Selection Criteria and Outcome of Liver Transplantation for Neoplastic Liver Diseases

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Overview

Liver malignancies have emerged as major indications of liver transplantation (LT) over the last decade. Indication for hepatocellular cancer (HCC), which was originally based on static staging, has moved to a more dynamic process including response to treatment and tumor behavior allowing transplantation of patients beyond Milan criteria without hampering LT results. Transplantation of perihilar cholangiocarcinoma (CC), as a part of a comprehensive approach including neoadjuvant chemoradiotherapy, especially in primary sclerosing cholangitis patients, has been proved feasible and encouraging results have been recently obtained with highly selected very early intrahepatic CC. Large-scale european liver transplant registry (ELTR)-based analysis of LT results in neuroendocrine metastases or rare tumors such as epitheloid haemangioendothelioma (EHE) has allowed better characterization of best candidates and adequate management. In countries with no or limited organ shortage, stimulating explorative approaches have revisited the concept of transplanting colorectal metastases. Paralleling those innovations, the dramatic reduction in LT indications for HCV liver diseases on the one hand and the hope for a sustainable expansion of the donor pool thanks to development of donor after cardiac death (DCD) transplantation combined with regional normothermic perfusion and different modalities of machine perfusion on the other hand have clearly opened the door to transplant oncology.

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5.1 Introduction

History of liver transplantation (LT) for liver malignancies started more than 50 years ago by transplanting for patients with large, unresectable tumors; however, it rapidly turned out that transplanting unselected patients resulted in rapid tumor recurrence and subsequent death, with no individual benefit and inappropriate use of liver grafts that might have been used more efficiently for another indication. In an era of organ shortage, those futile LT were rapidly abandoned. Considerable efforts have been done to identify, according to the major transplantation principle of utility, factors associated with post-LT recurrence and death and to restrict LT to patients with expected 5-year survival rates at best >70%, and recurrence rates <10–15%. However, despite this dramatic restriction in LT indications for malignancies, overall burden of patients listed for liver cancers rose rapidly over the last decades paralleling the epidemiology of liver cancers worldwide. Liver tumors that accounted for 10% of LT indications beginning of the 20th century, nowadays account for 40–60%. This new epidemiological situation results in a fierce competition between patients listed for malignancies and those listed for benign liver diseases. Allocation rules and priorities as well as specific management strategies during the waiting time have, therefore, been set up to guarantee equity between patients listed for malignant and non-malignant diseases.

The following section will focus on basic principles of LT indications for malignancies, allocation rules governing access to LT and principles of follow-up after LT.

5.2 Liver Transplantation for Hepatocellular Cancer (HCC)

Principle: Liver transplantation is accepted as a standard therapeutic option for nonresectable early HCCs. It is considered the best HCC treatment because of the removing both tumor and underlying pre-neoplastic liver disease.

5.2.1 Indications

For 25 years, Milan criteria [1] (1 nodule ≤ 5 cm or 3 nodules ≤ 3 cm with no macrovascular invasion on pre-LT imaging) have been considered as the benchmark [2] for LT because associated with a risk of recurrence around 10% and 5-year survival rate > 70%. Milan criteria are considered nowadays as too restrictive because excellent outcomes can be achieved when transplanting patients with expanded criteria. Several other criteria based on tumor staging have been proposed over the last decade, the most popular being the University of California in San Francisco (UCSF) [3], TTV [4], up-to-seven [5], or Toronto criteria [6]. However, none of those expanded criteria had prevailed against Milan criteria since most of them were derived from pathological analysis of the explant and based on suboptimal level of evidence (retrospective studies or lack of external validation). A significant improvement in identifying patients amenable to LT with expanded criteria was recently achieved by combining morphological tulor features as assessed radiologically with features reflecting tumor behavior and aggressiveness.

5.2.1.1 Expansion Based on Composite Models Combining Tumor Burden and Biomarkers

Simple biomarkers such alfa foetoprotein (AFP) and descarboxy-prothrombin (DCP) levels [7–13] and DCP [7] have been reported to be associated with the risk of recurrence at several cut-off values. In particular, pre-LT AFP abd DCP levels, which reflect tumor differentiation as well as macro- and microvascular invasion [14, 15], can be considered as a surrogate marker of tumor aggressiveness. The predictive value of AFP [12, 14, 16] and DCP [7] had been shown to be independent from tumor burden. Finally, several studies also show that an increase in AFP values during the waiting phase negatively impacted outcome [15, 17–19]. On this ground, a first composite model called "French AFP model" or AFP score combining AFP values and tumor features at listing, followed by a quarterly reassessment during pre-LT follow-up was designed and prospectively validated in France [14]. This model was proved more accurate than Milan criteria to predict recurrence in patients meeting or not Milan criteria. This score has been validated in Italy [20], Spain [21], and Latin America [22]. The model was adopted by the French Organization for Organ Sharing (Agence de la Biomédecine) in 2013 as the official tool to select HCC patients, introducing a major change in indications policy (Fig. 5.1). A second composite model following the same principle, named Metroticket 2.0 was recently designed to predict disease-free survival [23]. This model was validated in an external Asian retrospective cohort. According to 2018 HCC-EASL (European Association for the Study

Pre LT variables	Patients
Diametre (cm)	
≤ 3	0
3-6	1
> 6	4
Number of nodules	
1-3	0
≥ 4	2
AFP (µg/l)	
≤ 100	0
100-1000	2
> 1000	3

→ **Risk of recurrence**
≤ 2 = LOW; > 2 = HIGH

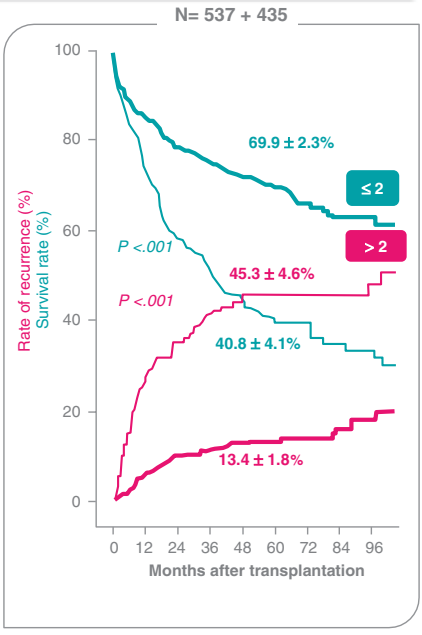

Fig. 5.1 Liver transplantation for hepatocellular carcinoma: A model including α-fetoprotein improves the performance of Milan criteria

of the Liver) guidelines, composite criteria that consider surrogates of tumor biology—*among which AFP is the most relevant*—are, likely to replace conventional criteria for defining inclusion criteria for LT [24].

