Liver transplantation in malignant disease

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Abstract

Liver transplantation for malignant disease has gained increasing attention as part of transplant oncology. Following the implementation of the Milan criteria, hepatocellular carcinoma (HCC) was the first generally accepted indication for transplantation in patients with cancer. Subsequently, more liberal criteria for HCC have been developed, and research on this topic is still ongoing. The evident success of liver transplantation for HCC has led to the attempt to extend its indication to other malignancies. Regarding perihilar cholangiocarcinoma, more and more evidence supports the use of liver transplantation, especially after neoadjuvant therapy. In addition, some data also show a benefit for selected patients with very early stage intrahepatic cholangiocarcinoma. Hepatic epithelioid hemangioendothelioma is a very rare but nonetheless established indication for liver transplantation in primary liver cancer. In contrast, patients with hepatic angiosarcoma are currently not considered to be optimal candidates. In secondary liver tumors, neuroendocrine cancer liver metastases are an accepted but comparability rare indication for liver transplantation. Recently, some evidence has been published supporting the use of liver transplantation even for colorectal liver metastases. This review summarizes the current evidence for liver transplantation for primary and secondary liver cancer.

Key Words: Liver transplantation; Hepatocellular carcinoma; Cholangiocellular carcinoma; Hepatic epithelioid hemangioendothelioma; Undifferentiated embryonal sarcoma of the liver; Colorectal cancer liver metastases; Neuroendocrine cancer liver metastases

Core Tip: This review focuses on the role of liver transplantation in the treatment of primary and secondary liver cancer. Particularly, we summarize the selection criteria for hepatocellular carcinoma and the available evidence for liver transplantation in perihilar and intrahepatic cholangiocarcinoma. Very rare indications such as hepatic epithelioid hemangioendothelioma, fibrolamellar carcinoma, hepatic angiosarcoma and undifferentiated embryonal sarcoma of the liver are reviewed. In secondary liver cancer, neuroendocrine liver metastases constitute the only established indication so far, and the existing data is recapitulated. Regarding colorectal liver metastases, current novel evidence and ongoing studies are summarized.

INTRODUCTION

Liver transplantation is increasingly recognized as the curative treatment option in various end-stage liver diseases. Over the last 50 years, progress in operative technique and perioperative management as well as increasing knowledge about patient selection and postoperative immunosuppression have led to significant improvement in peri- and postoperative outcomes. As a result, 1-year overall survival (OS) rates after liver transplantation nowadays range between 80% and more than 90%, while 5-year OS has been reported to be around 70%[1-3]. So far, a wide variety of indications for liver transplantation are generally accepted, including cirrhosis, acute liver failure, and metabolic disorders[4]. However, the initial attempts to employ liver transplantation as treatment for malignant diseases were disappointing because of early recurrence and disease progression. In 1996, Mazzaferro *et al*[5] introduced the so-called Milan criteria for patients suffering from hepatocellular carcinoma (HCC). The implementation of those strict criteria led to improvements of both OS and recurrence-free survival (RFS)[5], emphasizing the importance of careful patient selection as key factor when applying liver transplantation for malignant disease. Subsequently, promising results have been published regarding not only cholangiocarcinoma but also for neuroendocrine cancer liver metastases (NECLM). Recent evidence also suggests that colorectal liver metastases (CRLM) are a good indication for liver transplantation in certain situations. The latter shows that the meaning of liver transplantation in the field of oncology is constantly changing. To reflect its increasing importance, the term "transplant oncology" was established[6].

A breakthrough in solid organ transplantation was the development of immunosuppressive drugs to avoid organ rejection. Particularly, the implementation of the calcineurin inhibitor (CNI) cyclosporine reflects a cornerstone in immunosuppression. Subsequently, novel drugs such as the CNI tacrolimus[7], the antimetabolite mycophenolate mofetil[8], the monoclonal antibody basiliximab[9] and the mammalian target of rapamycin (mTOR) inhibitor everolimus[10] have been introduced into routine care after liver transplantation. Current regimes for early post-transplant immunosuppression are mainly based on a combination of two to three drugs, with CNI being the backbone. A major concern regarding the use of CNIs upon liver transplantation for malignant disease is their tumor-promoting effect, as suggested by experimental data[11,12], and also the risk of de-novo development of secondary malignancies. In contrast, mTOR inhibitors such as sirolimus and everolimus have shown antineoplastic efficacy in preclinical tumor models[13-15]. Hence, the obvious hope is that the implementation of mTOR inhibitors into immunosuppressive regimes will reduce the risk of recurrence and development of secondary malignancies. Although recent evidence suggests a beneficial effect of mTOR inhibitors in the context of transplantation for malignant disease, a number of questions regarding this issue remain to be answered[16,17].

An important problem in transplant oncology is the timing of liver transplantation. The current allocation algorithm in Eurotransplant (ET) and the United Network for Organ Sharing (UNOS) system is based on the Model for End-Stage Liver Disease

(MELD) score. The MELD score, which is calculated by creatinine, bilirubin, and the international normalized ratio, favors the sickest patients, is a disadvantage for patients listed for malignant disease as their hepatic and renal functions are usually compensated. For certain indications such as HCC, the MELD exception (or exceptional MELD in Eurotransplant) score has been introduced to overcome this drawback. However, the exceptions are currently not applicable to all indications for liver transplantation in malignant tumors. The increased use of living-donor liver transplantation (LDLT) to overcome the problem of prolonged waiting time and organ shortage is an option, but not the solution, for the problem of timing in transplant oncology even though LDLT has become a standard in various regions worldwide. The present review will focus on the current status of transplant oncology and summarize some of the results obtained for the most frequent indications in liver transplantation for primary and secondary malignant tumors.

PRIMARY LIVER CANCER

HCC

HCC is by far the most common primary liver cancer and accounts for more than 80% of primary liver tumors[18]. In addition, it is a major global health, burden being the fourth most common cause of cancer-associated mortality worldwide[19]. In about 80% to 90% of patients, HCC develops in a cirrhotic liver. The main risk factors for cirrhosis and subsequent development of HCC are hepatitis B and/or C infection, alcohol, autoimmune liver disease, and hemochromatosis as well as nonalcoholic steatohepatitis (NASH), which is becoming more and more important[20,21]. In patients with preserved liver function, liver resection is the treatment of choice mainly because of the shortage of organs[22]. Nonetheless, several studies that compared liver resection and liver transplantation reported a superior outcome for liver transplantation regarding RFS after 3 and 5 years, and OS after 10 years[23,24]. Although some patients with HCC in cirrhosis are prioritized through MELD exception, a number of patients still drop out following tumor progression while on the waiting list [25,26]. Nonetheless, liver transplantation is regarded as the best treatment option for HCC in cirrhotic livers as it cures both the tumor and the underlying liver disease.

