV-infected grafts in recipients with HCV has been proven safe.[66,67] Cotter *et al.* demonstrated that, in the DAA era, there has been an increase in the utilisation of HCV-viraemic donor livers, including into HCV-negative recipients, with good graft outcomes.[68]

Table 2. Biomarkers under research for HCC diagnosis and treatment beyond liver transplantation that could be utilised in the transplant setting.

Authors	Year	Biomarker	Phase	Applicability
Mehta *et al.*[40]	2018	AFP	V	Diagnosis and survival
Marrero *et al.*[45]	2009	DCP	III	Diagnosis and survival
Fedarko *et al.*[42]	2001	Osteopontin	III	Diagnosis
Vongsuvanh *et al.*[44]	2016	Midkine	III	Diagnosis
Berhane *et al.*[43]	2016	GALAD score	III	Survival
Marrero *et al.*[45]	2009	AFP-L3	II	Diagnosis and survival
Jang *et al.*[155]	2016	Dickkopf-1	II	Diagnosis
Qiao *et al.*[46]	2011	Glypican-3	II	Diagnosis
Giardina *et al.*[47]	1992	Alpha-1-fucosidase	II	Diagnosis
Ismail *et al.*[48]	2017	Golgi protein-73	II	Diagnosis and surveillance
Pozzan *et al.*[49]	2014	Squamous cell carcinoma antigen	II	Diagnosis and surveillance
Shi *et al.*[50]	2015	Micro RNA	I-II	Diagnosis
Wang *et al.*[52]	2013	Metabolomics	I	Diagnosis
Sengupta *et al.*[53]	2013	Proteomics	I-II	Diagnosis
Pantel *et al.*[54]	2017	Cell-free DNA	I	Diagnosis
MacParland *et al.*[41]	2018	Single-cell RNA	I	Treatment
Pellegrino *et al.*[55]	2010	Polo-like kinases	I	Diagnosis
Sangro *et al.*[156]	2013	CTLA-4	I-III	Treatment
Li *et al.*[56]	2016	PD-1 and TIM-3	I	Diagnosis
Sun *et al.*[157]	2018	PDL-1	I	Treatment

AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein-lecithin 3; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCP, des-gamma-carboxy prothrombin; GALAD, acronym for: Gender, Age, AFP-L3, AFP, DCP; PD-1, programmed cell death protein 1; PDL-1, programmed death-ligand 1; TIM-3, T-cell immunoglobulin and mucin-domain containing-3.

The use of DAAs has changed the landscape of HCV treatment and, annually, less patients with end-stage liver disease due to HCV are listed for LT.[68–74]

Living donor liver transplantation

The most important intervention to increase the donor pool is living donor liver transplantation (LDLT). Initial results on LDLT for HCC indicated an increased risk of recurrence.[75,76] However, more recent studies did not confirm this finding. In an intention-to-treat analysis, 2 studies have shown similar outcomes between patients who underwent LDLT and those undergoing LT with grafts from brain-death donors (DDLT).[77,78] Goldaracena *et al.* have shown that LDLT is associated with survival benefit for patients with HCC. In an intention-to-treat analysis, patients who had a potential living donor had a 5-year OS rate of 68% compared to 57% in patients without a potential donor.[79] The presence of a potential live donor was a protective factor for death (HR 0.67; 95% CI 0.53–0.86). Despite being an excellent strategy for patients with HCC waiting for a LT, the widespread use of LDLT must be limited to centres that perform high volumes of both advanced hepatobiliary surgery and LT to diminish the risk of complications for the donor.[80] After live donation, the rate of overall postoperative complications is reported to be around 25–30%, with major complications occurring in 9–10% of patients.[80,81] Donor mortality has also been reported and estimated between 0.1–0.3%.[82,83]

LT for HCC: future prospects

The future direction of LT for HCC will focus on the identification of patients at higher risk of recurrence to prevent futile transplantation. This selection will likely move away from tumour size and number, and allow for the incorporation of surrogates of tumour biology. The use of imaging methods such as ^{18}FDG-PET/CT or genomic technics that could identify circulating DNA or single-cell RNA as a genetic signature of recurrence may improve our current criteria for patient selection. Radiomics applied to pre-treatment imaging assessments may enable clinicians to predict tumour behaviour in the near future. Xu *et al.* have demonstrated its ability to identify the presence of microvascular invasion in 495 patients with resected HCC.[35]

In the context of LT, neoadjuvant therapies may also increase access to transplantation for patients who are currently not candidates. An example of this approach would be patients with macrovascular invasion who respond to neoadjuvant therapies and have a stable period of observation.[84] This should only be done under investigational protocols at this time.

