

WJG 20<sup>th</sup> Anniversary Special Issues (7): Liver transplant**Liver transplantation for malignancy: Current treatment strategies and future perspectives**

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**Abstract**

In 1967, Starzl *et al* performed the first successful liver transplantation for a patient diagnosed with hepatoblastoma. In the following, liver transplantation was considered ideal for complete tumor resection and potential cure from primary hepatic malignancies. Several reports of liver transplantation for primary and metastatic liver cancer however showed disappointing results and the strategy was soon dismissed. In 1996, Mazzaferro *et al* introduced the Milan criteria,

offering liver transplantation to patients diagnosed with limited hepatocellular carcinoma. Since then, liver transplantation for malignant disease is an ongoing subject of preclinical and clinical research. In this context, several aspects must be considered: (1) Given the shortage of deceased-donor organs, long-term overall and disease free survival should be comparable with results obtained in patients transplanted for non-malignant disease; (2) In this regard, living-donor liver transplantation may in selected patients help to solve the ethical dilemma of optimal individual patient treatment *vs* organ allocation justice; and (3) Ongoing research focusing on perioperative therapy and anti-proliferative immunosuppressive regimens may further reduce tumor recurrence in patients transplanted for malignant disease and thus improve overall survival. The present review gives an overview of current indications and future perspectives of liver transplantation for malignant disease.

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**Key words:** Hepatocellular; Fibrolamellar; Carcinoma; Cholangiocellular; Hepatoblastoma; Liver metastases

**Core tip:** Liver transplantation for malignancy is a medical and ethical challenge with regard to oncologic outcome and allocation justice. Childhood hepatoblastoma, epithelioid hemangioendothelioma, limited hepatocellular carcinoma and fibrolamellar carcinoma are proven indications for liver transplantation. Recent clinical trials have suggested cholangiocellular adenocarcinoma and hepatic metastases originating from neuroendocrine tumors as new indications in selected patients. Ongoing research may further widen indications for liver transplantation in malignant disease and therefore also complicate organ allocation. Living-donor liver transplantation may offer a solution for selected patients.

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## INTRODUCTION

Liver transplantation (LT) is the only curative treatment option for patients with irrevocable acute or chronic liver failure and, in the last four decades, has developed from an experimental approach with very high mortality to an almost routine procedure with good short and long-term survival rates. During the last 15 years, survival rates world-wide are relatively stable with an overall survival (OS) of > 80% in the first year and > 70% at 5 years<sup>[1,2]</sup>. However, approximately 10% of patients listed for LT die on the waiting list<sup>[3]</sup> and many potential candidates, including patients diagnosed with primary or metastatic liver cancer, are not listed due to shortage of deceased-donor organs. While liver cirrhosis caused by chronic viral hepatitis and alcohol abuse are the two major causes for end-stage liver disease, most malignant diseases remain contraindications for LT.

Timing is crucial for the success of LT. On the one hand, best results are achieved if the patient is in a good general condition. On the other hand, decompensated and sickest patients most urgently need transplantation - but have the worst outcome. Due to shortage of deceased-donor organs, different allocation solutions are intensively discussed and permanently adapted. A model for the sickest first policy, the Model of End Stage Liver Disease (MELD), was implemented in the allocation procedure within the UNOS in 2002 and within the Eurotransplant network in 2007 (Patient based allocation). It is calculated of serum creatinine, international normalized ratio (INR) and bilirubin. The MELD was originally developed to predict 3-mo survival after transjugular intrahepatic portosystemic shunt placement<sup>[4,5]</sup>. Since implementation of the MELD system, the waiting list mortality for LT has declined. However, patients with very high laboratory MELD scores (> 35) are normally ICU bound, on dialysis and often require vasopressor support and artificial ventilation. Priorization of these patients led to a deterioration of the OS rates after LT since introduction of the MELD score for LT allocation in some countries like Germany<sup>[6]</sup>. In contrast, patients diagnosed with primary hepatic malignancy or hepatic metastases normally present in good clinical condition with low MELD score and exception MELD scoring is needed to enable transplantation before excessive tumor progress. Center based allocation is in use especially in countries with few transplant centers, *e.g.*, in Australia, United Kingdom, and Austria. Moreover, it is used in parallel to the MELD system for extended criteria donor organs. The advantage of the center-based allocation is that the physicians can match the organ to the patient, which also enables allocation to

recipients with malignancies.

In many East-Asian countries, deceased-donor liver donation (DDL) is very rare due to religious and political reasons. This has led to sound establishment of living-donor liver transplantation (LDLT)<sup>[7-9]</sup> and might serve as an example for Western countries to reduce donor organ shortage.

## SHORT HISTORY OF LIVER

### TRANSPLANTATION

The pioneer of human orthotopic LT, Thomas E. Starzl, learned about experimental auxiliary liver transplant models in dogs while attending a lecture by C. Stuart Welch in 1957<sup>[10]</sup>. After discussing and refining these canine models, Starzl was the first to attempt an orthotopic liver transplant into a 3 years old human recipient suffering from biliary atresia in 1963<sup>[11]</sup>. The patient did not survive the operation. After several equally unsuccessful attempts, Starzl *et al*<sup>[12]</sup> succeeded in performing an orthotopic liver transplant in a patient diagnosed with hepatoblastoma in 1967. LT for malignancy thus became the first successful LT in humans. The patient survived for 18 mo before dying from metastatic disease. During the subsequent years, major breakthroughs such as the expansion of the organ donor pool by introduction of the brain death criteria in 1968<sup>[13]</sup>, refined surgical techniques and especially ongoing research in immunology leading to the introduction of immunosuppressive medication such as cyclosporine in 1979<sup>[14,15]</sup> led to significant increase in LT. In 1983, the NIH declared that LT was a valid therapy for end-stage liver disease<sup>[16]</sup> and, a few years later, the United Network for Organ Sharing (UNOS) was founded<sup>[17]</sup>. Already in 1967, Eurotransplant International Foundation (ET) had been founded in Leiden, The Netherlands. In 1988, Rudolph Pichlmayr was the first to perform a split LT, offering one liver to two recipients<sup>[18]</sup>.