Patient selection is crucial in liver transplantation for HCC. In this regard, the Milan criteria, established by Mazzaferro *et al*[5] in 1996, represent the gold standard for HCC. The criteria include patients with a single HCC lesion up to 5 cm in diameter or with 2 to 3 HCC lesions up to 3 cm in diameter without macrovascular invasion or extrahepatic tumor growth. Five-year OS after transplantation for patients within the Milan criteria is reported to be around 70% with 10% to 15% recurrence rates[5,27]. Although initially defined in a series of only 48 patients, the Milan criteria are nowadays widely accepted and have been adopted by many guidelines including those of the European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASL-EROTC), the American Association for the Study of Liver Diseases (AASLD), as well as by Asian guidelines. With growing experience in liver transplantation for HCC, the strict Milan criteria were extended by several groups. Yao *et al*[28] introduced the University of California San Francisco (UCSF) criteria in 2007[28]. The criteria comprise a single lesion up to 6.5 cm in diameter or two to three lesions with up to 4.5 cm for the largest, and a maximum tumor diameter up to 8 cm[28]. Soon afterwards, even the Milan group extended their criteria to the so-called "up-to-seven criteria" (the sum of the number of tumors and diameter of the largest tumor of up to 7 cm)[29]. Additional criteria have been published by several groups from all over the world[30-35].

Over the years, significant efforts have been made to include parameters to address differences in tumor biology into the selection criteria. Markers such as tumor differentiation[36,37], des-γ-carboxy prothrombin (DCP)[38] and FDG-PET imaging[39] have been proposed. Notably, alpha-1-fetoprotein (AFP) is the most widely accepted biomarker for HCC, and an AFP level above 1000 ng/mL has been identified as a surrogate marker for vascular invasion and a significant predictor for tumor recurrence after transplantation[40]. More recently, AFP was included in new, expanded criteria for LDLT candidates with HCC in Japan. These so-called "5-5-500 criteria" (nodule size ≤ 5 cm, nodule number ≤ 5 and AFP ≤ 500 ng/mL) were established based on a retrospective analysis of the Japanese nationwide survey. When applying the criteria, a recurrence rate of only 7.3% was observed after 5 years, while the number of eligible patients was increased by 19% compared with the conventional Milan criteria [41]. Interestingly, Korean groups published encouraging results for liver transplan-

tation in cases with tumor-associated portal vein thrombosis, which is usually considered to be an absolute contraindication for liver transplantation[42,43]. In particular, Lee and coworkers reported a 5-year OS of around 63% and a 5-year RFS of around 45% in 11 patients who underwent liver transplantation[43]. These are undoubtedly impressive results in patients with advanced malignancies. However, as the criteria for organ allocation regarding liver transplantation in HCC are much more restrictive in many areas of the world, the results are hardly transferable particularly to Western countries. The most commonly used selection criteria for liver transplantation in HCC are summarized in Table 1.

In 2007 Mazzaferro[44] summarized a number of selection criteria, defined at that time in the so-called Metroticket. The principle of the Metroticket is that the greater the number or the larger the size of tumor nodules (in the words of the Metroticket, "the longer the trip"), the lower the expected patient survival (in the words of the Metroticket, "the higher the price")[44]. While the initial model was based on the conventional criteria, tumor number and size, a group from Italy and China defined the Metroticket 2.0 several years later by including AFP as a biological surrogate in the prediction model[45]. Results show that a 70% chance of HCC-specific 5-year OS can be obtained if the AFP level is below 200 ng/mL and the sum of the number and size (cm) of the tumors does not exceed seven. With an AFP level of 200-400 ng/mL prior to transplantation, the tumor number and size (cm) should not exceed five, and in cases with an AFP between 400 and 1000 ng/mL, the number and size (cm) should not exceed four. Very recently, the latter prediction model was again refined by adding the response to neoadjuvant therapies as determined by modified Response evaluation criteria in solid tumors (RECIST) criteria. Results were stratified by the last radiological staging before liver transplantation. To maintain the HCC-related deaths below 30% within 5 years from transplantation, Metroticket 2.0 criteria had to be modified for patients with a partial response (PR) or stable disease and also for progressive disease (PD)[46]. Taken together, the Metroticket model including the upgrades can help to estimate the risk of recurrence and cancer-related death more precisely.

To overcome the problem of binary decision systems, continuous-risk scores were subsequently developed. Particularly, Sasaki *et al*[47] described the Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma (HALT-HCC) score, which includes the tumor burden score, AFP, and MELD-Na after initial evaluation of eight variables. This score was validated and recalibrated by an international study group using data from more than 4000 patients[48]. After recalibration, HALT-HCC increased in its prognostic utility regarding RFS and OS. Finally, Goldberg *et al*[49] recently published the Liver Transplant Expected Survival (LiTES)-HCC score, which emphasizes the issue that the majority of deaths after transplantation for HCC are not related to HCC recurrence. In addition, the etiology of liver disease is adjusted to the U.S. population (*e.g.*, the fraction of patients with NASH is higher). 11 variables were included and four groups based on the LiTES-HCC score were defined. Survival analysis showed a 1-year OS of 97% in the best group *vs* 90.2% in worst group, which were more pronounced with longer follow-up (5-year OS of 86.3% *vs* 67% and 10-year OS of 72.7% *vs* 47.7%)[49]. The data have the potential to change the current practice in prioritization of patients with HCC.