Cholangiocarcinoma

Cholangiocarcinoma represented 2% of all LTs performed for malignancies in Europe between 1988–2016.[85] Hilar CCA (hCCA) and intrahepatic CCA (iCCA) have distinct molecular pathogenesis

and biological behaviour and therefore are presented here as separated entities.

LT for CCA: initial experience

The initial experience with LT for CCA was disappointing. In 1988, the group from Kings College published a series of 93 patients who underwent LT for several malignancies of whom 26 had CCA (13 hilar and 13 intrahepatic).[86] The 5-year OS rate for this cohort was 10%.[86] In 1997, Pichlmayr *et al.* published a series of 24 patients with iCCA and 28 with hCCA who underwent LT.[87] The 5-year OS rates were 0% and 18% for patients with iCCA and hCCA, respectively.[87] This poor initial experience was explained mainly by the lack of criteria for patient selection and the absence of standardised pre- and postoperative treatment.

LT for hCCA

The first study with a strict patient selection and a neoadjuvant therapy protocol was published in 2000 by De Vreede *et al.*.[88] The so-called Mayo protocol consists of neoadjuvant treatment with 5-fluoracil (for radiosensitisation) and oral capecitabine (maintenance therapy) until LT is performed with preoperative external beam radiation therapy and local brachytherapy.[89] Gemcitabine along with capecitabine are applied in the neoadjuvant protocol in other centres.[90] The effectiveness of LT for hCCA was validated in North America by a study reporting on data from 12 US centres, including 287 patients who underwent LT, in which a 5-year DFS rate of 65% was achieved.[91] Mantel *et al.* have assessed the results of LT for hCCA in a cohort from the European Liver and Intestine Transplant Association (ELITA) and showed a 5-year OS rate of 59%.[92] After these satisfactory results, hCCA became an indication in many jurisdictions worldwide.[93–97]

The use of LT for patients with locally advanced hCCA and a low preoperative probability of achieving complete resection (*e.g.* tumours >3 cm and/or with ipsilateral intrahepatic portal branch invasion and/or positive lymph nodes) has been the topic of debate. One small retrospective study (13 patients in the LT group and 7 patients in the resection group) has shown superior results for LT.[98] The group from Nagoya published a series of 216 patients with type IV hCCA who were treated by resection.[99] The 5-year OS rate was 53% among those patients without lymph nodal metastasis.[99] The authors argue that this OS rate is comparable to that seen after LT for hCCA; but, unfortunately, this study did not have an LT group for comparison. Ethun *et al.* retrospectively compared the outcomes of LR and LT in 304 patients. Resection was attempted in 234 patients and successful in 191 (82%). In the LT group, 70 patients were listed and 46 (66%) underwent LT. Transplantation was associated with improved OS compared to LR (64% *vs.* 18% 5-year OS, p <0.001).[100] These results need to be analysed with caution given the observational nature of the design. Aiming to provide a definitive answer on the effectiveness of LT for patients with locally advanced hCCA, the TRANSPHIL trial (NCT02232932) is currently recruiting patients. This is a prospective, randomised, multicentre study comparing neoadjuvant chemoradiation plus LT to LR in patients with resectable hCCA.[101] Results are expected in 2021.