## INDICATIONS FOR LIVER

### TRANSPLANTATION

Indications for LT are manifold and can be classified into end-stage liver disease, acute liver failure and certain benign and malignant liver tumors. LT should be considered for any patient in whom anticipated OS exceeds life expectancy of the underlying disease or where significant increase in quality of life can be achieved. These criteria may also be valid for many patients diagnosed with primary liver tumors or hepatic metastases. However, LT for malignant disease is a medical and ethical challenge with regard to long-term oncologic outcome under immunosuppressive therapy and with regard to allocation justice due to organ shortage. Ongoing improvements in multimodality cancer therapy may in future widen indications for LT in malignant disease. Table 1 gives an overview of current indications for LT in malignancy

**Table 1 Indications and contraindications for liver transplantation in malignancy**

|  |
|--|
| Standard indications   |
| HCC in cirrhosis within Milan criteria                             |
| FLC  |
| Hepatoblastoma (pediatric patients)                                |
| Epithelioid hemangioendothelioma                                   |
| Investigational indications  |
| HCC in cirrhosis exceeding Milan criteria                          |
| HCC without cirrhosis  |
| CCA  |
| Neuroendocrine liver metastases                                    |
| Contraindications  |
| HCC with extrahepatic disease or macro-invasion into portal vein   |
| Hepatoblastoma with uncontrolled extrahepatic disease              |
| Malignancies other than the indications mentioned                  |
| Cancer Survivors with complete remission < 2-5 yr <sup>[153]</sup> |

HCC: Hepatocellular carcinoma; FLC: Fibrolamellar carcinoma; CCA: Cholangiocellular adenocarcinoma.

within the UNOS and ET network.

## LIVING-DONOR LIVER TRANSPLANTATION

Living-donor liver transplantation (LDLT) was successfully introduced in 1988 and 1989 respectively in the adult-to-pediatric and adult-to-adult setting<sup>[19]</sup>. In most East-Asian countries, LDLT is an established procedure and the main form of LT due to scarcity of deceased donor organs<sup>[7]</sup>. In western countries and especially in the UNOS area, use of living-donor organs for LT is less frequent and within UNOS even declining to currently < 10% of LT, although retrospective analyses have shown favorable or equal results as compared to DDLT<sup>[20-28]</sup>. The advantage of LDLT is the use of an optimal healthy donor, minimal ischemic time, elective surgery and timing of transplantation due to the recipients' need, which is particularly relevant for patients diagnosed with malignant disease. LDLT can also enable LT for patients not qualifying for deceased-donor LT according to allocation rules as well as early LT before the tumor exceeds transplantability. However, living donation is not without risk for the healthy donor and LDLT is surgically more demanding than whole organ transplantation. For the donor, major complications (exceeding Clavien grade II) of up to 44% after right-lobe LDLT and a mortality risk of up to 0.8% have been described<sup>[29-31]</sup>. Increasing the use of left-lobe liver donations also for adult recipients may here offer a solution<sup>[30]</sup>. A careful risk to benefit evaluation for the donor and the recipient must be performed in a multidisciplinary team for each individual case.

## IMMUNOSUPPRESSION

A highly relevant subject of translational research is post-transplant immunosuppression. In the early post-transplant phase, immunosuppressive therapy consists of complex combinations of drugs and needs to be adapted

for each patient individually. Components are steroids, anti-lymphocyte antibodies, calcineurin-inhibitors and inhibitors of B-/and T-cell proliferation<sup>[32]</sup>. Steroids are the back-bone of all immunosuppressive regimens. They inhibit T-cell activation and block IL-1 and IL-2 synthesis. Steroids are given already before reperfusion of the transplanted organ intra-operatively and are continued in high doses during the early postoperative phase, followed by dose reduction schemes. In many patients, steroids can be tapered six months after transplantation<sup>[33]</sup>.

The chimeric monoclonal T-cell IL2-receptor antibody basiliximab is given on day 0 and day 4 after liver transplant for induction therapy. Mycophenolate mofetil (MMF), a reversible inhibitor of inosine monophosphate dehydrogenase in purine synthesis, reduces proliferation of B- and T-cells and is well tolerated in LT patients<sup>[34]</sup>. Calcineurin-inhibitors such as cyclosporine inhibit T-cell production and excretion of IL-2. In cyclosporine A-based regimens, lowest-possible target levels have been linked to reduced tumor recurrence<sup>[35,36]</sup>. mTor-inhibitors such as sirolimus and everolimus also inhibit the proliferation of B- and T-cells. In contrast to calcineurin-inhibitors, mTor-inhibitors show no renal toxicity<sup>[37]</sup>. In LT for malignant disease, m-TOR inhibitors are highly promising immunosuppressive drugs, as they also block angiogenesis and tumor cell proliferation<sup>[38,39]</sup> and lower the risk of cancer recurrence<sup>[40]</sup>.