So far, the Milan criteria are the basis of selection for liver transplantation in numerous countries. However, there is a considerable risk of tumor progression for patients while on the waiting list, emphasizing the need for therapy as bridging until a suitable donor is available. The dropout rate without liver-directed treatment has been described as high as 25% after 6 mo and 38% after 1 year compared with 8.7% and 22.9% with locoregional therapy[25,26]. Usually, locoregional therapies including transarterial chemoembolization, local radiofrequency or microwave ablation, radioembolization, liver resection or stereotactic body radiation therapy are employed for bridging[25,50]. The choice of a certain locoregional therapy is based on liver function, size and number of tumors as well as institutional experience because of a lack of prospective randomized controlled trials comparing certain modalities before liver transplantation. An analysis of 18 studies by Kulik *et al*[50] found no significant impact on post-transplant survival or recurrence by pretransplant bridging therapy. Nonetheless, a recent subgroup analysis from the SiLVER study showed that patients who are progressing upon bridging have poorer OS compared with those with controlled disease[51].

Locoregional therapies can also be applied to decrease the number and/or size of tumors. This concept of downstaging to predefined criteria (usually the Milan criteria) is performed in many areas worldwide but not allowed in certain countries such as Germany. The success rate of downstaging to within the Milan criteria exceeds 40% as shown by Parikh *et al*[52] in a systematic review and pooled data analysis. Several

Table 1 Selection criteria for liver transplantation in hepatocellular carcinoma

Criteria	Definition	Overall survival, (%)	Comment
Milan criteria (MC) (1996)[5]	Single tumor ≤ 5 cm	75% (4-yr OS)	Gold standard
	2-3 tumors ≤ 3 cm	92% (4-yr OS; inside MC at pathological examination)	Validated by many subsequent studies
	No macrovascular involvement		
	No extrahepatic disease		
UCSF (2001)[28,163]	Single tumor ≤ 6.5 cm	90% (1-yr OS)	Initial definition on pathological examination
	3 tumors all ≤ 4.5 cm with total tumor diameter ≤ 8 cm	75% (5-yr OS)	Subsequently validated in preoperative imaging
Up-to seven (2009)[29]	Sum of the number of tumors and diameter of the largest tumor (in cm) ≤ 7	64% (beyond MC but within up-to-seven)	
		Without microvascular invasion: 71%	
		With microvascular invasion 47%	
Navarro criteria (2008)[32]	1 tumor ≤ 6 cm	92% (1-yr OS)	
	2-3 tumors ≤ 5 cm	73% (5-yr OS)	
Valencia criteria Silva *et al*[34] (2008)	Up to 3 tumors, each ≤ 5 cm, and a cumulative tumor burden ≤ 10 cm	69% (5-yr OS)	
		Recurrence probability: 12% and 28% after 1 and 5 yr, respectively	
TTV (2008)[164]	TTV ≤ 115 cm^3	80% (5-yr OS)	In some centers only LDLT for those beyond MC
	AFP ≤ 400 ng/mL[165]		
ETC (2011)[31]	No limits in size and number	68% (beyond MC but inside ETC)	
	No vascular invasion	68% (5-yr OS)[37]	
	No extrahepatic disease		
	No cancer-related symptoms		
	Biopsy of the largest lesion not poorly differentiated		
Asan criteria (2008)[33]	Largest tumor diameter ≤ 5 cm	76% (5-yr OS)	LDLT
	Number of HCC lesions ≤ 6		
	No vascular invasion		
Kyoto criteria (2007)[166]	Number of lesions ≤ 10	Beyond MC but within Kyoto criteria: 65% 5-yr OS	LDLT
	Size of the largest lesion ≤ 5 cm	82% (5-yr OS)[38]	
	DCP ≤ 400 mAU/mL		
Kyushu criteria (2011)[167, 168]	Any number of tumors with a maximum diameter ≤ 5 cm	- 81% (5-yr OS)[169]	LDLT
	DCP < 300 mAU/mL		
Tokyo criteria 8 (5-5 rule)[30, 35]	Up to 5 tumors	80% (5-yr OS)	LDLT
	Maximum diameter ≤ 5 cm		
Samsung[170]	Maximum tumor size ≤ 6 cm	90% RFS after 5 yr	LDLT
	Number of tumors ≤ 7		
	AFP ≤ 1000 ng/mL		
5-5-500[41]	Up to 5 tumors	- 76% (5-yr OS)	LDLT
	Maximum diameter ≤ 5 cm-		
	AFP ≤ 500 ng/mL		
Portal vein invasion			

Seoul National University Hospital[43]	PV tumor thrombus does not extend into the main PV	11 patients	LDLT
		64% (5-yr OS)	
	AFP × DCP score ≤ 20000 Additional risk factors for recurrence:	46% (5-yr RFS)	
	Tumor size > 7 cm		
	Preop. FDG-PET SUV ratio ≥ 2.1		
	Vp4 infiltration		

AFP: Alpha-fetoprotein; DCP: Des-γ-carboxy prothrombin; ETC: Extended Toronto criteria; FDG: Fluorodeoxyglucose; HCC: Hepatocellular carcinoma; LDLT: Living-donor liver transplantation; MC: Milan criteria; OS: Overall survival; PV: Portal vein; PET: positron emission tomography; RFS: Relapse-free survival; SUV: Standardized uptake value; TTV: total tumor volume; UCSF: University of California San Francisco.

studies have reported that the survival of patients who were successfully downstaged is similar to those who were always within the Milan criteria[53]. Kardashian *et al*[54] reported evidence that successful downstaging was predicted by waiting time, AFP response to locoregional therapy, and tumor burden, which in turn provided excellent outcomes after liver transplantation. Furthermore, Mazzaferro *et al*[55] published results from a phase IIb/III trial showing that liver transplantation improves survival after effective and sustained downstaging to within the Milan criteria compared with nontransplant therapies. Finally, novel systemic treatment options based on the use of immune checkpoint inhibitors have recently been approved for treatment of advanced-stage HCC [56,57]. However, there is almost no literature available regarding their use in neoadjuvant setting before liver transplantation. A major concern when using those drugs in the transplant setting is the risk of organ rejection and death following hyperactivation of the immune system[57]. Experience so far is limited to case reports. Schwacha-Eipper *et al*[58] recently published a case of successful liver transplantation after neoadjuvant use of nivolumab while two other case reports indicate fatal hepatic necrosis following treatment with an immune checkpoint inhibitor, based therapy prior to transplantation[59,60]. Hence, the exact role and handling of these novel agents in neoadjuvant strategies before liver transplantation remains to be elucidated[57]. Nonetheless, the data on expanding the criteria to patients who were downstaged to within the Milan criteria seems to be convincing.