LT for iCCA

LR is the first treatment option for iCCA. Since the early 2000s, several publications have shown that LT might be an option for patients with iCCA who are not candidates for LR. Robles *et al.* assessed 23 patients who underwent LT for HCC and were diagnosed with iCCA in the explant. The cohort had 13 (57%) patients with early/intermediate stage iCCA and 10 (43%) with advanced disease.[102] The median OS was significantly higher for patients with early/intermediate stage (60 months) compared to patients with advanced disease (22 months), p = 0.048.[102] Sapisochin *et al.* assessed a similar cohort of patients who underwent LT.[103] Among 29 patients, the 5-year OS rate was 45%.[103] However, patients with very early iCCA (defined as tumours ≤2 cm) had significantly lower 5-year risk of recurrence (18% *vs.* 65%, p = 0.01) and greater 5-year OS (65% *vs.* 45%, p = 0.02) than those with multifocal and larger tumours. Vilchez *et al.* studied 4,049 patients who underwent LT for malignancies from the UNOS database.[104] Of these patients, 3,515 patients had HCC, 440 had iCCA and 94 had mixed HCC-CCA in the explant. The 5-year OS rate was 62% for patients with HCC, 47% for patients with iCCA and 40% for patients with mixed HCC-CCA (p = 0.02).[104] Unfortunately, this study did not address the outcomes according to the tumour burden. The benefit of LT for patients with early stages of iCCA was confirmed in an international collaborative study. Among 48 patients with iCCA, the 5-year cumulative risk of recurrence was 18% for those with very early iCCA and 61% for those with more advanced disease (p = 0.01).[105] The 5-year OS rate between the very early iCCA and advanced iCCA was 65% and 45%, respectively (p = 0.02).[105] These retrospective studies demonstrated that patients with very early iCCA, who are not candidates for LR, might have acceptable OS with LT. The application of LT for patients with unresectable very early iCCA still requires validation by a prospective study. The validation study is currently recruiting (NCT02878473) and results are expected within 5 years.[106] Until further investigation, iCCA should remain a contraindication for LT outside of clinical trials.

In the non-cirrhotic population, Lunsford *et al.* have published a prospective case series of 21 patients with iCCA who were assessed for LT.[107] This series had a well-defined neoadjuvant protocol. Inclusion criteria were solitary tumour greater than 2 cm or multifocal disease confined to the liver

without radiological evidence of macrovascular or lymph nodal involvement. Among the initial 21 patients, 12 were listed for LT and 6 underwent LT. The 6 recipients were followed for a median of 36 months and 3 had CCA recurrence.[107] This approach of neoadjuvant chemotherapy with or without radiation therapy could be useful for downstaging therapy in patients with unresectable CCA or as a selection criteria for LT.[91,107] Le Roy *et al.* have studied patients with unresectable iCCA who received neoadjuvant chemotherapy. Of 74 unresectable patients, 39 (53%) patients were successfully downstaged and underwent LR.[108] The use of radioembolisation with yttrium-90 (Y90) has been investigated as an option for downstaging and/or neoadjuvant therapy before LT. In a study from Rayar *et al.,* patients with unresectable iCCA were treated with Y90 combined with systemic chemotherapy. In this study, 8/45 patients were successfully converted to resection.[109] The use of neoadjuvant therapies to convert unresectable patients might be preferable to LT in light of organ scarcity. However, even though some patients could be successfully downstaged for resection, it would be fair to offer LT to patients who remained unresectable in the absence of disease progression during neoadjuvant treatment. Therefore, future studies assessing neoadjuvant therapies for advanced iCCA should aim both to downstage patients for resection and to select patients for LT.

LT for CCA: future perspectives

A better assessment of patients that have aggressive tumoural biology or extrahepatic disease is key to avoid futile transplantation. For example, the presence of positive circulating tumoural DNA seems to be related to prognosis.[110] Genetic sequencing is also a very important tool in selecting patients with a lower likelihood of recurrence. Mutations in *KRAS, BAP1* and *CDKN2A* are related to a higher probability of recurrence, while mutations in *FGFR2* are related to more indolent phenotype.[111–113] In hCCA, mutations in *P53, BRCA1, BRCA2* and *PIK3CA* are related to a worse prognosis.[111,112] Whether these genetic profiles will be applied as a selection tool in LT for CCA is still under investigation and cannot be recommended.

The future of CCA treatment lies in the development of specific drugs directly targeting pathways of carcinogenesis. Several biomarkers are being studied, opening up opportunities for translational research initiatives in CCA. It is increasingly evident that the CCA desmoplastic microenvironment plays an important role in cancer cell development, and strategies targeting the tumour stroma in combination with the CCA cancer cell will present new diagnostic and therapeutic perspectives.[114]

Due to the rarity of this tumour, initiatives are necessary to develop international consortia such as the Thailand Initiative in Genomics and Expression Research for Liver Cancer (TIGER-LC), the European Network for the Study of Cholangiocarcinoma (ENS-CCA), the International Cholangiocarcinoma Research Network, along with patient advocacy groups like the Cholangiocarcinoma Foundation, to enable the creation of international translational and clinical research collaborations that can perform multicentre clinical trials with the aim of elucidating new therapies.