Other approaches related to tumor behavior are:

Tumor histology: The groups of Padova [25] and Toronto [6, 26, 27] reported that when selecting T3 HCC presenting with no poorly differentiated tumor cells on pre-LT-guided tumor biopsy, 5-year DFS rates >70% could be obtained pointing out again the critical importance of tumor biology in assessing the risk of recurrence. Applicability may be yet limited by the risk of tumor seeding along the needle tract and by sample effect because the biopsy may not accurately reflect the precise pathology of the tumor [27].

18 FDG PET CT: Several retrospective studies from Germany [28] and Korea [29] have consistently reported that tumors with high FDG uptake have a significantly higher risk of recurrence compared to HCC with no or lower uptake because high SUV is significantly associated with poor differentiation [30] and microvascular invasion [31, 32]. In one of those studies [33], transplantation of patients presenting both low SUV and low AFP pre-LT values was associated with 80% 5-year survival rates, irrespective of Milan criteria or tumor size and number. Such results point out again that the risk of recurrence might be better predicted by tumor biology than tumor staging.

So far no molecular tools have proved reproducible enough and applicable in routine practice to guide patients' selection.

5.2.2 Contraindications

Contraindications to LT include contraindications not related to HCC and HCC-related contraindications. Among the latter, evidence of extrahepatic metastases, and of intrahepatic macrovascular invasion on pre-LT imaging, including VP1 portal invasion, and tumor progression beyond transplantability criteria. Thoracic and abdominal CT scan should, be performed at listing and then repeated on a quarterly basis during the waiting time to detect such contraindications. Interestingly, 18 FDG PET CT during pre-LT workup has been shown to reveal undiagnosed extrahepatic metastases or additional intrahepatic tumors, allowing restaging of HCC in 10% of candidates [34]. 18 FDG PET, and at best PET MRI, can be, therefore, proposed as a complementary tool in pre-LT workup for decision-making.

5.2.3 Management in the waitlist

Median waiting time of a patient with HCC varies from 3 to 15 months. To control tumor growth and prevent dropout because of tumor progression beyond LT criteria, it is recommended to consider bridging therapies when waiting time is expected to be >6 months [2]. Modalities of bridging therapies [35] should be defined by

multidisciplinary staff meetings. The most frequently used is transarterial chemoembolisation (TACE). Around 25% of candidates are eligible to bridging (poetential curative) treatments such as thermoablation or surgical resection. Emerging modalities such as radioembolization (TARE), stereotactic external beam radiotherapy, and even tyrosinekinase inhibitors such as sorafenib and levantinib are more rarely proposed. Patients with compensated liver cirrhosis and small, central tumors are preferably treated with RFA, whereas patients with larger size but compensated liver function are treated with TACE/TARE. In patients with decompensated liver cirrhosis and larger tumor size, external radiotherapy may be proposed without increasing the risk of further deterioration of liver function [35]. Response to bridging therapy, based on tumor imaging and AFP serum levels, should be carefully regularly reassessed until LT. Tumor progression [36] and AFP increase [17, 37] while on bridging therapies are predictive of recurrence post-LT. Patients progressing beyond LT criteria should be dropped out from the waiting list. On the other hand, patients with criteria beyond transplantability at referral can be downstaged [38] and, thereafter, considered for LT. Downstaging within Milan (T2) criteria is achievable in 40% of those cases. The risk of HCC recurrence after a downstaging procedure is around 15% but still consistent with acceptable 5-year survival rates close to 70% [39]. A minimal test of time of 3–6 months and cautious quarterly imaging follow-up after efficient downstaging are recommended before considering LT.

5.2.4 Allocation rules and priorities

Allocation rules are driven by the major principle of equity and utility. Accordingly, once listed, all patients must get an equal probability of transplantation or death/dropout while waiting. The increasing prevalence of HCC patients has forced the organ allocation organisms to adjust allocation rules. Indeed, in the era of MELD-based allocation policies, HCC patients are basically unfairly served by MELD, scoring on average 12 points at listing. As a compensation, HCC patients usually receive extra MELD points [40] during the waiting period to allow access to transplantation. Yet, HCC patients compete not only with non-HCC patients but also with each other to get an allograft, resulting in an increased risk of death or dropout pre-LT. Given the burden of HCC and limited organ availability, additional rules and concepts had to be considered. According to the concept of transplant benefit, LT should be reserved to patients who may achieve significant benefit compared to nontransplant therapies [41]. On this ground, TNM1 patients eligible for other curative treatments than LT should not be listed for LT. An ablate-wiat strategy has been recently proposed for these patients [42] in TNM2 patients amenable to and benefitting from a (potentially) curative bridging therapy. LT can be postponed until recurrence, as a salvage LT. Such a strategy is currently under evaluation in several countries such as in France.

5.2.5 Reassessment of the Risk of Recurrence Based on Explant Pathology

Pre-LT imaging is considered to underestimate tumor burden in 20% of the cases compared to explant-based assessment. A critical step in the follow-up of HCC

patients after LT is, therefore, to refine the prediction of recurrence by carefully reviewing the explant pathology. For this purpose, predictive models taking into account pathological predictors of recurrence (tumor size and number, differentiation, and vascular invasion) [43], some of them also taking into account pre-LT AFP [44], are available. Revisiting the risk of recurrence after LT will drive screening strategies and also type and intensity of immunosuppression.

5.2.6 Follow-Up and Outcome; Prevention and Treatment of Recurrence

The prognosis of HCC patients after LT is driven by recurrence which accounts for half of post-LT deaths. Specific follow-up in those patients should aim at limiting the risk of recurrence by adjusting immunosuppression or considering adjuvant therapies. Early detection and treatment of recurrence [45] facilitated by screening policies are also critical, keeping in mind that most recurrence occurs within the first 2 to 3 years post-LT.