Regarding immunosuppression following liver transplantation for HCC, a recent systematic review and meta-analysis of 23 studies concluded that mTOR inhibitor-based immunosuppression is preferable, due to reduction of recurrence rate and improved RFS over at least 3 years[61]. That is further supported by earlier clinical data showing that reduction of CNI-based immunosuppression (> 10 ng/mL tacrolimus or > 300 ng/mL cyclosporin) reduces recurrence of HCC[62]. Evidence was also provided by a prospective randomized phase III trial (the SiLVER study) showing better RFS and OS at 3 to 5 years in HCC patients receiving immunosuppression with sirolimus compared with standard CNI-based immunosuppression, although the primary endpoint of the study (long-term RFS beyond 5 years) was not met[17]. A recent subgroup analysis from the SiLVER study emphasized that sirolimus treatment is most beneficial in patients with active HCC as determined by elevated AFP levels [63]. However, when using mTOR inhibitors for immunosuppression, the side effect profile has to be balanced with higher rates of proteinuria, peripheral edema, and incisional hernia on the one hand and preserved renal function on the other hand[64]. Nonetheless, some evidence supports the use of mTOR inhibitors as immunosuppression after liver transplantation for HCC.

Taken together, selection is crucial in patients with HCC who are scheduled for liver transplantation. Although the Milan criteria are still the standard in most countries, several efforts have been made to refine and extend the inclusion criteria for liver transplantation in HCC. Bridging therapies while being on the waiting list are commonly used, and downstaging strategies are performed in most countries. Finally, the optimal immunosuppression after liver transplantation for HCC is still a matter of ongoing research.

Fibrolamellar carcinoma
Fibrolamellar carcinoma (FLC) is a rare liver tumor that accounts for less than 1% of primary liver tumors[65]. Initially regarded as a subtype of HCC, this tumor entity has received its own classification code from the World Health Organization in 2010[66].

FLCs are usually detected in younger patients between 10 and 30 years of age but a second peak has been reported in patients between 60 and 69 years of age[65]. As the tumor arises without an underlying liver disease, liver resection including lymphadenectomy is the preferred treatment, with 5-year OS between 50% and 70%[67-69]. Liver transplantation is considered in selected cases with unresectable FLC. However, patients with FLC do not get a MELD exception, which often precludes them from liver transplantation because of the usually preserved liver function. Because of the low incidence and the possibility to perform extended liver resection, experience with liver transplantation is limited to case reports or small case series. Atienza *et al*[70] analyzed data from 63 patients from the UNOS database who underwent liver transplantation between 1988 and 2013. 1-, 3- and 5-year OS were 90%, 80% and 48%, respectively, with a 10% recurrence rate. Mavros *et al*[68] summarized data from 484 patients, of whom 109 underwent liver transplantation. Survival was reported in six studies with 1-, 3-, and 5-year OS between 63%-100%, 43%-75%, and 29%-55%, respectively. Unlike HCC with coexistent cirrhosis, no selection criteria for liver transplantation have been defined for FLC. Therefore, results from the case series have to be handled with caution. Nonetheless, given the acceptable outcome published in the aforementioned reports, liver transplantation seems to be a treatment option in selected patients with FLC who are not candidates for liver resection.

Combined hepatocholangiocarcinoma

Combined hepatocholangiocarcinoma (HCC-CC) is also rare, accounting for 0.75% to 1% of primary liver tumors. The incidence is reported to be around 0.5 per 1,000,000 and has been slightly increasing in the last decades[71]. Because of difficulties in preoperative imaging, the diagnosis of combined HCC-CC is usually made in the postoperative pathological report, and even if suspected intraoperatively, confirmation of combined HCC-CC is often difficult in frozen sections. Liver cirrhosis is detected in more than 50% of cases. So far, liver resection is the treatment of choice, if liver function is preserved[72]. Experience with liver transplantation is limited to small case series or case reports. In 2013, Groeschl *et al*[73] compared patients who underwent either resection or transplantation for HCC and HCC-CC. Results showed that liver transplantation for HCC-CC had a 3-year OS (48%) similar to liver resection (46%) but was inferior to transplantation for HCC (78%)[73]. Garancini *et al*[74] analyzed data from 485 patients in the Surveillance, Epidemiology, and End Results (SEER) database who were treated for HCC-CC between 1988 and 2009. Among them, 13% underwent liver transplantation with 5-year OS of 41%[74]. A recent report from 19 patients from Germany also found a 1-year OS of 57% and a 5-year OS of 38%[75]. In contrast to these disappointing results, Sapisochin *et al*[76] analyzed data from 15 patients with HCC-CC and 30 patients with HCC in a retrospective 1:2 matched cohort analysis. Results showed no difference when comparing the OS rates of liver transplantation for HCC-CC (1-, 3-, 5-year OS: 93%, 78%, 78%, respectively) with the matched group of HCC (1-, 3-, 5-year OS: 97%, 86%, 86%, respectively. Similarly, a series from Korea described encouraging 1- and 5-year OS of 84% and 66%, respectively, in 32 patients who were transplanted between 2005 and 2014. Notably, the recurrence rate was 16% after 1 year and 32% after 5 years. The authors also found that patients with very early stage combined HCC-CC (1 or 2 tumors ≤ 2.0 cm) had only 13% tumor recurrence and as much as 93% OS at 5 years[77]. De Martin *et al*[78] described a group of 49 patients with either intrahepatic cholangiocarcinoma (iCC) (*n* = 24) or HCC-CC (*n* = 25) who received liver transplantation. Overall, 1- and 5-year survival were 90% and 67%, respectively. When comparing iCC and HCC-CC, OS and RFS in the two groups were comparable[78]. In line with those results, Dageforde *et al*[79] analyzed data from more than 3000 patients with HCC (*n* = 2998) or HCC-CC (*n* = 208) who underwent either liver resection or liver transplantation in an American multicenter analysis. In the subgroup of patients within the Milan criteria, 67 with HCC-CC underwent liver transplantation. Those patients had similar OS compared to patients who underwent transplantation for HCC (5-year OS 70% for HCC-CC *vs* 73% for HCC) despite higher recurrence rates (23% with HCC-CC *vs* 12% with HCC at 5 years)[79]. The largest registry data comprises 220 patients from the National Cancer Database who underwent liver transplantation for HCC-CC and reported a 5-year OS of 52%[80]. However, the aforementioned results are still not conclusive. Therefore, a recent working group manuscript from the International Liver Transplantation Society (ILTS) Transplant Oncology Consensus Conference states that there is still no consensus about the role of liver transplant in the treatment of HCC-CC[81].