Colorectal liver metastasis

LR is the only curative treatment for CRLM. Recent advances in medical and surgical treatments have allowed for an important expansion in the limits of resectability and life expectancy in this population.[115] Only 30–40% of patients are candidates for LR at the time of disease presentation.[116] The main reason for precluding LR in patients with CRLM is insufficient liver remnant volume. For patients with insufficient liver remnant and no extrahepatic involvement, LT is becoming an option given that total hepatectomy will remove all viable disease.

LT for unresectable CRLM: A new hope

Initial reports on the use of LT for unresectable CRLM showed poor results. In 1991, Mühlbacher *et al.* reported their experience with 17 patients transplanted for CLRM, showing a 5-year OS rate of 12% and a 60% recurrence rate.[117] To improve outcomes they restricted LT to patients with negative lymph node disease in the primary specimen.[118] Penn published the results from a North American cohort.[5] This was a retrospective report of 637 patients with liver cancer; of those 8 patients underwent LT for CRLM. The recurrence rate was 70% and the 30-day mortality was 11%. Due to these poor results, in the early 1990s the use of LT for CLRM was abandoned.

The use of LT for CRLM has regained momentum after the work of Hagness *et al.*.[119] Scandinavia is a region where the liver graft offer exceeds the demand.[120] In the SECA-I (SEcondary CAncer I) study, 21 patients underwent LT for CRLM.[119] The OS rate was 95% at 1 year and 60% at 5 years; the DFS rate was 35% at 1 year. Nineteen of 21 patients had tumour recurrence after a median 6 months (range 2–24 months). The most common site of recurrence was pulmonary (17/19 patients). In a subsequent publication, the authors assessed the recurrence patterns, showing a 57% 5-year post-recurrence survival. Patients with pulmonary-only metastasis, had slow growing recurrences despite immunosuppression, allowing for resection in 9/13 patients.[121] The remaining 8/17 recipients developed metastases in multiple sites, including hepatic recurrence, which was associated with the worst outcomes.[121] In the SECA-I study, the exclusion criteria were not very restrictive. The exclusion criteria were presence of extrahepatic disease and weight loss >10%. This approach allowed for the isolation of independent factors predicting worse OS: carcinoembryonic antigen

(CEA) >80 ug/L, progression of the metastases under neoadjuvant chemotherapy, tumour diameter >5.5 cm, time interval from resection of the primary to LT <2 years.[119] An international consortium published the results of 12 patients with CRLM who underwent LT.[122] The OS rate was 50% with 6 patients having cancer recurrence after a median follow-up of 26 months. In accordance with previous studies, the most common site of recurrence was pulmonary.

LT for CRLM: beyond the initial enthusiasm

As the concept of transplant benefit is gaining recognition over classic survival after transplantation or simplistic urgency criteria,[123,124] LT for CLRM will likely find its place in future practice. However, before it becomes a recognised indication, definitive evidence is required to address a few outstanding issues:

It has to be proven that transplantation is superior to chemotherapy

The SECA-I study provided encouraging evidence in favour of transplantation. Aiming to compare the results after LT to those seen after palliative chemotherapy, Dueland *et al.* compared the outcomes of their transplanted population (21 patients) to a matched cohort of patients who underwent palliative therapy.[125] They demonstrated improved 5-year OS in favour of LT (56%) compared to the chemotherapy (9%).[125] The cost-effectiveness of LT for CRLM in highly selected patients was recently shown.[126]

Definitive confirmation of these retrospective findings will hopefully come from several ongoing trials. The SECA-III trial (NCT03494946) will compare LT to best multimodal alternative treatment (chemotherapy +/- locoregional therapies). The TRASNMET trial (NCT02597348) is a multicentric trial comparing LT for unresectable CRLM to chemotherapy only. Our centre is currently enrolling patients in a pilot study to assess the safety and effectiveness of neoadjuvant chemotherapy followed by LDLT for patients with unresectable CRLM (NCT02864485).