Future immunosuppressive strategies in LT have to imply 3 main goals: (1) reduction of side effects like renal insufficiency; (2) reduction of cancer recurrence and *de novo* cancer after transplantation (particularly in LT for malignant disease); and (3) induction of tolerance. Studies are ongoing which try to induce tolerance by either stem cell therapy<sup>[41-43]</sup> or by transfusion of regulating cells in the setting of living donation ([www.onestudy.org](http://www.onestudy.org)).

## LIVER TRANSPLANTATION FOR PRIMARY MALIGNANCIES

### Hepatocellular carcinoma

Hepatocellular carcinoma presents the sixth most common malignancy, and the third leading cause of cancer-related deaths world-wide<sup>[44]</sup>. Incidences vary from 38 per 100000 in male Chinese (14 per 100000 in female Chinese) to < 5 per 100000 in Northern Europe and North America<sup>[44]</sup>. Main risk factors for Hepatocellular carcinoma (HCC) are liver cirrhosis in the context of chronic HBV or HCV infection. Furthermore, alcohol-induced cirrhosis, aflatoxin intake, diabetes, obesity and hemochromatosis have been associated with a higher risk for developing HCC<sup>[45-48]</sup>. R0 resection combined with cure from the underlying liver pathology can only be achieved by LT. Disappointingly, first results of LT in HCC had shown a high perioperative mortality, 80% tumor recurrence and 5-year OS of 15.2%<sup>[49]</sup>. However, in 1991, Iwatsuki *et al*<sup>[50]</sup> could show that in the context of cirrhosis, long-term survival after LT for HCC was significantly higher than after liver resection with not signif-

icantly different tumor recurrence rates (50% and 43% after resection and LT, respectively). Retrospective analysis of patients where incidental, small HCC were found in the explanted liver after LT for cirrhosis showed no significant difference in OS compared to recipients transplanted for cirrhosis without incidentalomas<sup>[51]</sup>. In 1996, a landmark paper by Mazzaferro and colleagues established LT as standard indication for HCC within the “Milan criteria”, *i.e.*, limited HCC (1 lesion  $\leq$  5 cm, or 2 to 3 lesions each  $\leq$  3 cm), no macro-vascular invasion and no regional nodal or distant metastasis<sup>[52]</sup>. Patients who, after retrospective pathologic review, met these criteria, showed a 4-year OS of 85%. In contrast, patients, in which HCC size, after retrospective pathologic review, exceeded these criteria, had a 4-year OS of 50%<sup>[52]</sup>. In the following, many retrospective analyses have confirmed these results<sup>[53]</sup> and a 2012 meta-analysis of 1763 patients undergoing liver resection *vs* LT for HCC within the Milan criteria confirmed a survival advantage for LT (5-year OS 63% *vs* 53%, OR = 0.581, 95%CI: 0.359-0.939,  $P = 0.027$ )<sup>[54]</sup>.

Patients diagnosed with HCC often show sufficient liver function and thus, their urgency for LT is not adequately represented in their MELD scores. Therefore, cirrhotic HCC patients within the UNOS and ET network receive exception MELD (eMELD) scoring when diagnosed as American Liver Tumor Study Group (ALTSG) stage II HCC (*i.e.*, single HCC 2-5 cm or 2-3 lesions < 3 cm) for UNOS patients and within Milan criteria for ET patients. The eMELD given is equivalent to a 15% probability of death within 3 mo and, at present, is 22. Subsequently, the eMELD is increased every 3 mo by the number of points equivalent to a 10% increase in mortality until transplantation or drop-out of Milan criteria. Continued documentation to prove that patients are still within the Milan criteria must be made by abdominal CT or MRI scanning every 3 mo<sup>[55]</sup>. Therefore, surgical resection and therapeutic interventions to control HCC progress during the waiting period (= “bridging”) are a focus of ongoing clinical research<sup>[56]</sup>. Bridging can be achieved by local interventional measures such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), selective internal radiation therapy (SIRT) and irreversible electroporation (IRE) or surgical resection<sup>[57-64]</sup>. Bridging has shown to reduce drop-out rate of HCC patients listed for LT by 10%-20%<sup>[65-67]</sup>. Furthermore, good response after interventional bridging has been described as positive predictive factor for improved outcome after LT<sup>[68-70]</sup>.

LT for patients exceeding Milan criteria is controversially discussed. In 2001, Yao<sup>[56]</sup> showed comparable long-term outcome for LT in patients exceeding Milan criteria, and defined the “UCSF-criteria” as single lesion < 6.5 cm or up to 3 lesion with a total diameter of < 8 cm, the largest nodule being  $\leq$  4.5 cm in diameter<sup>[51]</sup>. In Australia and New Zealand, liver allocation for HCC is performed according to the UCSF criteria. In 2012,

an international European-North American consensus agreed upon restriction of LT for HCC to patients meeting Milan criteria<sup>[71]</sup>. Listing of patients exceeding Milan criteria and/or neoadjuvant interventional downstaging of HCC patients to meet Milan criteria is recommended as individual center specific regulation within UNOS and limited to randomized clinical trials within the Eurotransplant network<sup>[67]</sup>.