iCC

iCC is the second most common primary liver tumor and its incidence is increasing worldwide, especially in Western countries[82-84]. This tumor can arise in both, noncirrhotic and cirrhotic livers. To date, liver resection with lymphadenectomy is the treatment of choice, in cases of resectable disease. iCC is considered to be a contraindication for liver transplantation because of poor OS and RFS results reported in historical data[85,86]. In fact, several case series report 5-year OS rates between 0% and 30%[86-90]. However, in the last decade some encouraging results were published. A very recent multicenter study from Japan including 19 patients with incidentally detected iCC reported tumor recurrence in 10 patients (53%). OS at 1-, 3- and 5-years was 79%, 63% and 46% while RFS was reported to be 79%, 45% and 45%, respectively [91]. Furthermore, Sapisochin *et al*[76] performed a retrospective matched cohort study of incidentally detected iCC showing 51% 5-year OS and 5-year RFS of 36% in 27 patients. The results were inferior compared with the control group of HCC, but was still better than in previous reports. Moreover, the authors confirmed their results in a larger multinational study with 48 patients. In particular, patients with single iCC of up to 2 cm in diameter who underwent liver transplantation (*n* = 15) had a 5-year OS of 65% and an RFS of 82%. In contrast, patients with tumors larger than 2 cm or multiple lesions (*n* = 33) had a 5-year OS of 45% and RFS of 39%[92]. Similar results were reported by Facciuto *et al*[93], with a 5-year OS of 57% and an RFS of 57% in seven patients. In that study, patients with iCC features within the Milan criteria had a tumor recurrence of only 10% and a 5-year survival of 78%, which is comparable to patients with HCC within Milan criteria. However, the studies mentioned so far included almost exclusively patients with incidentally detected iCC. Currently, a prospective phase II trial from Canada is evaluating the impact of liver transplantation in patients with very early iCC (≤ 2 cm) and 5-year OS as the primary endpoint (NCT02878473).

In contrast, Lunsford *et al*[94] prospectively analyzed the impact of neoadjuvant gemcitabine-based chemotherapy in the context of liver transplantation for iCC. Patients had to be stable for 6 mo before getting on the waiting list for transplantation. Of 12 patients enrolled in the protocol, six finally underwent liver transplantation. OS at 1-, 3-, and 5-years was 100%, 83%, and 83%, respectively. Three patients (50%) developed recurrence after a median of 7.6 mo while the other three patients remained free of recurrence (5-year RFS 50%)[94]. Finally, Wong *et al*[95] recently reported results from a prospective pilot study of neoadjuvant therapy for downstaging of locally advanced cholangiocarcinoma prior to liver transplantation. Of 18 patients who started neoadjuvant treatment, 11 dropped out because of tumor progression or uncontrolled infection. Five received transplantation, with two of them suffering from iCC. The 1-year OS was 80%, three patients were recurrence free, and one developed tumor recurrence[95]. A very recent systematic review and meta-analysis by Ziogas *et al*[96] summarized the available data from 355 patients in 18 studies. Pooled 1-, 3- and 5-year OS was reported to be 75%, 56%, and 42%, while pooled 1-, 3-, 5-year RFS was 70,%, 49%, and 38%, respectively. However, in the subgroup with very early iCC (a single tumor, ≤ 2 cm) 5-year RFS was 67% compared with 34% in more advanced stages[96]. Taken together, although encouraging results have been reported for patients with a single iCC ≤ 2 cm and those who are stable or respond to a neoadjuvant therapy, liver transplantation for iCC is still not a standard of care and should best be performed in the context of clinical trials.

Perihilar cholangiocarcinoma

Perihilar cholangiocarcinoma (pCC) accounts for about 50% of all cholangiocarcinomas. The tumor develops either without liver disease or on the basis of primary sclerosing cholangitis. Radical resection is the state-of-the art therapy and provides a 5-year OS of between 20% and 50% in cases with R0 resection[97,98]. However, a significant proportion of patients cannot undergo resection either because of distant metastases, a locally advanced tumor, quality of liver parenchyma, or underlying liver disease[99]. Hence, liver transplantation might be the only remaining curative option for those patients. Initial results published 20 to 30 years ago were poor, with high recurrence rates and 5-year OS between 0% and 25%[86,100]. Almost two decades ago, more encouraging results were published by De Vreede *et al*[101] from the Mayo Clinic and Sudan *et al*[102] from Nebraska. Both studies employed neoadjuvant treatment including brachytherapy and systemic chemotherapy with or without external beam radiation. In addition, strict criteria for patient selection were introduced (*e.g.*, no extrahepatic disease, no lymph node metastases as determined by lymphadenectomy.). Results were impressive, with tumor recurrence in one of 11

patients in the study by De Vreede *et al*[101] and two of 11 patients in the study by Sudan *et al*[102]. Subsequently, a number of case series were published confirming this data. Cambridge *et al*[103] very recently summarized the evidence in a meta-analysis and meta-regression of survival after liver transplantation for unresectable pCC. Results from 20 studies including 428 patients showed pooled 1-, 3-, and 5-year OS of 77%, 55%, and 45%, respectively. However, when neoadjuvant chemoradiotherapy was employed, OS improved to 83%, 66%, and 65% at 1, 3, and 5 years, respectively. In addition, the recurrence rate was as low as 24% after 3 years with neoadjuvant treatment compared to 52% when no neoadjuvant treatment was applied[103]. An important issue is the percentage of patients who undergo neoadjuvant chemoradio-therapy but do not proceed to transplantation. Several studies report that the dropout rate ranges between 0% and 66%, mostly for local or distant tumor progression[104-108]. The impressive results obtained by the neoadjuvant therapy and subsequent liver transplantation led to the introduction of a MELD exception for pCC in the U.S. (UNOS) and also in Eurotransplant[109,110]. Nonetheless, prioritization is currently performed similar to HCC which in turn leads to higher waitlist drop out in patients with pCC[111]. Hence, refinement of the current practice is warranted.