Patient selection has to be refined

The population of patients enrolled into the SECA-I study was quite heterogeneous, helping with the identification of 4 factors associated with better survival (see above). Low CEA levels were also confirmed as a good prognostic factor by another study from an international consortium.[122] Moreover, a retrospective analysis using the SECA-I data was able to select a low-risk population (Oslo score 0-3) with a 5-year OS rate of 75%.[127] Another retrospective analysis on the SECA study data helped identify other predictors of post-transplant OS, such as the 'metabolic tumour volume' and 'the total lesional glycolysis' of the CLRM measured by ^{18}F-FDG PET/CT,[128] which could have a role in identifying patients with minor extrahepatic disease.[129] The recently published SECA-II trial showed that response to neoadjuvant chemotherapy is, in fact, important. Patients with a minimal response to chemotherapy of 10% had OS rates of 100%, 83% and 83% at 1-, 3- and 5-years , respectively.[130] The TRANSMET study contemplates additional criteria such as *BRAF* mutations, in order to exclude patients with aggressive tumour biology. This is also an exclusion criterion in the Toronto trial.

A standardised chemotherapy protocol has to be defined

Thanks to modern neoadjuvant chemotherapy protocols, around 10–15% of patients with initially unresectable CRLM become candidates for LR.[131,132] Therefore, it is clear that upfront chemotherapy should be offered to every patient potentially considered for LT, with the aim of conversion. In addition, as supported by the SECA-I and SECA-II trials, poor response to chemotherapy might be a criterion to identify high-risk candidates, who may not benefit from LT. Whether or not it is beneficial to administer post-transplant chemotherapy, instead, is a point yet to be explored. Patients enrolled in the SECA-I study were not given adjuvant (post-transplant) chemotherapy. The SECA-II/III and RAPID (see Table 3) trials do not have it as a formal requirement. With the exception of the SECA-II study, all the patients enrolled in these trials undergo liver transplant after multiple cycles of chemotherapy, some of them having already received second- and third-line treatments. In this context, the benefit of additional cycles may be marginal compared to their toxic effects, especially when involving small grafts (RAPID, LIVERT(W)OHEAL) and liver regeneration should not be impaired. Patients enrolled in the TRASMET study receive limited post-transplant chemotherapy, while in the trial from Toronto, adjuvant standard-of-care chemotherapy is given. This last study will provide the more valuable information about the real benefit of post-transplant chemotherapy in the context of LT for CRLM, although only a randomisation would provide definitive evidence.

Current ongoing trials in the field of LT for CRLM are summarised in Table 3.

LT for CRLM: future perspectives

Coping with a potentially very high demand

LT is a victim of its own success, with already accepted indications exhausting a very limited resource. If the ongoing trials confirmed a superior benefit of LT for unresectable CRLM over other treatments, organ allocation policy will have to deal with a considerable problem. Fortunately, most of the centres where LT for CRLM will become an option, are testing different strategies to mitigate this issue.

Some centres have proposed the use of auxiliary grafts in 2-staged procedures. The so-called RAPID procedure (Resection And Partial Liver Segment 2/3 Transplantation With Delayed Total Hepatectomy)

Table 3. Ongoing studies on LT for CRLM.