LDLT can offer a treatment option for selected HCC patients to minimize waiting time<sup>[22]</sup>. Due to very limited access to deceased-donor organs, LDLT is an established procedure and the main form of LT in most East-Asian countries<sup>[7]</sup>. In contrast, within the UNOS, only 5% of all LT are LDLT although retrospective analyses have shown favorable or equal results as compared to DDLT<sup>[20-25]</sup>. Furthermore, LDLT can enable LT also for patients exceeding Milan criteria. In 2012, an international European-North American consensus stated that LDLT is an acceptable procedure for patients with expected 5-year OS similar to DDLT<sup>[67]</sup>. Based on a data-collection of > 1200 HCC patients transplanted outside the Milan criteria, the “Metroticket”-calculator has been developed to predict survival of patients with HCC listed for LT<sup>[72]</sup>. Based on these data, individual evaluation of the potential risks and benefits has to be carefully discussed with each potential donor and recipient of LDLT.

Ongoing research in LT for HCC is focusing on mTor-based immunosuppressive regimens. In a first meta-analysis, the mTor-inhibitor sirolimus significantly decreased tumor recurrence in LT for HCC (OR = 0.30, 95%CI: 0.16-0.55)<sup>[73]</sup>. At present, a first randomized phase 3 clinical trial investigates the role of mTor-inhibition in LT for HCC ([www.clinicaltrials.gov: NCT00355862](http://www.clinicaltrials.gov: NCT00355862))<sup>[37]</sup>.

### **Fibrolamellar carcinoma**

Fibrolamellar carcinoma is a very rare primary hepatic malignancy with an incidence of 0.02 per 100000<sup>[74]</sup>. In contrast to HCC, it mostly occurs in young adults (median age at diagnosis: 33 years) with no underlying liver pathology and no known risk factors. Overall survival in fibrolamellar carcinoma (FLC) patients is 32% at 5 years<sup>[74]</sup>. Surgical resection is the standard therapeutic approach for FLC and 5-year OS rates of 45% to 80% have been described<sup>[75-77]</sup>. In unresectable cases, LT has been described with acceptable 1- and 5-year OS rates of 90% and 50%, respectively<sup>[76,78]</sup>. Other than HCC patients, FLC patients listed for LT are not prioritized within the MELD score. Therefore, LDLT should be considered in unresectable FLC patients. For this decision, however, the high rate of early lymph node metastasis of this tumor - which may be a cause for early recurrence after LT, has to be considered.

### **Cholangiocellular adenocarcinoma**

Cholangiocellular adenocarcinoma, although being the second most common primary hepatic malignancy, is a rare tumor with an incidence of < 2 per 100000 in the



Western World. However, higher incidences have been reported in several East-Asian countries<sup>[79]</sup>. Risk factors associated with cholangiocellular adenocarcinoma (CCA) are primary sclerosing cholangitis, ulcerative colitis, choledochus cysts, hepatic tremadodes, hepatolithiasis and HCV<sup>[79]</sup>. In contrast to HCC, CCA originates in the bile duct epithelium and can be defined as intrahepatic, perihilar, or distal CCA<sup>[80]</sup>. If untreated, the 5-year OS of CCA is < 10%. Surgical resection, which is feasible in 70%-75% of CCA patients, results in a 5-year OS of < 50%<sup>[81-83]</sup>. For lymph node negative patients, long-term survival rates of up to 67% after R0 resection have been described<sup>[81-83]</sup>. A nomogram to predict long-term OS after CCA resection, based on retrospective analysis of 367 patients undergoing partial hepatectomy for intrahepatic CCA and using the parameters CEA, CA19-9, vascular invasion, lymph node metastasis, local metastasis, number of tumor nodules and diameter of the tumor, has been published by Wang *et al.*<sup>[84]</sup>.

First results of LT in CCA have shown a high perioperative mortality, 100% tumor recurrence and a 1-year OS of 20%<sup>[85]</sup>. A European transplantation registry analysis of 187 patients after LT for CCA showed a 5-year OS of 29% and a > 40% rate of recurrence<sup>[85,86]</sup>. CCA was thus not considered an indication for LT. By establishing a strict selection protocol and a neoadjuvant chemoradiotherapy regime, combined with staging laparotomy to exclude metastatic disease, the Mayo Clinic has in 2005 re-established CCA as investigational indication for hilar, lymph-node negative CCA in PSC patients<sup>[87]</sup>. In this landmark publication, 1-/3-/5-year OS rates after LT were 92%, 82%, and 82% *vs* 82%, 48%, and 21% in patients undergoing liver resection. Furthermore, recurrence rate after LT was significantly lower than after liver resection (13% *vs* 27%)<sup>[87]</sup>. A weakness of this study was the high rate (7 of 38 transplanted patients) of absent histologic CCA confirmation prior to LT combined with negative histology in hepatectomy specimen after LT. A consecutive intention-to-treat analysis, however, showed 1-/3-/5-year OS rates of respectively 82%, 63%, and 55% after LT for CCA<sup>[88]</sup>. In subsequent years, several analyses have confirmed these results for selected patients and in 2012, a first meta-analysis of 605 patients undergoing LT for CCA during 1995-2009 has shown pooled 1-/3-/5-year OS rates of 75%, 42% and 39%<sup>[89]</sup>. Importantly, in patients transplanted after neoadjuvant therapy, 5-year OS was 65% and is thus comparable to survival rates of LT for HCC within the Milan criteria.

Within the UNOS, individual patients diagnosed with unresectable hilar CCA can be listed for LT by individual transplant centers<sup>[90]</sup>. For approval of exception MELD scoring for these patients, transplant centers need to submit a written application to the UNOS transplantation committee. Patients potentially qualifying for LT must have a tumor of < 3 cm in abdominal CT, ultrasound or MRI. Transperitoneal biopsy should not be performed to avoid tumor spread. A neoadjuvant therapy protocol

must be completed<sup>[91]</sup>, followed by operative abdominal staging to exclude regional hepatic lymph node metastases, intrahepatic metastases, and/or extrahepatic disease. Thoracic metastases must be excluded by chest CT. UNOS can then grant exception MELD scoring of 22, increasing every 3 mo by the number of points equivalent to a 10% increase in mortality until LT or drop-out. Chest and abdominal CT restaging to prove listing criteria must then be performed every 3 mo<sup>[90]</sup>.