Another important question is whether resection or transplantation should be the preferred treatment of pCC. Regarding that issue, the group from Nagoya published a 5-year OS of 53% after the resection of pCC without nodal metastases, emphasizing a similar outcome compared to liver transplantation after neoadjuvant chemoradiation [98]. In contrast, Ethun *et al*[112] analyzed data from 191 patients who underwent resection and 41 who underwent transplantation for pCC from 10 institutions. The results showed a benefit for transplantation regarding 3- and 5-year OS (72% *vs* 33% and 64% *vs* 18%, respectively). Even patients who underwent resection within the strict selection criteria for transplantation (a tumor < 3 cm, no lymph node metastases, no extrahepatic disease) had inferior outcomes compared with transplantation, with a 5-year OS of 54% *vs* 29%[112]. An ongoing multicentric randomized trial in France is comparing capecitabine-based chemoradiotherapy with subsequent liver transplantation to standard liver and extrahepatic bile duct resection (NCT022322932; TRANSPHIL). Regarding selection criteria, most case series included only patients with tumors ≤ 3 cm, absence of lymph node metastases, and without signs of distant metastases. The neoadjuvant concept was also recommended by a recent working group report from the ILTS Transplant Oncology Consensus Conference. In addition, a dominant stricture and at least either positive cytology from brush endoscopy or biopsy demonstrating pCC or elevated CA19-9 above 100 U/mL in the absence of cholangitis were suggested. Finally, the use of arterial and venous jump grafts in the setting of liver transplantation was advised[81].

Hepatic epithelioid hemangioendothelioma

Hepatic epithelioid hemangioendothelioma (HEHE) is a very rare primary liver sarcoma accounting for approximately 1% of all vascular tumors[113]. The incidence is reported to be around 1-2/1000000 with a predominance in females[114]. The natural course of HEHE is unpredictable, ranging from aggressive growth to indolent behavior[115,116]. The tumor affects only the liver in about 21% of patients. Most common tumor sites other than the liver are the lungs, bone, and lymph nodes[115]. Regarding treatment modalities, no consented algorithm exists for EHE. However, Lerut and Iesari suggested a treatment algorithm for HEHE in 2017, with liver transplantation playing a central role[113]. Regarding surgical therapy, Konstantinidis analyzed a cohort of liver sarcomas from the National Cancer Database who underwent surgery between 2004 and 2014. The subgroup of HEHE who underwent either liver resection or transplantation showed no significant difference in OS. However, results from several case series and analyses from national and international transplant databases suggest that liver transplantation provides a high survival advantage. In particular, Rodriguez *et al*[117] analyzed data from 110 patients in the UNOS database and found 1- and 5-year OS of 80% and 64%, respectively. Of note, about a quarter of the patients were younger than 4 years of age at the time of transplantation[117]. Lerut *et al*[118] used data from 59 patients in the European Liver Transplant Registry (ELTR) with 1-, 5-, and 10-year OS of 93%, 83%, and 72%, respectively. Interestingly, the authors found that extrahepatic disease (EHD) did not influence the outcome after transplantation (up to 78% OS after 10 years in cases of EHD)[118]. A follow-up analysis of 149 patients who underwent liver transplantation for HEHE between 1984 and 2014 confirmed the aforementioned results regarding 1-, 5- and 10-year OS (89%, 80%, and 74%, respectively). However, in that study, pretransplant waiting time less than 120 d, macrovascular invasion, and hilar lymph node invasion but no other extrahepatic manifestations were found to be associated

with significant risk of recurrence. Based on the three parameters of pathological macrovascular invasion, hilar lymph node positivity, and a waiting time of < 120 d, the authors calculated a score to estimate the risk of recurrence, with 93.9% 5-year disease-free survival (DFS) in the low-risk situation (≤ 2 points) compared with 38.5% 5-year DFS in the high-risk situation (≥ 6 points)[119]. A recent study by Brahmbhatt *et al*[120] showed comparable results after liver transplantation for HEHE and HCC (inside the Milan criteria). However, the authors observed an increased rate of graft failure because of arterial thrombosis in patients with HEHE within the first 14 d after transplantation[120]. In summary, liver transplantation can provide excellent long-term results in patients suffering from HEHE, even in the presence of EHD.

Hepatic angiosarcoma

Hepatic angiosarcoma (HAS) is a very aggressive mesenchymal liver tumor. Fortunately, with an incidence of 0.5-1 cases per 1000000 people, it is extremely rare. HAS gained some attention because of its association with environmental factors such as vinyl chloride, thorotrast, radium, and cyclophosphamide[121]. According to a recent pooled analysis of the literature over the last 20 years, the prognosis of HAS is very poor. The review included 219 patients with a median survival of 6 mo and 1- and 2-year OS of 30%, and 17%, respectively[122]. If possible, liver resection is the treatment of choice. Some small series report a median OS between 17 and 19 mo, which can be extended in case of R0 resection[122,123]. Regarding liver transplantation only small case series have been reported. A retrospective analysis of 22 patients from the ELTR in 2013 found that no patient survived longer than 23 mo after transplantation. Indeed, recurrence was diagnosed after a median of 5 mo and almost 80% of patients died of recurrence[124]. Interestingly, in about 70% of patients, the diagnosis of HAS was not known prior to transplantation. Similar results, a median OS of 6 mo, were reported in a study by Konstantinidis *et al*[125]. However, some case reports have been published showing at least some success with liver transplantation and subsequent adjuvant chemotherapy and/or mTOR inhibitor-based immunosuppression[126-129]. Nonetheless the data do not affect the overall dismal results after liver transplantation for HAS. As a consequence, HAS is regarded as a contraindication for liver transplantation in Europe and the US[124,130].

Undifferentiated embryonal sarcoma of the liver

Undifferentiated embryonal sarcoma (UES) is a very rare indication for liver transplantation. The tumor was first described by Stocker and Ishak in 1978[131]. In fact, UES of the liver (UESL) in mainly diagnosed in children between 6 and 10 years of age and it accounts for 1%-4% of all solid childhood tumors[132,133]. Surgical resection with or without chemotherapy is currently recommended for therapy of this tumor[133,134]. Very recently, Babu *et al*[135] summarized the experience with liver transplantation for UESL. Only 28 cases we reported, among them only four patients were 18 years of age or older[135]. Notably, the oldest patient was described by Dhanasekaran *et al*[136] in 2012. The patient underwent liver transplantation in 2002. Although retransplantation was necessary following ductopenic rejection, he was tumor free for more than 10 years after the second transplantation[136]. In summary, although very rare, the option of liver transplantation for UESL should be kept in mind even in adults when liver resection is not possible.