Study Name Sponsor NCT	Study design	Start/end estimated year	Patients enrolled (n)	Arms	Outcome(s)	Main inclusion criteria	Main exclusion criteria
SECA II Oslo University Hospital NCT 01479608	Clinical trial monocentric randomised (*A*) Open label	2012 / 2025	25	*A1*: Transplantation *vs.* *A2*: resection (randomised) *B*: Liver transplantation For non-resectable patients metachronous disease *C*: Liver transplantation For non-resectable patients synchronous disease	OS (10 years)	Histologically verified adenocarcinoma in colon/rectum No signs of extrahepatic metastatic disease/local recurrence (PET/CT) Received at least 3 cycles of chemotherapy with no increase in size of the lesions (*A* only) Six or more liver metastases technically resectable	Weight loss >10% the last 6 months Patient BMI >30
TRANSMET Paris Hospitals NCT 01479608	Clinical trial multicentric randomised open label	2015 / 2027	90	Intervention: liver transplantation *vs.* Non-intervention: non-experimental standard chemotherapy	OS (5 years) DFS Quality of life	Histologically verified adenocarcinoma in colon/rectum Liver metastases, not amenable to liver resection ≥ 3 months of tumour control during the last chemotherapy line BRAF wild-type CRC on primary tumour or liver metastases ≤ 2 lines of chemotherapy for metastatic disease.	General contraindication to LT Patients not having received standard treatment for the primary CRC according to recommended guidelines
SECA III Oslo University Hospital NCT 03494946	Clinical trial monocentric randomised open label	2016 / 2027	30	Intervention: liver transplantation *vs.* Comparator: any other treatment (including chemotherapy, ablation, TACE, SIRT)	OS (2 years after randomisation)	Histologically verified adenocarcinoma in colon/rectum Liver metastases, not amenable to liver resection All patients should have progressive disease according to RECIST criteria, or intolerance to 1st line chemotherapy No signs of extrahepatic metastatic disease, except patients may have 1-3 resectable lung lesions all <15 mm	Weight loss >10% the last 6 months Patient BMI >30 Liver lesion>10 cm Three negative prognostic factors at time of randomisation (CEA>80, less than 2 years from diagnosis, diameter of largest liver lesion >5.5 cm)
RAPID Oslo University Hospital NCT 02215889	Clinical trial single group assignment	2014 / 228	20	Intervention: 2-stage total hepatectomy + liver transplantation of segments 2/3 from deceased donor	Percent of transplanted patients receiving second stage hepatectomy within 4 weeks of segment 2/3 transplantation. OS (5 years)	Histologically verified adenocarcinoma in colon/rectum Liver metastases, not amenable to liver resection Received at least 3 cycles of chemotherapy No signs of extrahepatic metastatic disease, except patients may have 1-3 resectable lung lesions all <15 mm	Weight loss >10% the last 6 months Patient BMI >30
LIVERT(W)OHEAL Jena University Hospital NCT 03488953	Clinical trial single group assignment	2018 / 2023	40	Intervention: 2-stage total hepatectomy + liver transplantation of segments 2/3 from living donor	OS 3 years after 2nd-stage of hepatectomy (3 years) DFS 3 years after 2nd-stage of hepatectomy (3 years)	Non-resectable colorectal liver metastases without extrahepatic tumour burden, except resectable pulmonary metastases Stable disease or regression after at least 8 weeks of systemic chemotherapy	General contraindication to LT

Table 3 (*continued*)

Study Name Sponsor NCT	Study design	Start/end estimated year	Patients enrolled (n)	Arms	Outcome(s)	Main inclusion criteria	Main exclusion criteria
University Health Network, Toronto NCT 02864485	Clinical trial single group assignment	2016 / 2023	20		OS (5 years) DFS (5 years)	Bilateral and non-resectable CRLM Received at least 3 cycles of chemotherapy with proven stable disease Primary CRC tumour stage is ≤T4a	General contraindication to LT BRAF+ tumours

BMI, body mass index; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal liver metastasis; DFS, disease-free-survival; LT, liver transplant; OS, overall survival; PET/CT, positron-emission tomography/CT; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation.

was designed by the Oslo group (NCT02215889).[133] It aims to perform a left lateral hepatectomy with a left lateral segment graft implantation. The rationale is to delay the completion of the total hepatectomy to allow the graft to grow. The first step is a limited segment 2-3 resection, which leaves the room for the auxiliary graft from a deceased donor. After reperfusion, the right portal vein is clamped and subsequently ligated if the pressure does not exceed 20 mmHg (if not, other measures are undertaken to lower the pressure: portal banding instead of complete interruption, splenic artery ligation, porto-caval shunting). The graft's volume increase is assessed regularly until liver/body weight ratio reaches 0.8. At that point patients undergo a second procedure, with totalisation of the hepatectomy. The LIVERT(W)OHEAL study (NCT03488953) from 2 German university hospitals, applies the RAPID concept to live donation.

Transplantation of patients with resectable CRLM

R0 surgical resection is the gold standard treatment for patients with resectable CRLM. Recently, thanks to the advent of extremely effective chemotherapy protocols, even R1 resections can be considered curative if patients have positive response to systemic treatments.[134,135] Interestingly, very large series on LR for CRLM showed 5-year OS rates of <40% for patients presenting with more than 3 metastases,[136] which is inferior to the overall 60% OS rate at 5 years of patients enrolled in the SECA-I study (median 8 metastases). On the other hand, the SECA-I population had very stable disease on chemotherapy, in contrast with the large case series on LR that included a broad heterogeneity of cases.

The feeling is that some selected patients with borderline resectable disease and large tumour burden may benefit more from transplantation than from resection.