Within the ET network, CCA is generally not regarded as indication for LT outside clinical trials. In Italy, a 2010 consensus statement has agreed upon performing LT for CCA in experimental settings<sup>[92]</sup>. However, an Italian clinical trial to validate the Mayo Clinic results is underway ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT01549795). Also in the United States, a clinical trial to validate the Mayo Clinic results is performed ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT00301379) and results are expected in 2015. At the Mayo Clinic, a pilot phase 1 clinical trial is testing application of sirolimus, gemcitabine and cisplatin for patients at high risk of CCA recurrence after LT ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT01888302) and results are expected in 2014.

Since DDLT for CCA remains investigational and, in many countries, is not indicated, LDLT may offer a treatment option for highly selected CCA patients. First clinical results of LDLT for CCA have shown results comparable to DDLT<sup>[93-95]</sup>. Further research is needed to identify prognostic factors for transplant candidate selection.

### **Hepatic epithelioid hemangioendothelioma**

Epithelioid hemangioendothelioma was first described and characterized as soft tissue low-grade malignant tumor in 1982<sup>[96]</sup>. Clinicopathologic characteristics of hepatic epithelioid hemangioendothelioma (HEHE) were defined by Ishak and colleagues<sup>[97]</sup> and a first series of LT for this malignancy was published in 1988<sup>[98]</sup>.

HEHE shows an incidence of one per million<sup>[99]</sup> and diagnosis often is challenging. Clinical presentation is unspecific with abdominal pain, hepatomegaly, and fatigue<sup>[100,101]</sup> and clinical course varies between almost benign behavior like hemangioma to rapid progress like angiosarcoma<sup>[102]</sup>. Histologic characteristics combined with immunohistochemical diagnostic markers (factor-VIII related antigen, CD31, CD34, cytokeratin, podoplanin), together with ultrasound/CT/MR imaging are needed to confirm diagnosis. Although CEA and CA19-9 have been reported to be elevated in some patients with HEHE<sup>[101,103]</sup>, there are no confirmed tumor markers identified for HEHE so far<sup>[102]</sup>. No clinical, radiological or histological markers exist to individually predict the natural course of HEHE. Although yearlong stable disease has been described, 5-year survival rates of untreated patients have been shown to be 5%<sup>[102]</sup>.

The majority of patients diagnosed with HEHE show extensive, multifocal intrahepatic disease at time of diagnosis and up to 37% of patients present with synchronous extrahepatic metastases<sup>[102]</sup>. For patients diagnosed

**Table 2** Liver transplantation for hepatic epithelioid hemangioendothelioma

| Database   | Author    | Year | Year of LT | n   | Age of patients             | Female | Mean follow-up | Overall survival in % |      |         | DFS in % |      |      | LDLT | Extrahep. | Recurrence |
|------------|-----------|------|------------|-----|-----------------------------|--------|----------------|-----------------------|------|---------|----------|------|------|------|-----------|------------|
|            |           |      |            |     |                             |        |                | 1 yr                  | 3 yr | 5 yr    | 1 yr     | 3 yr | 5 yr |      |           |            |
| Mayo       | Grotz     | 2010 | 1984-2007  | 11  | 21-79 yr<br>(mean 46.7 yr)  | 77%    | 42 mo          | 91                    | 73   | 73      | 64       | 46   | 46   | NR   | 18%       | NR         |
| UNOS       | Rodriguez | 2008 | 1987-2005  | 110 | 0-70 yr<br>(median 36 yr)   | 68%    | 24 mo          | 80                    | 68   | 64      | NR       | NR   | NR   | n.t. | NR        | NR         |
| Canada     | Nudo      | 2008 | 1991-2005  | 11  | 18-52 yr<br>(mean 38.7 yr)  | 77%    | 81 mo          | 82                    | 82   | calc 82 | 80       | 69   | 69   | 0%   | 36%       | 45%        |
| Europe     | Lerut     | 2007 | 1989-2004  | 59  | 4-65 yr<br>(median 41 yr)   | 57%    | 79 mo          | 93                    | NR   | 83      | 90       | NR   | 82   | 5%   | 17%       | 24%        |
| Review     | Mehrabi   | 2006 | 1984-2006  | 128 | mean 41.7 yr                | 58%    | NR             | 96                    | 77   | 54      | NR       | NR   | NR   | 2%   | NR        | NR         |
| Pittsburgh | Madariaga | 1995 | 1976-1993  | 17  | 28-58                       | 53%    | 56 mo          | 100                   | 86   | 67      | 88       | 68   | 59   | NR   | NR        | NR         |
| Review     | Yokoyama  | 1990 | 1980-1988  | 8   | NR                          | NR     | 25 mo          | 88                    | 73   | 48      | NR       | NR   | NR   | NR   | NR        | 50%        |
| Pittsburgh | Marino    | 1988 | 1963-1987  | 10  | 24-52.5 yr (median 29.5 yr) | 60%    | NR             | NR                    | NR   | calc 76 | NR       | NR   | NR   | NR   | 50%       | 30%        |

