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Liver transplantation in primary liver tumors

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As transplant medicine has evolved in recent decades so too have the indications for liver transplantation (LT). Active or suspected malignancy has stopped being considered as a contraindication for organ transplantation, and nowadays LT plays a major role in the treatment strategies of liver tumors. It offers excellent long-term outcomes for certain patients with hepatocellular carcinoma (HCC) and carefully selected patients with cholangiocarcinoma (CCA), who undergo neoadjuvant chemoradiatotherapy. In certain clinical courses of rare primary liver tumors, hepatic epithelioid haemangio-endothelioma (HEHE) and hepatic adenoma (HA), liver transplantation is also considered the best treatment option. Optimal patient selection has become the key issue to achieve the best possible outcomes and to deal with the alleviating shortage of organs. The recent tendency to incorporate markers of tumor biology into selection criteria, rather than simply focusing on tumor size and number, has led to further extension of indications for LT in patients with liver malignancy. This review article focuses on the current place of liver transplantation in the treatment strategy for patients with primary liver tumors, mainly primary liver cancers.

Key words: orthotopic liver transplantation, primary liver tumor, hepatocellular carcinoma, cholangiocarcinoma, hepatic epithelioid haemangio-endothelioma

Introduction

Liver transplantation (LT) with its more than 60-year-history is widely recognized as a treatment of choice of both acute and end-stage chronic liver failure. Immunosuppressive therapy, routinely administered after LT, plays an essential role in overcoming immune-related allograft rejection, at the same time it has the potential to promote neoplastic transformations in graft recipients. At the early stage of the development of transplant programs, both the history of oncological treatment as well as active malignancy were considered as contraindications for organ transplantation. Over the years, together with the great progress in transplant medicine, we have witnessed the milestone extension of indications for liver transplantation. Transplant centers have started to register patients with primary or metastatic liver tumors on the transplant waiting lists and liver transplantation has been established as a standard treatment of liver tumors in carefully selected patients. As a result of the significant discrepancy between graft demand and supply, optimal patient selection has become the key issue and the most challenging element of organ allocation. This review article focuses on the current place of liver transplantation in the treatment strategy for patients with primary liver tumors, most of all primary liver cancers.

Liver cancer

Liver cancer is one of the leading malignancies responsible for the global cancer burden. According to current statistics, primary liver cancer is the sixth most commonly diagnosed cancer and the third most common reason for cancer-related

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death worldwide. In 2020 approximately 906,000 new cases and 830,000 deaths for primary liver cancer were reported. Incidence and mortality rates are 2 to 3 times greater among men than among women [1].

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the principal histologic type of liver cancer, accounting for 75–85% of all primary liver tumors worldwide [2]. Well-established risk factors of HCC comprise chronic liver disease and cirrhosis due to hepatitis B virus and/or hepatitis C virus, excessive alcohol intake, aflatoxin contamination of crops, type II diabetes, obesity, metabolic syndrome and non-alcoholic fatty liver disease (NAFLD). The most important global risk factors for HCC are hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. HBV is a DNA virus that commonly integrates into the host genome and directly promotes mutations in liver cells, while HCV is an RNA virus that can cause liver cirrhotic changes and promotes tumorigenesis through repetitive damage, regeneration and fibrosis. Introduction of HBV universal vaccination as well as effective therapies against chronic HBV and HCV infections gradually lessen the role of those risk factors and contribute to the decreasing prevalence of HCC in most high-risk countries in Eastern and South-Eastern Asia. On the other hand, however, due to the increasing prevalence of metabolic risk factors, the global incidence of HCC has tended to increase in recent decades. The upward trend has been observed in most European countries, Americas, Australia and in India [2–4].