Immunosuppressive strategies: calcineurin inhibitors (CNI) favor tumor growth in experimental models and high CNI trough levels have been reported to increase the risk of recurrence [46]. On the contrary, mTOR inhibitors have antitumor properties both in in vitro and in animal models, and some data suggest that they may reduce or delay the risk of recurrence [47–50]. Interestingly, the beneficial impact of mTOR inhibitors on recurrence may be more pronounced in low-risk patients [51], in whom recurrence rates as low as 3–5% [52] have been reported. Although based on limited evidence, the following principles can be proposed to guide immunosuppression after LT for HCC: rapid minimization of CNI in combination with MMF and secondary introduction of mTOR inhibitors targeting trough levels around 5–6 ng/mL. Next CNI can be further tapered till withdrawal during a six month period of time until withdrawal, the patient going on with a combination of mTOR inhibitors and MMF, that has been proved feasible with a limited risk of rejection [53].

Adjuvant therapies: Conventional chemotherapy post-LT does not significantly impact the risk of recurrence [54]; preliminary data suggest that adjuvant sorafenib [55] may reduce the risk but evidence is not high enough to recommend it on a routine basis. Other targeted therapies should also be tested in studies adjusted on the risk of recurrence as assessed on the explant.

Screening strategies: In patients confirmed with low risk of recurrence after LT, intervals between screening procedures could be extended to semiannual surveillance during the first 2 years and then every 12 months for up to 5 years. Higher-risk patients should have a closer follow-up, using three-monthly chest CT and dynamic liver CT scan for 2 years and on a 6-month rythm thereafter.

Treatment of recurrence: HCC recurrence after LT mainly involves the liver graft itself and extrahepatic sites, usually lungs, bone, and lymph nodes. In historical cohorts, recurrence happened within the first year post-LT and was rapidly followed by death within 6 months. Recent data indicate that prognosis of HCC recurrence may have changed over the last decade, with time from LT to recurrence tending to increase, and with an increase in time from recurrence to death [47, 49, 51]. This phenomenon

may be related to better screening strategies, earlier diagnosis, and changes in the management of recurrence. Aggressive management, including surgical resection of solitary intra- or extrahepatic metastasis, has been associated with prolonged survival and should be proposed [45]. CNI withdrawal after recurrence and a shift to mTOR inhibitors may slowdown tumor progression. Although tolerability is questionable, sorafenib in combination with mTOR inhibitors having a strong antitumor effect in animal models, may be tested. Second-line chemotherapy, and immunotherapy, may be proposed afterwards. Because of associated risk of rejection, recently available immunotherapies should be tested only in the setting of clinical trials.

5.2.7 Liver Transplantation for Other Malignancies

The globally rising incidence of cholangiocellular carcinoma (CCC) triggered during the recent years the interest of the transplantation community for this disease. Cholangiocellular carcinoma covers three cancer types: the intrahepatic mass-forming CC (ICC) (10%), the perihilar (PCC) or Klatskin tumor (60–70%), and the distal bile duct (DCC) (20–30%) [56], with distinct etiologies, genetic profiles, pathogenesis, and clinical presentations. Advanced immunohistochemical (IH) staining techniques allow to identify more frequently mixed HCC-CCC [57]. Liver resection, whenever possible, is the cornerstone of the therapeutic CCC algorithm [58, 59]. If not possible, LT can be considered in highly selected patients. Yet, due to prohibitive high recurrence, morbidity (30–40%), and mortality (10–20%) rates, CCC had been until recently considered as a contraindication to LT accounting for only 0.4% (249 patients) of recipients in the european liver transplant registry (ELTR) database. Encouraging results, based on a combination of neoadjuvant radiochemotherapy and total hepatectomy, with 5-year overall survival (OS) and disease free recurrence (DFS) survival rates reaching 50% to 60% [60], incited LT centers to revisit CCC, notably PCC, as an indication for LT [61, 62].

5.2.8 Perihilar Cholangiocellular Carcinoma (PCC)

PCC can develop “de novo” or in the context of primary sclerosing cholangitis (PSC). PSC patients have a 7–14% cancer risk during their lifetime. Long-term DFS can be obtained after R0 partial liver resection but this needs careful planning and advanced liver surgery [58]. “En bloc resection” allows nowadays to obtain 40–58% 5-year OS and DFS rates in patients with advanced (T3–T4) disease [63]. Lymph node status remains the most important prognostic factor. If unresectable, LT can be considered.

Based on the pathophysiology of PCC, the Mayo Clinic team [64] developed very strict LT selection criteria. In case of PSC, LT has the advantage to treat radically both cancer (R0 resection) and underlying disease. Inclusion criteria for LT are an unresectable tumor above the cystic duct with a radial diameter < 3 cm. Exclusion criteria are prior biliary resection or attempt to do, prior to radio- or chemotherapy, direct transperitoneal (including endoscopic) biopsy or fine-needle aspiration, other malignancy within the last 5 years, intrahepatic metastases, and uncontrolled infection (after

radiochemotherapy). The LT protocol combines external (4500 cGy; 150 cGy twice daily) and internal (brachy-) radiotherapy (2–3000 cGy at 1 cm radius), capecitabine-based neoadjuvant chemotherapy, and, finally, staging laparoscopy. In the absence of metastases (nodes, peritoneal, or organ involvement), the patient is listed. Twenty percent of patients dropout from the LT project following this strict process. This Mayo protocol generated 5 and 10 years post-LT OS rates of 70 and 65%. Five-year DFS was better in 162 PSC patients compared to 107 "de novo" recipients (61% vs. 37%) [61]. The Mayo results were corroborated by 12 US centers (65% and 59% for 5 and 10-year OS rates) [61]. Recurrence rate was 24%, with a median time from LT of 18 months (ranging from 3 to 120 (!) months). Prognostic factors were CA19.9 > 100 mg/ml, perineural invasion, residual cancer (distal bile duct), attempt at previous resection, and "de novo" PCC. Five-year OS and DFS rates reported in recent series applying the neoadjuvant LT approach are 55% and 65%, respectively [62].

This Mayo protocol needs some adaptations in view of the encountered problems and morbidity (20–40%). Combined radio- and chemotherapy can cause liver toxicity and lead to liver failure and refractory infection contraindicating LT. The transplant procedure is difficult and often complicated with portal vein and hepatic artery stenosis and thrombosis [65]. The use of free vascular grafts allowing to do anastomoses outside the irradiated area and the use of living donor LT (LDLT) overcome these problems [66]. LDLT has the advantage to time optimally transplant procedure and neo-adjuvant therapy. In case of invasion of the distal bile duct, a pancreatoduodenal resection, needs to be done. This procedure has however a high morbidity and mortality and less favorable results.