LT: Liver transplantation; NR: Not reported; DFS: Disease-free survival; LDLT: Living-donor liver transplantation; UNOS: United Network for Organ Sharing.

with localized hepatic disease, liver resection can result in 5-year OS rates of 75%<sup>[102]</sup>. However, reports of major hepatic resection for extended intrahepatic disease show contradictory results: On the one hand, long-term disease control<sup>[102]</sup> with successful rescue LT after HEHE recurrence<sup>[104]</sup> has been described; on the other hand, aggressive tumor regrowth after resection<sup>[105]</sup>, potentially triggered by pro-angiogenic hepatotrophic signaling after surgery, can occur. In a Mayo Clinic analysis of 30 HEHE patients treated between 1984 and 2007, no significant difference in long-term OS and disease-free survival (DFS) was seen comparing liver resection *vs* LT for resectable HEHE<sup>[106]</sup>. Furthermore, the clinicopathological factors tumor size  $\leq 10$  cm,  $\leq 10$  tumor nodules and nodular disease in  $\leq 4$  hepatic segments were identified as predictors for prolonged OS and LT was suggested for patients with unresectable disease and favorable predictors.

Multiple reports have shown that the presence of extrahepatic disease is no obligatory contraindication to perform LT for HEHE<sup>[98,104,106,107]</sup>. Thus, LT remains the only potentially curative approach for unresectable HEHE with or without extrahepatic tumor manifestation.

Table 2 gives an overview of original reports (including  $> 5$  patients) and two reviews analyzing LT for HEHE, including synopsis of UNOS, European and Canadian databases<sup>[98,100,102,104,106-109]</sup>. With 5-year OS of up to 83% (even in the presence of extrahepatic disease) and 5-year DFS of 46%-82%, outcome of LT for HEHE is comparable with non-malignant indications for LT and LT should thus be offered to all patients with unresectable HEHE or resectable HEHE with unfavorable predictors.

### Hepatoblastoma

Hepatoblastoma, first described in 1954 by Debre and colleagues<sup>[110]</sup>, is the most common primary hepatic malignancy in children and shows an incidence of one to two per million<sup>[111,112]</sup>. Increased incidence of hepatoblastoma (HEBLA) is seen in prematurely born infants and infants with a low birth weight, as well as in patients

diagnosed with Beckwith-Widemann Syndrome, Glycogen storage diseases 1-4, trisomy 18 and familial adenomatous polyposis<sup>[113-117]</sup>. Definite diagnosis can mostly be made upon characteristic ultrasound/CT/MRI imaging and elevated AFP levels  $> 1000$  ng/mL and biopsy is not recommended<sup>[118]</sup>. If resectable, 5-year OS rates of 80% can be reached with combined chemotherapeutic and surgical treatment<sup>[99]</sup>. However, the majority of patients present with unresectable disease at first diagnosis; only up to 40% of patients are diagnosed with resectable disease<sup>[111]</sup>. Due to a high sensitivity to perioperative chemotherapy (90%-95%), the European International Society of Pediatric Oncology (SIOPEL) recommends neoadjuvant chemotherapy to downstage HEBLA before resection or LT<sup>[119]</sup>. In contrast, many North American Centers prefer resection without prior chemotherapy in resectable patients<sup>[111]</sup>. For unresectable HEBLA, LT remains the only curative treatment option and long-term survival of 67%-93% after LT has been described. Presence of extrahepatic disease, if chemo-sensitive and potentially resectable, is no contraindication to perform LT for HEBLA<sup>[111]</sup>.

Table 3 gives an overview of original reports and reviews analyzing LT for HEBLA, including synopsis of UNOS and European (SIOPEL) databases<sup>[120-131]</sup>. With long-term OS rates of 65%-87% (even in the presence of extrahepatic, chemo-responsive disease) and recurrence rates of less than 26% (data not shown), LT should be offered to all patients with unresectable HEBLA. In borderline-resectable HEBLA, LT should be considered since publications have shown long-term OS of 85%-90% in patients receiving primary LT for HEBLA compared to 25%-40% in rescue-transplantation for recurrent disease after prior liver resection<sup>[121,128]</sup>.