SECONDARY LIVER CANCER

Liver transplantation for secondary malignant liver tumors was initially investigated more than 30 years ago. As results from early case series were poor, with 5-year OS between 0% and 20%[137-139], liver transplantation for this indication has been abandoned for years, with liver metastases from neuroendocrine tumors being the only exception. However, for liver metastases of colorectal cancer, the refusal of liver transplantation as a therapeutic option has diminished over the last decade.

NECLM

Over the years, NECLM was the only accepted indication for liver transplantation in patients with secondary liver tumors. However, the clinical course of patients suffering from neuroendocrine tumors (NET) is extremely variable and mainly dependent on differentiation. While low-grade NET (G1/G2) often has a slow-growing, indolent clinical course, High-grade tumors are usually more aggressive. Most NETs are located in the gastroenteropancreatic system, with pancreas being the

most frequent location within that area[140]. Regarding the primary tumor location, liver transplantation for NETs other than those from gastroenteropancreatic system are considered to be a relative contraindication by some groups, although 5-year OS was 53% in 16 patients who underwent liver transplantation after resection of a pulmonary NET in an ELTR study[141]. Evaluation of distant metastases outside the liver is important in NET with octreotide or gallium-68 DOTATATE or DOTATOC-PET being the most sensitive examinations[140]. The liver is the only metastatic location in about 50% of patients but only 0.2%-0.3% of all liver transplantations are performed for NECLM. Variability in the clinical course and the presence of a wide range of treatment options (*e.g.*, liver resection, local ablation, peptide receptor radionuclide therapy, transarterial approaches, and medical therapies) makes it difficult to define the optimal place and timing for liver transplantation in the therapy algorithm of NECLM[140]. However, the largest systematic review that summarized data on liver transplantation for NECLM between 1974 and 2016, comprised more than 1,000 patients[142]. 1-, 3-, and 5-year OS was 89%, 69%, and 63%, respectively. The recurrence rates after transplantation ranged from 31% to 57%. The largest study in the review was conducted by Le Treut *et al*[141] and was based on 213 patients included in the ELTR over a 27-year period. The authors found a 5-year OS and DFS from the time of liver transplantation of 52% and 30%, respectively[141]. Three factors associated with adverse outcomes were identified, simultaneous major resection (*e.g.*, primary tumor resection), poor differentiation (G3/4) and hepatomegaly. In 2007 Mazzaferro *et al*[143] had already defined selection criteria for liver transplantation of NECLM, the so-called "Milan NET" (Table 2). By applying these criteria, the group from Milan published results from 42 patients who underwent liver transplantation with impressive 5- and 10-year OS of 97% and 89%, respectively. Survival rates were significantly higher than those of 46 patients with a similar tumor burden who did not undergo liver transplantation (5-, 10-year OS 50.9% and 22.4%, respectively). Of note, the recurrence rate following liver transplantation in this study was only 13%, which is comparable to that of HCC patients undergoing liver transplantation within the established criteria[144]. However, some of the selection criteria used in the Milan NET score are debatable (*e.g.*, the cutoff age of 55 years). The UNOS guidelines and a revision of the Milan NET from 2016 advise an age cutoff of 60 years[144,145]. Another important issue is the use of certain immunosuppressants after liver transplantation for NECLM. mTOR inhibitors have been used for both immunosuppression after liver transplantation and for the treatment of NET[17,140,146]. Hence, the obvious hope is that using mTOR inhibitors as an immunosuppressant might reduce recurrence rates. In summary, although numerous questions remain to be answered, liver transplantation has the potential to improve the prognosis of patients suffering from NECLM.

CRLM

Colorectal cancer is one of the most common tumor entities worldwide[147]. About 50% of patients develop liver metastasis, a major predictor of OS. The current mainstay for the treatment of CRLM is surgical resection if possible as a 5-year OS of around 30% to 60% can be reached even in advanced stages. However, only 20% to 30% of patients with CRLM are eligible for surgery[148,149]. In cases of irresectable disease, the prognosis dramatically decreases even with novel chemotherapeutic regimes[150-152]. The group from Vienna was among the first to report long-term results of liver transplantation for CRLM. Twenty-five patients underwent transplantation, and the reported 5-year OS was only 12%[137]. In 2013, Hagness *et al*[153] published first results of the SECA-I trial including 21 patients with irresectable liver metastases from colorectal cancer who underwent transplantation. The authors reported an impressive OS of 95%, 68%, and 60% at 1, 3, and 5 years, respectively. DFS at 1 year was as low as 35%, but only six of 21 patients died after a median 26 mo after transplantation because of disseminated cancer progression[153]. The results show that recurrence after transplantation was quite common but treatment of post-transplant recurrence using chemotherapy or surgery was comparatively effective. Nonetheless, the report by the Oslo group brought new enthusiasm to the issue of liver transplantation in CRLM. In particular, the OS reported by Hagness *et al*[151,154] was far superior to that obtained by chemotherapy alone. More recently, the same group published even better results from the follow-up SECA-II study, including 15 patients with irresectable CRLM. The 1-, 3- and, 5-year OS were 100%, 83%, and 83%, respectively. Furthermore, the DFS was improved compared with the SECA-I trial with 53%, 44%, and 35% at 1, 2 and 3 years, respectively[155]. Since then, several other groups have reported their experiences with liver transplantation for CRLM over the past years. Giannis *et al*[156] performed a pooled data analysis comprising 18 studies with 110 patients showing a 5-

Table 2 2007 Milan neuroendocrine tumor criteria[143]

Inclusion criteria
Histology G1/G2 neuroendocrine tumor with or without syndrome
Primary tumor drained by the portal system (pancreas and intermediate gut: from distal stomach to sigmoid colon)
Primary tumor removed with a curative resection (pretransplant removal of all extrahepatic tumor deposits) through surgical procedures separate from transplantation
Less than 50% tumor load in the liver parenchyma
Response to treatment or stable disease for at least 6 mo pretransplantation
Age younger than 55 yr (relative criteria)
Exclusion criteria
High-grade neuroendocrine carcinomas
General contraindications for liver transplantation, including previous tumors
Non-gastrointestinal NET or tumors not drained by the portal system

NET: Neuroendocrine tumor.

year OS of 51%. Of note, patients who underwent liver transplantation after 2005 had a 5-year OS of 66%, but the reported RFS after 5 years was similar compared with the period before 2005 (26%)[156].