5.2.9 Intrahepatic Cholangiocellular Carcinoma (ICC)

At MRI, ICC typically presents as a mass lesion with hyperintense T2 central filling, venous phase enhancement, followed by peripheral late enhancement, capsular retraction (due to fibrosis) and distal bile duct dilatation. ICC is the second-most common liver malignancy and must, therefore, be taken into consideration when confronted with a lesion in a liver disease patient. The clinical presentation is aspecific and tumor markers such as CA19.9 are not very sensitive. Most patients are unfortunately diagnosed with large and multifocal tumors and frequently have lymph node (30%) and microvascular invasion (40%) [59].

Partial hepatectomy allows to obtain 30% 5-year DFS [59]. In case of small (≤2 cm) ICC without vascular invasion, this number even raises to 80%. If ICC is unresectable, LT may be considered in well-selected patients; the reported 5-year OS and DFS rates of 24–65% and 36–82% [62]. Similar to partial resection, outcome is dominated by tumor size (cut-off 2–3 cm), number (solitary lesion), lymph node and microvascular invasion [59, 62]. No recurrence was reported in the Spanish multicenter experience of LT for solitary ≤2 cm ICC [67]; in larger or multifocal tumors, 5-year recurrence rate was 42% [68].The Mayo team limits the indication for LT to solitary ICC with a *radial* (not a longitudinal) diameter of up to 3 cm [64].

Results of small series of LT for mixed HCC-ICC-HCC are contradictory; in some series, they are in line with those obtained for HCC with 5-year OS between

50 and 60%. Larger tumors have worse outcome [69, 70]. In the larger UNOS experience, the results were significantly worse (40% 5-year OS) [71]).

To improve results, a protocol similar to the one used in PCC has been proposed, integrating biopsy, neoadjuvant therapy, staging, and, finally, adjuvant chemotherapy adapted to definitive pathology of the hepatectomy specimen [72].

On the abovementioned background, CCC can be considered as an indication for LT: (a) when PCC meets the Mayo Clinic criteria and (b) on a case-by-case basis in early ICC made of *a single nodule* not exceeding 3 cm diameter. Yet, further studies comparing LT and neoadjuvant radiochemotherapy to standard-of-care liver and bile duct resections are mandatory to confirm applicability of LT in CCC.

5.3 Liver Transplantation for Vascular Tumors

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare (<1/pmp) vascular tumor with an epithelioid and histiocytoid appearance, originating from vascular endothelial or pre-endothelial cells. HEHE represents <1% of all vascular tumors of EHE are as a "low-malignancy" tumor [73]. The most common presentations are in liver alone (21%), liver and lung (18%), lung alone (12%), and bone alone (14%) [74]. The treatment algorithm of hepatic (and pulmonary) EHE is difficult because of the lack of predictive clinical or histological criteria and the well-documented spontaneous, long-term survivals (up to 28 years), the high incidence of asymptomatic patients (up to 25%), the frequent extrahepatic disease localization seen at the moment of diagnosis (up to 45%), and the high incidence (up to 33%) of (even very late) recurrence in the liver allograft [75, 76]. Partial resection is unfortunately only possible in about 10% of HEHE patients, those presenting with the favorable condition of single or faw (up to ten) lesions. In multifocal disease, long-term DFS can be obtained by LT including eventual en bloc resection of involved and/or adhering organs and/or structures and lymphadenectomy. When LT is planned, complete assessment, including thoracic CT scan, and FDG-PET scanning is mandatory in order to evaluate extrahepatic localizations [77].

The 2007 and 2017 "HEHE-European Liver Intestine Transplantation Association (ELITA)-ELTR" studies with long-term (7.6 years) follow-up of 147 liver recipients [78, 79] and the MEHRABI review (including 286 patients) [80] underlined the role of surgery as the therapeutic mainstay, even in the presence of extrahepatic localization at moment of transplantation [76, 80]. In the HEHE-ELITA-ELTR study [78], 5- and 10-year post-LT OS rates reached 81 and 77%; and DFS rates were 79% and 73%. Invasion of lymph node and (limited) extrahepatic disease (present in 25% of patients) did not influence outcome after LT, but micro- and macrovascular invasion (present in 13 and 48% of patients) did. Lau et al. identified presence of pulmonary lesions, multiorgan involvement, disease progression, ascites, age ≥ 55 years, and male gender as poor prognostic factors [74]. In the case of associated multifocal thoracic disease, the Leuven group has even proposed sequential transplantation (liver followed by lung) or simultaneous liver-lung transplantation; a prolonged survival was reported prolonged survival despite the presence of pleural and diaphragmatic metastases [81].

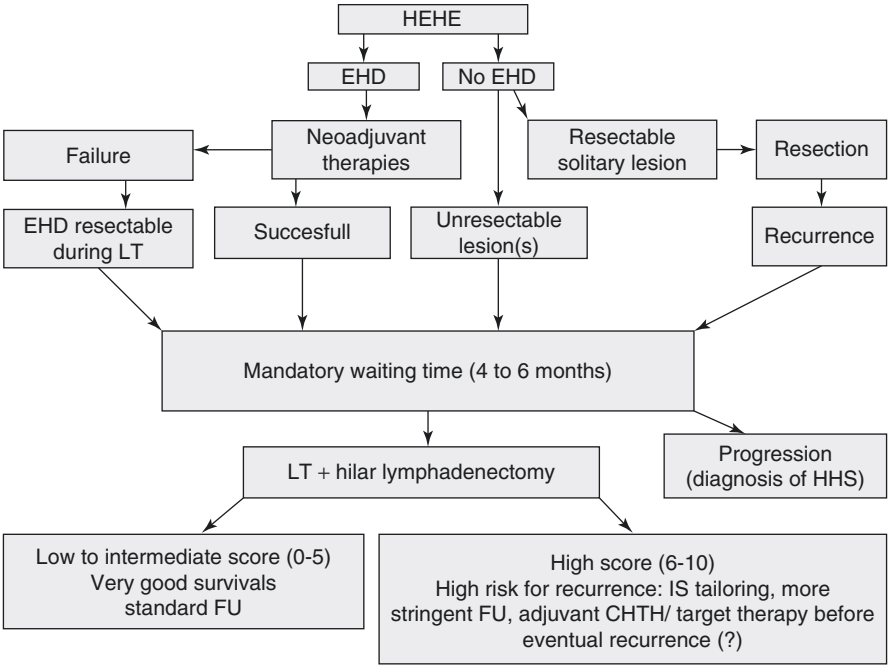

Fig. 5.2 Liver transplantation for hepatic epithelioid hemangioendothelioma (HEHE): A decision-making algorithm

Prediction of outcome after LT is critical before considering transplantation in HEHE patients. For that purpose, a prognostic HEHE-LT score [78], based on macrovascular and lymph node involvement and waiting time, was recently designed. A low score correlated with a 94% 5-year DFS. According to these results, a therapeutic algorithm for the treatment of HEHE has been proposed including neo- and adjuvant medical therapy (Fig. 5.2).