## LIVER TRANSPLANTATION FOR HEPATIC METASTASES

### Neuroendocrine liver metastases

Neuroendocrine carcinomas were first described in 1907

**Table 3** Liver transplantation for hepatoblastoma

| Database        | Author    | Year | Year of LT | n   | Age of patients at LT                  | % female | Median FU    | Overall survival in %        |      |      | LDLT |
|-----------------|-----------|------|------------|-----|--|----------|--------------|------------------------------|------|------|------|
|                 |           |      |            |     |  |          |              | 1 yr                         | 3 yr | 5 yr |      |
| SIOPEL-3HR      | Zsiros    | 2010 | 1998-2004  | 31  | < 16 yr (median 21 mo)                 | NR       | 54 mo        | NR                           | 75%  | NR   | NR   |
| Chicago/Toronto | Browne    | 2008 | 1990-2004  | 14  | 18 mo-13 yr (mean 57 mo)               | 36       | 46 mo        | 71% @ 46 mo                  |      |      | NR   |
| London          | Faraj     | 2008 | 1993-2007  | 25  | 0.5-10 yr (median 2.5 yr)              | 32       | 6.8 yr       | 91                           |      | 78   | 28%  |
| Stanford        | Beaunoyer | 2007 | 1988-2006  | 15  | 0.3-9.7 yr (mean 2.6 yr)               | 47       | 3.3 ± 3.5 yr | 87                           | 87   | 87   | 0    |
| Spain           | Avila     | 2006 |            | 11  | 6 mo-14 yr                             |          |              | 91                           | 91   | 82   | 25%  |
| UNOS review     | Austin    | 2006 | 1987-2004  | 135 | 2.9 ± 2.5 yr                           |          |              | 79                           |      | 69   |      |
| Texas           | Mejia     | 2005 | 1995-2003  | 10  | mean 5.8 yr                            | 50       | Mean 10.8 yr | 70% @ last FU (mean 10.8 yr) |      |      | 20%  |
| Kyoto           | Kasahara  | 2005 | 1990-2004  | 14  | NR                                     | NR       | NR           | 78.6                         | NR   | 65.5 | 100% |
| SIOPEL-1        | Otte      | 2004 | 1990-1994  | 12  | 1.25-11.6 yr (median 3.8 yr)           | 42       | 117 mo       | NR                           | NR   | 75   | NR   |
| Dallas          | Molmenti  | 2002 | 1984-2000  | 9   | 6 mo-16 yr (mean 6.4 yr)               | 44       | NR           | NR                           | 67%  | NR   | 0%   |
| France          | Chardot   | 2002 | 1998-1999  | 4   | 10-60 mo (mean 17 mo)                  | NR       | NR           | 75% at last FU (13-24 mo)    |      |      | 100% |
| Birmingham      | Pimpalwar | 2002 | 1991-2000  | 12  | 0.15-8.78 yr at diag. (median 1.32 yr) | NR       | NR           | NR                           | 93%  | 83%  | 0    |
| Pittsburgh      | Reyes     | 2000 | 1989-1998  | 12  | NR                                     | NR       | NR           | 92                           | 92   | 83   | 0    |

LT: Liver transplantation; FU: Follow-up; LDLT: Living-donor liver transplantation; NR: Not reported; UNOS: United Network for Organ Sharing.

by Siegfried Oberndorfer, defining them as “benign carcinomas”<sup>[132]</sup>. In 1927, he revised his definition after discovering their potential for malignant growth and metastasis<sup>[132]</sup>. Neuroendocrine carcinomas have an incidence of  $\leq 5$  per 100000 and show a variable location (60% in the gastrointestinal tract and almost 30% in the pancreas; other locations: endocrine organs, lung, skin, liver, breast; partly in the context of inherited syndromes<sup>[133]</sup>), and a very variable natural course of the disease<sup>[134]</sup>. According to the World Health Organization, neuroendocrine tumors are classified by mitotic index and Ki67 labelling index as low grade G1 [mitotic index (MI) < 2 per 10 high-power fields (HPF), Ki67 positivity < 3%], intermediate grade G2 (MI 2-20 per 10 HPF, Ki67 positivity 3%-20%), or high grade G3 (MI > 20 per 10 HPF, Ki67 positivity > 20%)<sup>[134]</sup>. Neuroendocrine tumors can be symptomatic dependent on their hormonal activity, but the majority remains hormonally inactive and/or shows unspecific symptoms<sup>[135]</sup>. Diagnosis is made by CT and MRI scan, (endo)sonography, 18FDG/DOTATOC/DOTATATE-PET and Octreotide-Scintigraphy, potential serum tumor markers in the serum can be chromogranin A, 5-HIAA, NSE and p38<sup>[134]</sup>. Treatment strategies for neuroendocrine liver metastases (mNET) include antihormonal therapy, interferone and chemotherapeutic treatment, regional ablation and surgery<sup>[136,137]</sup>. Analyses of SEER databases have shown 5-year OS rates of 35% in G1 and G2 neuroendocrine tumors and of < 5% for G3 tumors. However, 5-year OS of > 50% have been described of selected G1 patients after combined medical-surgical therapy without LT<sup>[138]</sup>.

Table 4 gives an overview of original reports and reviews LT for mNET with > 100 patients, including a synopsis of UNOS and European databases<sup>[139-142]</sup>. 5-year OS rates of 47%-58% have been reported. In the largest reports from UNOS (194 patients, 1988-2011) and European databases (213 patients, 1982-2009), 5-year OS was 49% and 52%, respectively. Importantly, patients receiving LT for mNET in these publications have previously undergone non-transplant medical and surgical therapy and, in the European database analysis, 5-year

OS rates from first diagnosis of mNET were 73% (84% for patients diagnosed after 2000). In the UNOS database, the 5-year OS rates after LT were comparable to the 5-year OS rates of 4693 patients transplanted for HCC during the same period. Current NCCN guidelines define LT for mNET as an investigational procedure, and ongoing research is performed in order to define positive predictors for appropriate patient selection. A European Consensus states that “in patients suffering from life-threatening hormonal disturbances refractory to medical therapy or patients with non-functioning tumors with diffuse unresectable liver metastases refractory to all other available treatments, LT may be a possible therapy option. Minimal requirements for consideration of LT are the following criteria: mortality should be < 10%, absence of extrahepatic disease as determined by PET/CT, primary tumor removed prior to transplantation, well-differentiated NET (NET G1, G2). Patients less than 50 years old who are free of extrahepatic tumor and have low Ki67 are those who are most likely to benefit from LT. However, a long-term disease-free survival by transplantation will be an exceptional event even in this highly selected subgroup”<sup>[138]</sup>. Tumor recurrence after LT is described as 60% and ongoing research is performed to define further prognostic markers such as Ki67, p53 and E-cadherin immunohistochemistry, hepatomegaly, location of primary, age of patients, percentage of liver involvement and time of transplantation after resection of primary<sup>[139,142-146]</sup>.