Neuroendocrine tumours

Liver metastases are common in neuroendocrine tumours (NETs) arising from the small intestine and pancreas.[137] Patients with unresectable NET metastases to the liver are candidates for LT if their tumours have low biological aggressiveness. NET represents 0.3% of the LTs performed in Europe, according to the European Liver Transplant Registry.[138] The level of evidence on the use of LT for NET metastasis is not high given the absence of information about DFS. In many studies there is a lack of uniform follow-up and assessment of quality of life.[139] Therefore, there is certain controversy on the selection criteria for LT and the best time to perform LT in patients with unresectable NET liver metastases. In 2007, Mazzaferro *et al.* published the most widely used criteria for the selection of patients with NETs for LT: low-grade tumour (G1-G2 or Ki-67 less than 5–10%), primary tumour drained by the portal system completely removed, metastatic diffusion to less than 50% of liver volume, stable disease for at least 6 months with medical therapies and age lower than 60 (relative criteria).[140] These criteria are very similar to those adopted by UNOS.[141] In Europe, LT for patients with NETs was assessed by Le Treut *et al.* in 2013.[142] Among 213 patients from the European Liver Transplantation Association Registry, they identified a 5-year OS rate of 73%.[142] Risk factors for worse outcomes were primary tumour arising from the pancreas, resection of the primary tumour during the LT, presence of hepatomegaly, hepatic involvement >50%, tumour bulk, poor differentiation, margin-positive and presence of lymph node involvement.[142] Worse survival in patients with pancreatic NETs was also reported by van Vilsteren *et al.*.[143] In 2016, the group behind the Milan criteria published a retrospective study showing the long-term results of applying these criteria. They compared 42 patients who underwent LT to 46 who received other therapies in a retrospective cohort. The 5-and 10-year OS rates were 97% and 89%in the LT group and 51% and 22.4% in the control group, respectively (p <0.001). The HR for death was 7.4

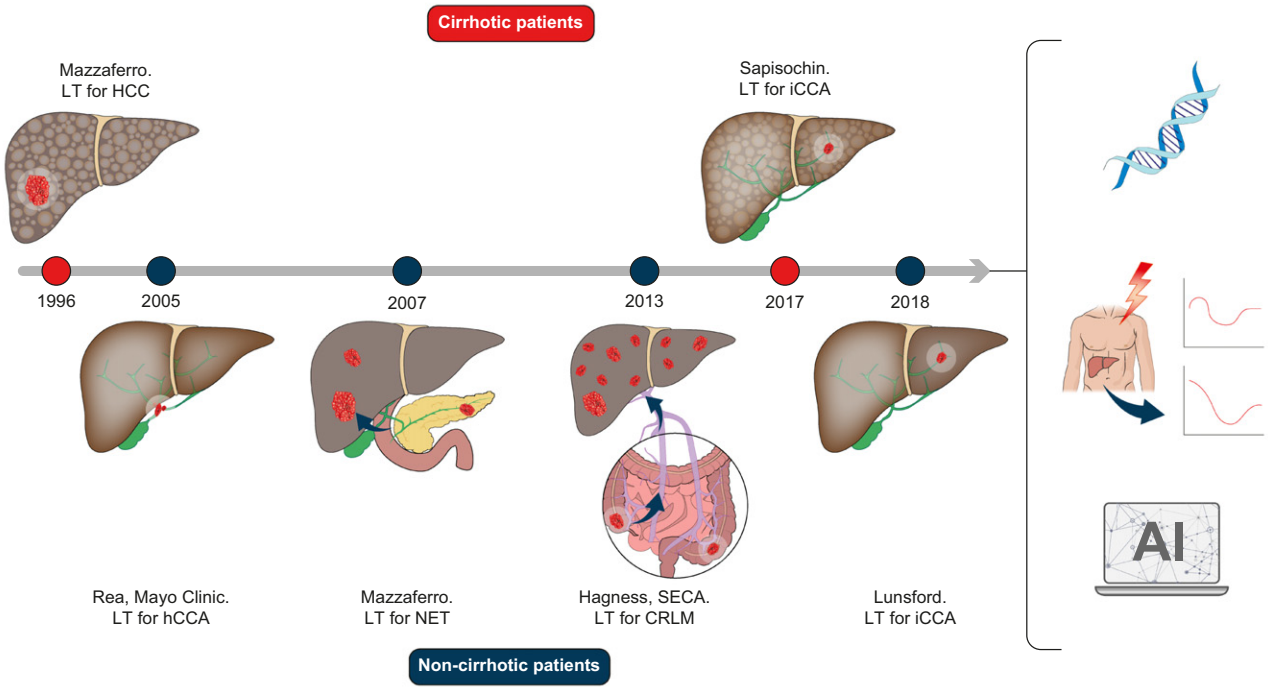

Fig. 1. Timeline of greatest advances in transplant for cancer.