Recurrent disease in and outside the graft was recorded in 25% of patients. This high number still remains of concern and makes periodical reassessment for recurrence mandatory post-LT. When recurrence is detected, it should be treated aggressively as prolonged survival can be obtained. The role of re-LT, considered in case of isolated intrahepatic recurrence, remains till now unclear.

Hepatic hemangiosarcoma is the most common primary sarcoma in the liver and accounts for up to 2% of all primary liver tumors. HAS is seen most in the sixth and seventh decades of life and more frequently in males (M/F ratio: 3/1). Most cases are sporadic and often associated with many environmental carcinogens (thorotrast, vinyl-chloride monomer, radium, pesticides, external radiation, cyclophosphamide, arsenical compounds, use of androgenic/anabolic steroids, and iron). The "ELITA-ELTR HAS study" [82], based on detailed analysis of 20 liver recipients, allowed to get a better insight into the disease, the differential diagnosis with HEHE and the place if LT in its' treatment. Results of surgery, partial or total hepatectomy (LT), are extremely disappointing as all patients die after a median of 6 months due to

tumor recurrence [83, 84]. European and American experiences confirmed that HAS is an absolute contraindication for LT due to the universal rapid recurrence (at 6 months) and short-term survival (less than 24 months) [83].

5.4 Liver Transplantation for Hepatic Metastases

The success of LT in the treatment of primary liver tumors has led to renewed interest in its' role as a treatment for secondary liver tumors (SLTs) [85–87]. Standard treatment for SLTs includes a combination of chemotherapy and liver resection. However, despite recent advances, curative liver resection remains applicable in only 20% of patients mainly owing to multifocality and the bilobar extent of the disease. Total hepatectomy followed by transplantation for liver-only secondaries is by definition a R0 procedure and is, therefore, a potential curative therapy. In preliminary experiences, 5-year OS and DFS, comparabl to state-of-the-art oncological treatments, have been reported after LT for neuroendocrine tumors (NET) as well as colorectal metastases (CRLM) and, therefore, merited further investigation.

5.5 LT for Neuroendocrine Tumors (NET) Metastases

Gastroenteropancreatic NETs are merely diagnosed at an advanced stage. Fortunately, the metastatic disease often remains confined to the liver so R0 primary tumor resection may represent a curative option. Liver resection is rarely appropriate as detailed intraoperative imaging and thin-slice examination of the resected parenchyma often reveal many more lesions than those identified by routine imaging and pathology [88]. In unresectable NET, LT may be considered. Pre-LT workup should include sensitive scintigraphy with octreotide derivatives to reliably exclude extrahepatic disease.

5.6 Indications and Outcome

Until recently, LT experience for NET was based on small, single-center, and heterogeneous multicenter experiences. Recent reports, however, have shed new light on the value of LT [85, 89]. The ELTR [85] and Milan [89] series, including 213 and 24 recipients, respectively, identified a number of factors as a prerequisite for success: presence of a well-differentiated, low-grade tumor with Ki-67 less than 5–10%; primary tumor localization within the portal venous drainage area; tumor burden less than 50% of liver volume; age below 55 years; response to pre-LT treatment with somatostatin analogues and mTOR inhibitors and stable or controlled disease for at least 6 months. By adhering to these criteria, 5-year OS rates of were 92 and 79%, and DFS rates of 75% and 57% were obtained. Careful post-transplant follow-up, including PET-CT and monitoring of tumor markers, (eg. chromogranin) is considered mandatory to enable reintervention for recurrence. As no other treatment has produced similar results for advanced stages of the disease [90], it is time for the oncological community to integrate LT into the therapeutic NET algorithm [87].

5.7 LT for Colorectal Metastases

Colorectal cancer is diagnosed in more than 700 people per million each year worldwide. Only 15–20% of them with apparent metastatic disease are candidates for curative surgery following state-of-the-art chemotherapy alone or in conjunction with surgical procedures. Successful hepatic resection may result in 5-year overall survival rates of 30–40% [91]. In a pilot study [86] of LT, including patients with CRLM, 1-, 3-, and 5-year OS rates of 96%, 70%, and 60% were obtained. Predictors for survival were: diameter of the largest metastasis less than 55 mm; time interval more than 2 years between colorectal and transplant surgeries pre-LT CEA level < 80 ng/ml and responsive or stable disease under chemotherapy. With aggressive surgical treatment of recurrences, 8 of 21 (38%) patients in the Oslo SECA-study were alive 4–8 years after LT and all 4 with metachronous CRLM were alive 5–8 years after transplantation. These results are markedly superior than those obtained with conventional treatment in similar patients [87]. Of note, micropulmonary metastases at the time of LT did not negatively impact overall survival. The results of this pilot LT study should be interpreted with caution owing to the small number of patients, the absence of a control group, and a high rate of relapse with pulmonary metastases. In addition, the burden of potential indications balanced with limited organ availability may limit large-scale applicability of LT in this indication.

Important

LT for liver malignancies accounts for 40–60% of LT indications nowadays. Indications are restricted to patients with expected disease-free survival >70%, depending on frequency and type of liver tumors.

HCC accounts for >97% of oncologic LT indications. LT is considered in patients not amenable to other curative treatments, when the estimate risk of recurrence is <10–15%, based on composite predictive models.

Bridging therapies and specific allocation policies are part of pre-LT management. Dropout should be considered in case of uncontrolled tumor/AFP progression in the waitlist.

Patients experiencing a successful downstaging procedure are eligible for LT after a 3- to 6-month test of time.

After LT, surveillance protocols and immunosuppressive regimen adjusted to the risk of recurrence, and aggressive treatment in case of recurrence may improve long-term outcome.