Hepatocellular carcinoma is known to be associated with poor prognosis. The overall survival in untreated patients with HCC does not exceed 10 months [5]. Only approximately 50% of cases are detected in the early stages when radical treatment is still possible to achieve [6]. For decades the mainstay of curative treatment for HCC has been hepatectomy. Despite the progress in surgical techniques and perioperative care, the high incidence of intrahepatic recurrence has been observed contributing to unsatisfactory long-term survival. Moreover, considering that the majority of HCC occurs in cirrhotic livers, the use of hepatectomy has often been limited by the presence of portal hypertension and poor hepatic function. That has led to the introduction of liver transplantation, performed instead of resection. The above issues have led to the introduction of liver transplantation, performed instead of resection, to treatment methods in HCC as well as to the prompt development of a number of forms of locoregional therapy that have been used with curative intent in irresectable and/or recurrent HCC. Those are radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection (PEI) together referred to as "curative locoregional therapy (CLRT)" [7–10].

Primary liver transplantation (PLT) for HCC represents the ideal treatment because it targets both the neoplastic tumor and the underlying liver disease. Since the turn of the 20th and 21st centuries, PLT has been established as a standard treatment of HCC, but only in carefully selected patients. Early PLTs performed for HCC had been associated with unsatisfactory outcomes mainly because of poor patient selection. In 1996, based on the results of the observational study, Mazzaferro et al. defined the criteria, widely known as Milan criteria (MC), to select HCC patients for PLT [11]. In accordance with MC, primary liver transplantation was performed only in HCC patients with single lesion ≤5 cm, or up to 3 lesions ≤3 cm each in the absence of tumor vascular invasion or evidence of extra-hepatic metastases. That approach resulted in outcomes of HCC patients comparable to patients without HCC (75% 4-year survival rate and 83% recurrence-free survival rate). The Milan criteria have been successfully adopted worldwide and incorporated into the United Network for Organ Sharing (UNOS) criteria since 2002, for listing patients with HCC for liver transplant [12].

The growing experience over the last two decades has shown, however, that adherence to MC could be too strict and patients beyond MC may also benefit from LT. Consequently, a number of expanded criteria have been developed based both on tumor morphometry as well as on biomarkers and tumor response to locoregional therapy, parameters that are likely to reflect the real tumor biology and aggressiveness. Further investigations have proven that expanded criteria are still associated with favorable 5-year survival rates up to 64–79% [13, 14]. Among LT-HCC criteria based on tumor morphometry, University of California, San Francisco (UCSF), and among expanded criteria based on tumor morphometry, the criteria of University of California, San Francisco (UCSF) and the up-to-seven criteria have become most popular and widely used. The University of California, San Francisco (UCSF) criteria, established in 2001 by Yao et al. [15] considered a single lesion ≤6.5 cm, or 2–3 lesions ≤4.5 cm each, with total tumor diameter ≤8 cm. The 5 year post-LT survival was estimated to be 72.4% with tumor recurrence up to 11.4%. Initially the criteria had been based on explant pathology, but subsequently were validated with the use of pre-LT imaging. In the prospective study from 2007 by Yao et al. [16], patients who fell within the UCSF criteria demonstrated 80% 5 year post-LT recurrence-free survival (RFS). In 2009, another extended criteria were proposed by Mazzaferro et al. [17] based on a cohort of 1556 patients undergoing cadaveric LT and LDLT for HCC from 36 transplant centers. The criteria were defined as hepatocellular carcinomas with seven as the sum of the size of the largest tumor (in cm) and the number of tumors and named Up-to-seven criteria. The 283 patients without microvascular invasion from the investigate cohort, who fell within the Up-to-seven criteria achieved a 5-year overall survival of 71.2%. The limitation of the above criteria was that they utilized data from postoperative histology concerning microvascular invasion. Among other extended morphometric-based criteria, Toronto criteria from 2016 [18]

are worth mentioning. With the implementation of the Toronto criteria, the 5-year overall survival rate was 68% and did not differ significantly from survival in patients within Milan criteria. The main limitation was the need for a preoperative biopsy, what is not routinely recommended.