A crucial point in liver transplantation for CRLM is careful patient selection. Kappel *et al*[157] found the detection of micrometastases in lymph nodes of the primary tumor to be associated with impaired survival after liver transplantation for CRLM. The latter SECA-I study had rather broad and arbitrary inclusion criteria: irresectable liver metastases, complete resection of the primary tumor, good performance status (ECOG 0 or 1), completion of 6 wk of chemotherapy. Patients were excluded in case of a weight loss of > 10%, extrahepatic tumor growth, or general contraindications for liver transplantation. In subsequent analyses, a Norwegian group identified risk factors for inferior outcomes. The factors included a tumor diameter > 5.5 cm, CEA level > 80 µg/L, time lapse of < 2 years from resection of the primary tumor to liver transplantation, and progression while on chemotherapy. Hagness *et al*[153] summarized those four parameters in the so-called Oslo score (1 point for each). For the SECA-II study, the inclusion criteria were more strict. Response to chemotherapy and at least 1 year from diagnosis of colorectal cancer to listing for liver transplantation were required[155]. Moreover, the Oslo group reported that patients with an Oslo score of 2 or less had a 5-year OS of 67% compared with only 17% in patients with an Oslo score of 3 or 4[158]. In addition, the primary tumor seems to be of particular importance for patient selection. Right-sided tumor location, *BRAF* mutation, and signet ring cell carcinoma are associated with poor outcome similar to the data from liver resection[158-161]. Furthermore, lymph node status of the primary seems to have some relevance although that is not an independent prognostic factor [159,160]. Remarkably, the group from Oslo recently published data comparing the results after PVE and subsequent liver resection with those of liver transplantation for CRLM[159]. Analysis of the subgroup of patients with a high tumor load determined as > 9 metastases and a high tumor burden score, showed a survival advantage for patients who underwent liver transplantation (median survival of 40.5 mo with liver transplantation *vs* 19.2 mo with PVE and resection). Of course, these impressive results have to be confirmed, but nonetheless harbor the potential to change the current management for CRLM. Regarding patient selection, the ILTS Transplant Oncology Consensus Conference working group gave recommendations for the use of liver transplantation in patients with CRLM. They include only liver involvement, an Oslo score ≤ 2, minimization of immunosuppression, and aggressive treatment of recurrence after transplantation[162].

The issue of immunosuppression after liver transplantation for CRLM is a matter of ongoing discussion. The Oslo group used CNI-free mTOR inhibitor-based immunosuppression in the SECA-I and -II trials because of its anticipated antineoplastic effects. Rejection was observed in 38% of patients in the SECA-I study, which is a marked increase compared with 28% with calcineurin-inhibitor based immunosuppression in a historical cohort from the Oslo group[153]. However, patient numbers in

the above mentioned studies were low, and further studies are needed to determine whether treatment with mTOR inhibitors has an inhibitory effect on tumor recurrence after liver transplantation for CRLM.

Currently, a number of questions are being addressed by ongoing studies. The SECA-II study aims to report 10-year OS. Although initial results regarding 5-year OS have already been published, final results are expected in 2025. The Oslo group also launched the SECA-III study to compare liver transplantation with any other treatment including chemotherapy, ablation, SIRT or other available treatment options (NCT03494946). The study plans to recruit 30 patients and is scheduled to report in 2027 with 2-year OS from the time of randomization being the primary outcome parameter. Another ongoing study is TRANSMET, launched by a French group. The study compares liver transplantation followed by standard chemotherapy to standard chemotherapy alone and plans to recruit 90 patients. The primary endpoint is 5-year OS (NCT02597348). The study is recruiting and is scheduled to report in 2027. The issue of LDLT is currently being investigated by a group in Toronto. The study plans to include 20 patients with liver-only metastases to receive LDLT. The primary endpoints are 5-year OS and DFS. Of note, a main exclusion criteria in this study is the presence of BRAF-positive tumors (NCT02864485). A stepwise approach with partial hepatectomy and transplantation of segment II/III from deceased donors during the first operation, followed by (second step) hepatectomy in 4 wk, is being investigated again by the Norwegian group. This so-called RAPID trail will include 20 patients, and the primary endpoint is 5-year OS (NCT02215889). Finally, the LIVERT(W)OHEAL trial from two German centers is currently ongoing. The study combines LDLT of segment II/III with the aforementioned stepwise approach of partial hepatectomy + segment II/III transplantation during the first operation and completion hepatectomy during the second operation. Primary endpoints are 3-year OS and DFS after the second-stage hepatectomy in 40 patients (NCT03488953). Study end is supposed to be 2023.

These studies will certainly answer a number of questions, but even more remain to be addressed. For instance, the issue of adjuvant chemotherapy after successful liver transplantation, impact of certain mutations (*e.g.*, *SMAD4*) that are known to be associated with impaired survival, or the optimal immunosuppression regime, to name just a few. Furthermore, the dramatic organ shortage remains a major issue that can only partly be relieved by LDLT. Nonetheless, liver transplantation for CRLM will gain more and more attention in light of the above mentioned evidence. Based on published data and the results from ongoing studies, it is assumed to find its place in treatment armamentarium for CRLM.

CONCLUSION

Liver transplantation for malignant disease has become a part of the armamentarium of cancer therapy. In HCC and HEHE, liver transplantation is an established treatment option. Increasing evidence supports the use of liver transplantation in pCC after neoadjuvant therapy, whereas the outcome of transplantation for iCC is not yet well defined. In FLC, liver transplantation might be an option, while patients with HAS are not considered to be optimal candidates. Regarding secondary liver cancer, NECLM remain an indication in selected patients, and recent evidence strongly supports liver transplantation for liver-only CRLM, although optimal selection criteria have to be defined.

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