LT can be considered on a case-by-case basis and under strict conditions in patients presenting with unresectable perihilar cholangiocarcinoma, hepatic epithelioid hemangioendothelioma, neuroendocrine and colorectal liver metastases.

Additional studies are ongoing to determine better the indications of LT for intrahepatic cholangiocarcinoma and colorectal metastases.

Tips

- **Hepatocellular cancer** To evaluate probabilities of recurrence and survival after LT for HCC, refer to the recently published AFP model and Metroticket 2.0, two user-friendly tools to assess prognosis after LT for HCC.
- Define bridging therapies by a multidisciplinary approach in patients with expected waiting time > 6 months.
- Schedule quarterly imaging and AFP surveillance during the waiting phase to evaluate tumor progression and response to bridging therapies.
- Reassess the risk of recurrence after LT by explant pathology analysis to adapt immunosuppression and surveillance strategies.
- In case of recurrence, consider aggressive surgical treatment of single metastases to prolong survival.

Other Tumors

- Do not rule out LT and discuss this therapeutic possibility in case of patients presenting in expert multidisciplinary meetings.
- Perihilar cholangiocarcinoma meeting the Mayo Clinic Criteria.
- Very early intrahepatic cholangiocarcinoma (single, <3 cm).
- Multifocal neuroendocrine metastases controlled by medical treatment.
- Epithelioid hemangioendothelioma, even in the presence of contained extrahepatic localizations.

Key Points

- New composite predictive models including AFP and DCP allow transplantation of HCC patients beyond Milan criteria without hampering outcome.
- In HCC patients, response to therapy is a critical aspect to take into account when listing, either in patients undergoing successful resection or different modalities of locoregional treatment such as radiofrequency and TACE, in whom LT can be postponed, or in patients progressing on bridging therapy in whom dropout should be considered.
- LT is a valuable option in the treatment of unresectable highly selected patients with perihilar CC when combined with neoadjuvant therapy (Mayo protocol), especially in perihilar CC developed in primary sclerosing cholangitis.
- LT is a valuable option in unresectable rare tumors such as multifocal NET metastases or HEHE. LT as a treatment for CRLM is now under full investigation.
- LT may be an indication for unresectable, small (2–3 cm) solitary intrahepatic CC.

References

1. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–9.
2. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012;13(1):e11–22.
3. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001;33(6):1394–403.
4. Toso C, Trotter J, Wei A, Bigam DL, Shah S, Lancaster J, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. Liver Transpl. 2008;14(8):1107–15.
5. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35–43.
6. DuBay D, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. Ann Surg. 2011;253(1):166–72.
7. Fujiki M, Takada Y, Ogura Y, Oike F, Kaido T, Teramukai S, et al. Significance of des-gamma-carboxy prothrombin in selection criteria for living donor liver transplantation for hepatocellular carcinoma. Am J Transplant. 2009;9(10):2362–71.
8. Shetty K, Timmins K, Brensinger C, Furth EE, Rattan S, Sun W, et al. Liver transplantation for hepatocellular carcinoma validation of present selection criteria in predicting outcome. Liver Transpl. 2004;10(7):911–8.
9. Todo S, Furukawa H, Tada M, Group JLTS. Extending indication: role of living donor liver transplantation for hepatocellular carcinoma. Liver Transpl. 2007;13(11 Suppl 2):S48–54.
10. Onaca N, Davis GL, Goldstein RM, Jennings LW, Klintmalm GB. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a report from the international registry of hepatic tumors in liver transplantation. Liver Transpl. 2007;13(3):391–9.
11. Ioannou GN, Perkins JD, Carithers RL. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology. 2008;134(5):1342–51.
12. Toso C, Mentha G, Majno P. Selection of patients with hepatocellular carcinoma before liver transplantation: need to combine alpha-fetoprotein with morphology? Hepatobiliary Pancreat Dis Int. 2010;9(5):460–1.
13. Lai Q, Avolio AW, Manzia TM, Agnes S, Tisone G, Berloco PB, et al. Role of alpha-fetoprotein in selection of patients with hepatocellular carcinoma waiting for liver transplantation: must we reconsider it? Int J Biol Markers. 2011;26(3):153–9.
14. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology. 2012;143(4):986–94. e3; quiz e14-5
15. Dumitra TC, Dumitra S, Metrakos PP, Barkun JS, Chaudhury P, Deschenes M, et al. Pretransplantation alpha-fetoprotein slope and Milan criteria: strong predictors of hepatocellular carcinoma recurrence after transplantation. Transplantation. 2013;95(1):228–33.
16. Yang SH, Suh KS, Lee HW, Cho EH, Cho JY, Cho YB, et al. A revised scoring system utilizing serum alphafetoprotein levels to expand candidates for living donor transplantation in hepatocellular carcinoma. Surgery. 2007;141(5):598–609.
17. Vibert E, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, et al. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. Am J Transplant. 2010;10(1):129–37.