(95% CI 2.4–23.0) for the control group compared to the LT group.[144] The use of time as a selection tool has also been reported. UNOS guidelines require patients with liver metastasis to be free of other sites of progression by 6 months before listing for LT. However, some agree that patients with indolent progression probably do not achieve the greatest survival benefit from LT.[145] It is also still not clear whether patients with more aggressive disease would benefit from LT given their lower probability of benefit from other therapies. Those are questions that need to be addressed by future research in the field.

Hepatic epithelioid haemangioendothelioma

Due to its rarity, the management of hepatic epithelioid haemangioendothelioma (HEHE) is still not well established. Furthermore, HEHE natural history varies from indolent to rapidly progressive disease.[146] For instance, the 5-year OS rate is reported to be 50% after LR and 30% with systemic chemotherapy.[147] In 2006, Mehrabi *et al.* have reviewed the published series of HEHE to date.[148] They identified 434 patients with HEHE, of those nearly 45% underwent LT with a 5-year OS rate of 54.5%.[148] The 5-year OS rates of patients with HEHE who underwent watchful waiting, systemic chemotherapy or radiation therapy and LR were 4.5%, 30% and 75%, respectively. In 2018, Konstantinidis *et al.* compared 91 patients with HEHE who underwent LR to 40 LT patients. Not surprisingly, patients in the LT group had more advanced disease (tumour size 44.6 cm in LT *vs.* 14.8 cm in resection) and positive lymph nodes (76.5% in LT *vs.* 15.4% in resection). Despite the more advanced disease, patients who underwent LT had better (but not statistically significant) OS when compared to patients treated by resection (median OS 97 months after LT and 90.5 after resection, $p = 0.06$).[149] Lerut *et al.* have published the ELITA series of 59 patients with HEHE who underwent LT, 96% with bilobar disease.[150] In this series, the 5- and 10-year OS rates were 83% and 72%, respectively. More recently, this European experience was expanded by Lai *et al.*.[147] The 5- and 10-year OS rates were 77% and 74%, respectively. The risk factors for recurrence were presence of macrovascular invasion, waiting time greater than 120 days and presence of lymph nodal invasion.[147] A polish group reported a 3-year OS rate of 87% after LT.[151] A study from the UNOS database on 110 transplanted patients with HEHE showed 5-year OS and DFS rates of 70% and 55%, respectively.[152] The best management of HEHE is still to be defined, but LT might offer a survival benefit for these patients compared to other therapies. Controversies around the best criteria for patient selection and pre- and post-LT management need to be addressed by further investigations.

Conclusion

In conclusion, the field of LT is evolving rapidly to expand the indications of LT for patients with primary and secondary liver cancer. Fig. 1 presents a summary of the most important advances in LT for cancer. The current results are promising; however, caution should be taken when expanding LT criteria for cancer patients, to avoid compromising patients awaiting LT for chronic liver diseases. In the context of improvements in preoperative selection criteria, surgical technique and post-LT care, the dismal results from previous decades are not currently valid. Moreover, the better treatment of patients with chronic liver diseases (*e.g.* DAAs for HCV infection) will reduce the number of patients on the waiting list because of end-stage liver disease. Furthermore, techniques for donor pool expansion (*e.g.* donation after cardiac death, live donation, *etc.*) will likely improve the imbalance between the number of available grafts and the number of patients on the waiting list. In the era of *transplant oncology*, surgeons, hepatologists, radiation and medical oncologists should work towards the careful expansion of the use of LT for cancer patients.

Abbreviations

AFP, alpha-fetoprotein; AFP-L3, alpha-fetoprotein-lecithin 3; BMI, body mass index; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal liver metastasis; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DAA, direct-acting antiviral; DCP, des-gamma-carboxy prothrombin; DFS, disease-free-survival; GALAD, acronym for: Gender, Age, AFP-L3, AFP, DCP; HCC, hepatocellular carcinoma; LRT, locoregional therapy; LT, liver transplant; OS, overall survival; PD-1, programmed cell death protein 1; PDL-1, programmed death-ligand 1; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TIM-3, T-cell immunoglobulin and mucin-domain containing-3; TTD, total tumour diameter; TTV, total tumour volume; UCSF, University of California at San Francisco.

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Conflict of interest

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Supplementary data

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