### Colorectal cancer liver metastases

Although the majority of patients diagnosed with colorectal cancer (CRC) can undergo initially curative local resection, the leading cause of death from CRC is metastatic disease. The primary metastatic site for patients diagnosed with CRC is the liver: 60%-70% of metastatic recurrences in CRC patients occur in the liver and up to 35% of metastatic CRC patients have metastases only in this organ<sup>[147]</sup>. Up until now, colorectal liver metastases (CLM) are a contraindication for LT due to (1) allocation justice in the light of deceased-donor organ shortage

**Table 4** Liver transplantation for hepatic metastases of neuroendocrine tumors: reports with > 100 patients

| Database | Author  | Year | Year of LT | n   | Age of patients | Female | Follow-up          | Overall survival in % |      |               | DFS in % |      |               | LDLT | Recurrence |
|----------|---------|------|------------|-----|-----------------|--------|--------------------|-----------------------|------|---------------|----------|------|---------------|------|------------|
|          |         |      |            |     |                 |        |                    | 1 yr                  | 3 yr | 5 yr          | 1 yr     | 3 yr | 5 yr          |      |            |
| Europe   | LeTreut | 2013 | 1982-2009  | 213 | Mean 46 yr      | 46%    | Mean 56<br>± 49 mo | 81                    | 65   | 52            | 65       | 40   | 30            | 6%   | 53%        |
| UNOS     | Gedaly  | 2011 | 1988-2008  | 150 | Mean 45 yr      | 44%    | Mean<br>36.8 mo    | 81                    | 65   | 49            | NR       | NR   | 32            | 7%   | NR         |
| UNOS     | N'Guyen | 2011 | 1988-2011  | 194 | Mean 45 yr      | 46%    | NR                 | 80                    | 61   | 49            | NR       | NR   | NR            | NR   | NR         |
| UNOS     | N'Guyen | 2011 | 2002-2011  | 110 | Mean 45 yr      | 46%    | NR                 | 85                    | 65   | 58            | NR       | NR   | NR            | NR   | NR         |
| France   | LeTreut | 2008 | 1989-2005  | 85  | Mean 46 yr      | 46%    | Mean 46<br>± 47 mo | 72                    | 59   | 47            | 56       | 37   | 20            | 2%   | NR         |
| Review   | Lehnert | 1998 | 1981-1997  | 103 | Median 48 yr    | 50%    |                    | Calculated 60         |      | Calculated 47 |          |      | Calculated 24 | NR   | 40%        |

LT: Liver transplantation; DFS: Disease-free survival; LDLT: Living-donor liver transplantation; NR: Not reported; UNOS: United Network for Organ Sharing.

and (2) high rates of tumor recurrence after transplantation<sup>[148,149]</sup>. However, in a Norwegian landmark paper, Hagness and colleagues performed LT for 21 patients diagnosed with unresectable CLM and reported estimated 1-, 3- and 5-year OS rates of respectively 95%, 68% and 60%<sup>[150]</sup>, with good quality of life, monitored during the first year after transplantation<sup>[151]</sup>. Furthermore, equivalently to the Milan criteria, prognostic factors such as diameter of largest metastasis < 55 cm, time since CRC surgery > 2 years, CEA-level < 80 mcg/L, and stable disease or partial response after chemotherapy before LT were defined and may in future serve as criteria selecting patients eligible for LT in CLM<sup>[150]</sup>. Hagness and colleagues showed that 5-year OS rates exceeded reported OS after systemic chemotherapy alone and were comparable to OS rates after liver resection for resectable CLM. Furthermore, this is the first study showing 5-year OS rates after LT for CLM comparable to survival rates of patients needing repeat LT for non-malignant disease and only slightly minor to long-term survival rates after LT for benign indications<sup>[150]</sup>. An ongoing and controversially discussed clinical trial evaluates, for the first time, liver resection *vs* LT in resectable CLM (www.clinicaltrials.gov, NCT01479608). Furthermore, LT may be a therapeutic option for CLM survivors with secondary liver failure caused by aggressive therapy with liver resection and local chemotherapy<sup>[152]</sup>.

## CONCLUSION

Ongoing research in LT for primary hepatic malignancies and metastatic liver disease may in future further widen indications for LT in malignant disease. However, although LT may significantly increase quality of life and OS rates for many patients diagnosed with malignancies, the shortage of deceased-donor organs enforces strict allocation rules, rendering LT inaccessible for many cancer patients. Thus, the ethical dilemma of organ allocation will increase - comparable to mass casualty incidences, when individualized medicine is limited by the available resources for the greatest possible number of beneficiaries. Furthermore, patients diagnosed with malignant disease often present in better general condition and with

better liver function compared to patients needing LT for non-malignant disease, and thus are not adequately represented by the MELD allocation system. New organ allocation rules must therefore be defined for individual malignancies.

LDLT can here offer a solution for selected patients and may on the one hand increase the organ donor pool, on the other hand enable LT for borderline indications and last but not least enable early LT before the tumor exceeds transplantability.

To increase evidence-based indications for LT, further clinical trials are needed for the (1) comparison of long-term oncologic and overall outcome of living- *vs* deceased-donor LT in malignant disease; (2) establishment of predictive criteria to select patients benefiting most from LT; (3) standardization of organ allocation rules outside the MELD-criteria for defined malignancies; (4) establishment of standard perioperative chemotherapeutic regimens combined with LT; and (5) improvement of long-term antiproliferative immunosuppressive therapy.

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