18. Han K, Tzimas GN, Barkun JS, Metrakos P, Tchervenkov JL, Hilzenrat N, et al. Preoperative alpha-fetoprotein slope is predictive of hepatocellular carcinoma recurrence after liver transplantation. Can J Gastroenterol. 2007;21(1):39–45.
19. Lai Q, Avolio AW, Graziadei I, Otto G, Rossi M, Tisone G, et al. Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation. Liver Transpl. 2013;19(10):1108–18.
20. Notarpaolo A, Layese R, Magistri P, Gambato M, Colledan M, Magini G, et al. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. J Hepatol. 2017;66(3):552–9.
21. Varona MA, Soriano A, Aguirre-Jaime A, Garrido S, Oton E, Diaz D, et al. Risk factors of hepatocellular carcinoma recurrence after liver transplantation: accuracy of the alpha-fetoprotein model in a single-center experience. Transplant Proc. 2015;47(1):84–9.
22. Piñero F, Tisi Baña M, de Ataide EC, Hoyos Duque S, Marciano S, Varón A, et al. Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multicenter cohort from Latin America. Liver Int. 2016;36(11):1657–67.
23. Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. Gastroenterology. 2018;154(1):128–39.
24. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
25. Cillo U, Vitale A, Bassanello M, Boccagni P, Brolese A, Zanus G, et al. Liver transplantation for the treatment of moderately or well-differentiated hepatocellular carcinoma. Ann Surg. 2004;239(2):150–9.
26. Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. Hepatology. 2016;64(6):2077–88.
27. Decaens T, Roudot-Thoraval F, Badran H, Wolf P, Durand F, Adam R, et al. Impact of tumour differentiation to select patients before liver transplantation for hepatocellular carcinoma. Liver Int. 2011;31(6):792–801.
28. Kornberg A, Küpper B, Tannapfel A, Büchler P, Krause B, Witt U, et al. Patients with non-[18 F]fludeoxyglucose-avid advanced hepatocellular carcinoma on clinical staging may achieve long-term recurrence-free survival after liver transplantation. Liver Transpl. 2012;18(1):53–61.
29. Lee SD, Kim SH, Kim YK, Kim C, Kim SK, Han SS, et al. (18)F-FDG-PET/CT predicts early tumor recurrence in living donor liver transplantation for hepatocellular carcinoma. Transpl Int. 2013;26(1):50–60.
30. Boussouar S, Itti E, Lin SJ, Decaens T, Evangelista E, Chiaradia M, et al. Functional imaging of hepatocellular carcinoma using diffusion-weighted MRI and (18)F-FDG PET/CT in patients on waiting-list for liver transplantation. Cancer Imaging. 2016;16:4.
31. Lin CY, Liao CW, Chu LY, Yen KY, Jeng LB, Hsu CN, et al. Predictive value of 18F-FDG PET/CT for vascular invasion in patients with hepatocellular carcinoma before liver transplantation prognostic value of (18)F-FDG PET/CT in liver transplantation for hepatocarcinoma. Clin Nucl Med. 2017;42(4):e183–e7.
32. Lee SD, Kim SH. Role of positron emission tomography/computed tomography in living donor liver transplantation for hepatocellular carcinoma. Hepatobiliary Surg Nutr. 2016;5(5):408–14.
33. Hong G, Suh KS, Suh SW, Yoo T, Kim H, Park MS, et al. Alpha-fetoprotein and (18)F-FDG positron emission tomography predict tumor recurrence better than Milan criteria in living donor liver transplantation. J Hepatol. 2016;64(4):852–9.
34. Chalaye J, Costentin CE, Luciani A, Amaddeo G, Ganne-Carrie N, Baranes L, et al. Positron emission tomography/computed tomography with 18F-fluorocholine improve tumor staging and treatment allocation in patients with hepatocellular carcinoma. J Hepatol. 2018;69(2):336–44.
35. Kollmann D, Selzner N, Selzner M. Bridging to liver transplantation in HCC patients. Langenbeck's Arch Surg. 2017;402(6):863–71.

36. Lai Q, Avolio AW, Manzia TM, Sorge R, Agnes S, Tisone G, et al. Combination of biological and morphological parameters for the selection of patients with hepatocellular carcinoma waiting for liver transplantation. Clin Transpl. 2012;26(2):E125–31.
37. Giard JM, Mehta N, Dodge JL, Roberts JP, Yao FY. Alpha-fetoprotein slope >7.5 ng/mL per month predicts microvascular invasion and tumor recurrence after liver transplantation for hepatocellular carcinoma. Transplantation. 2018;102(5):816–22.
38. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology. 2015;61(6):1968–77.
39. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. Liver Transpl. 2015;21(9):1142–52.
40. Rich NE, Parikh ND, Singal AG. Hepatocellular carcinoma and liver transplantation: changing patterns and practices. Curr Treat Options Gastroenterol. 2017;15(2):296–304.
41. Vitale A, Morales RR, Zanus G, Farinati F, Burra P, Angeli P, et al. Barcelona clinic liver cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study. Lancet Oncol. 2011;12(7):654–62.
42. Mehta N, Dodge JL, Goel A, Roberts JP, Hirose R, Yao FY. Identification of liver transplant candidates with hepatocellular carcinoma and a very low dropout risk: implications for the current organ allocation policy. Liver Transpl. 2013;19(12):1343–53.
43. Costentin CE, Amaddeo G, Decaens T, Boudjema K, Bachellier P, Muscari F, et al. Prediction of hepatocellular carcinoma recurrence after liver transplantation: comparison of four explant-based prognostic models. Liver Int. 2017;37(5):717–26.
44. Mehta N, Heimbach J, Harnois DM, Sapisochin G, Dodge JL, Lee D, et al. Validation of a risk estimation of tumor recurrence after transplant (RETREAT) score for hepatocellular carcinoma recurrence after liver transplant. JAMA Oncol. 2017;3(4):493–500.
45. Sapisochin G, Goldaracena N, Astete S, Laurence JM, Davidson D, Rafael E, et al. Benefit of treating hepatocellular carcinoma recurrence after liver transplantation and analysis of prognostic factors for survival in a large Euro-American series. Ann Surg Oncol. 2015;22(7):2286–94.
46. Vivarelli M, Dazzi A, Zanello M, Cucchetti A, Cescon M, Ravaioli M, et al. Effect of different immunosuppressive schedules on recurrence-free survival after liver transplantation for hepatocellular carcinoma. Transplantation. 2010;89(2):227–31.
47. Toso C, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. Hepatology. 2010;51(4):1237–43.
48. Zimmerman MA, Trotter JF, Wachs M, Bak T, Campsen J, Skibba A, et al. Sirolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. Liver Transpl. 2008;14(5):633–8.
49. Chinnakotla S, Davis GL, Vasani S, Kim P, Tomiyama K, Sanchez E, et al. Impact of sirolimus on the recurrence of hepatocellular carcinoma after liver transplantation. Liver Transpl. 2009;15(12):1834–42.
50. Duvoux C, Toso C. mTOR inhibitor therapy: does it prevent HCC recurrence after liver transplantation? Transplant Rev (Orlando). 2015;29(3):168–74.
51. Geissler EK, Schnitzbauer AA, Zulke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. Transplantation. 2016;100(1):116–25.
52. Cholongitas E, Mamou C, Rodríguez-Castro KI, Burra P. Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review. Transpl Int. 2014;27(10):1039–49.
53. Saliba F, Duvoux C, Gugenheim J, Kamar N, Dharancy S, Salame E, et al. Efficacy and safety of everolimus and mycophenolic acid with early tacrolimus withdrawal after liver transplantation: a multicenter randomized trial. Am J Transplant. 2017;17(7):1843–52.
54. Duvoux C, Kiuchi T, Pestalozzi B, Busuttil R, Miksad R. What is the role of adjuvant therapy after liver transplantation for hepatocellular carcinoma? Liver Transpl. 2011;17(Suppl 2):S147–58.

55. Shetty K, Dash C, Laurin J. Use of adjuvant sorafenib in liver transplant recipients with high-risk hepatocellular carcinoma. J Transp Secur. 2014;2014:913634.
56. Blechacz B, Komuta M, Roskams T, Gores GJ. Clinical diagnosis and staging of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2011;8(9):512–22.
57. Brunt E, Aishima S, Clavien PA, Fowler K, Goodman Z, Gores G, et al. cHCC-CCA: consensus terminology for primary liver carcinomas with both hepatocytic and cholangiocytic differentation. Hepatology. 2018;68(1):113–26.
58. Ebata T, Mizuno T, Yokoyama Y, Igami T, Sugawara G, Nagino M. Surgical resection for Bismuth type IV perihilar cholangiocarcinoma. Br J Surg. 2018;105(7):829–38.
59. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg. 2014;149(6):565–74.
60. Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg. 2005;242(3):451–8. discussion 8-61
61. Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology. 2012;143(1):88–98. e3; quiz e14
62. Goldaracena N, Gorgen A, Sapisochin G. Current status of liver transplantation for cholangiocarcinoma. Liver Transpl. 2018;24(2):294–303.
63. Neuhaus P, Thelen A, Jonas S, Puhl G, Denecke T, Veltzke-Schlieker W, et al. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. Ann Surg Oncol. 2012;19(5):1602–8.
64. Rosen CB, Heimbach JK, Gores GJ. Surgery for cholangiocarcinoma: the role of liver transplantation. HPB (Oxford). 2008;10(3):186–9.
65. Mantel HT, Rosen CB, Heimbach JK, Nyberg SL, Ishitani MB, Andrews JC, et al. Vascular complications after orthotopic liver transplantation after neoadjuvant therapy for hilar cholangiocarcinoma. Liver Transpl. 2007;13(10):1372–81.
66. Mantel HT, Westerkamp AC, Adam R, Bennet WF, Seehofer D, Settmacher U, et al. Strict selection alone of patients undergoing liver transplantation for hilar cholangiocarcinoma is associated with improved survival. PLoS One. 2016;11(6):e0156127.
67. Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, López-Andujar R, Palacios F, et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: a Spanish matched cohort multicenter study. Ann Surg. 2014;259(5):944–52.
68. Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. Hepatology. 2016;64(4):1178–88.
69. Elshamy M, Presser N, Hammad AY, Firl DJ, Coppa C, Fung J, et al. Liver transplantation in patients with incidental hepatocellular carcinoma/cholangiocarcinoma and intrahepatic cholangiocarcinoma: a single-center experience. Hepatobiliary Pancreat Dis Int. 2017;16(3):264–70.
70. Sapisochin G, Fidelman N, Roberts JP, Yao FY. Mixed hepatocellular cholangiocarcinoma and intrahepatic cholangiocarcinoma in patients undergoing transplantation for hepatocellular carcinoma. Liver Transpl. 2011;17(8):934–42.
71. Vilchez V, Shah MB, Daily MF, Pena L, Tzeng CW, Davenport D, et al. Long-term outcome of patients undergoing liver transplantation for mixed hepatocellular carcinoma and cholangiocarcinoma: an analysis of the UNOS database. HPB (Oxford). 2016;18(1):29–34.
72. Rana A, Hong JC. Orthotopic liver transplantation in combination with neoadjuvant therapy: a new paradigm in the treatment of unresectable intrahepatic cholangiocarcinoma. Curr Opin Gastroenterol. 2012;28(3):258–65.
73. Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW. Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. Hum Pathol. 1984;15(9):839–52.

74. Lau K, Massad M, Pollak C, Rubin C, Yeh J, Wang J, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: insights from an internet registry in the study of a rare cancer. Chest. 2011;140(5):1312–8.
75. Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer. 1999;85(3):562–82.
76. Grotz TE, Nagorney D, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic epithelioid haemangioendothelioma: is transplantation the only treatment option? HPB (Oxford). 2010;12(8):546–53.
77. Nguyen BD. Epithelioid hemangioendothelioma of the liver with F-18 FDG PET imaging. Clin Nucl Med. 2004;29(12):828–30.
78. Lai Q, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M, et al. Hepatic epithelioid hemangioendothelioma and adult liver transplantation: proposal for a prognostic score based on the analysis of the ELTR-ELITA registry. Transplantation. 2017;101(3):555–64.
79. Lerut JP, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D, et al. The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry. Ann Surg. 2007;246(6):949–57. discussion 57
80. Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, et al. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer. 2006;107(9):2108–21.
81. Desie N, Van Raemdonck DE, Ceulemans LJ, Nevens F, Verslype C, Vansteenbergen W, et al. Combined or serial liver and lung transplantation for epithelioid hemangioendothelioma: a case series. Am J Transplant. 2015;15(12):3247–54.
82. Orlando G, Adam R, Mirza D, Soderdahl G, Porte RJ, Paul A, et al. Hepatic hemangiosarcoma: an absolute contraindication to liver transplantation—the European Liver Transplant Registry experience. Transplantation. 2013;95(6):872–7.
83. Tran Minh M, Mazzola A, Perdigao F, Charlotte F, Rousseau G, Conti F. Primary hepatic angiosarcoma and liver transplantation: radiological, surgical, histological findings and clinical outcome. Clin Res Hepatol Gastroenterol. 2018;42(1):17–23.
84. Husted TL, Neff G, Thomas MJ, Gross TG, Woodle ES, Buell JF. Liver transplantation for primary or metastatic sarcoma to the liver. Am J Transplant. 2006;6(2):392–7.
85. Le Treut YP, Gregoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, et al. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg. 2013;257(5):807–15.
86. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800–6.
87. Lerut J, Foss A. Liver transplantation for secondary liver tumours. Br J Surg. 2015;102(13):1589–90.
88. Elias D, Lefevre JH, Duvillard P, Goere D, Dromain C, Dumont F, et al. Hepatic metastases from neuroendocrine tumors with a "thin slice" pathological examination: they are many more than you think. Ann Surg. 2010;251(2):307–10.
89. Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol. 2007;47(4):460–6.
90. Mazzaferro V, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. Am J Transplant. 2016;16(10):2892–902.
91. Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol. 2012;4:283–301.