In order to avoid pretransplant invasive methods and to achieve an adequate prognosis of tumor recurrence, the investigators searched for the best prognostic serologic biomarkers for HCC. AFP has been the biomarker most commonly investigated in relation to HCC and has been recently adopted by UNOS as a marker to exclude or include patients from transplant listing [12]. However, the optimal cutoff AFP value clearly indicating higher risk for HCC recurrence has not been found. One of the most popular HCC-LT extended criteria including AFP level are the Hangzhou criteria from 2008 (absence of macrovascular invasion and total tumor diameter ≤ 8 cm; in case of tumor diameter >8 cm, non--poorly differentiated HCC and AFP level ≤400 ng/ml) [19]. With the use of those criteria an additional 37.5% of patients who would have been beyond Milan criteria were able to be transplanted. However, once again a pretransplant biopsy was needed in greater lesions, limiting the clinical application of the Hangzhou criteria.

A significant association between AFP levels and vascular invasion has been reported [20]. AFP greater than 1000 ng/ml was observed to be the strongest pretransplant predictor of vascular invasion and consequently tumor recurrence. In the model of Duvoux et al., an AFP level ≤100 ng/ml in the setting of patients with 1-3 lesions with a maximum tumor diameter of 6 cm was associated with 5-year survival near 70% [21]. Grąt et al. [22] reported a nearly linear association between AFP and the risk of HCC recurrence. In the retrospective cohort study based on 121 HCC patients after LT, the AFP cutoff level <100 ng/ml in combination with either UCSF or Up-to-seven criteria was associated with superior (100%) 5-year recurrence-free survival. Several molecular signatures have also been investigated as potential biomarkers of HCC. In the study of Dwornik et al. [23] a higher rate of mutations in 9 suppressor genes was associated with a poorer outcome independently of tumor mass or the presence of vascular invasion. German investigators analyzed specific microRNA expression patterns in tumor samples and observed more accurate prediction of HCC recurrence with the use of Milan criteria along with a predictive score based on the miR-214 and miR-3187 expression levels compared to prediction based on MC alone. [24].

The idea to down-stage the tumor by applying LRT has arisen with the aim to initially reduce tumor burden and subsequently meet transplant criteria. Many studies have reported favorable long-term outcomes for transplant patients with HCC beyond Milan criteria which were successfully downstaged to within Milan criteria by applying LRT [25, 26]. Moreover, the response of HCC to different types of locoregional therapy has been shown to be an important marker for patient survival [27]. Interestingly, the wait times after locoregional therapy prior to transplant can also serve as surrogate markers of tumor biology. Shorter wait times have been associated with higher posttransplant mortality [28]. The most current UNOS policy requires a 6-month waiting period for patients listed with HCC prior to receiving MELD exception points in order to accurately assess tumor biology over time [12].

Owing to the increasing shortage of organs, the limited availability of appropriate living donors and the associated risk of drop-out from the transplant waiting list, mainly attributed to tumor progression, another surgical strategy has been introduced to clinical practice. Patients with resectable and transplantable HCC are offered primary liver resection that can be followed by so called "salvage liver transplantation" (SLT) in case of transplantable tumor recurrence. Nowadays SLT is proposed as a curative option for the intrahepatic recurrence of HCC, but it is still not widely used because of insufficient number of organs. A systematic review of treatment strategies for recurrent HCC published in 2019 evaluated SLT to be superior to curative locoregional therapy in terms of the 5-year overall survival and 1-, 3-, 5-year disease-free survival. Patients after SLT had a significantly higher 3- and 5-years disease-free survival compared to those who underwent the repeated hepatectomy (RH) [7, 29]. However, in an intention-to-treat analysis from 2018, the SLT strategy was revealed to be curative in only 56% of patients with cirrhosis and CC. Lower MELD score, transarterial chemoembolization (TACE) performed prior to resection, postoperative complications after initial resection, and higher T-stage in the resected specimen were shown to diminish the chance for successful SLT [29]. The largest current meta-analysis concerning STL strategy had been published in 2022 [30]. SLT and PLT were shown to have comparable surgical outcomes. The 1-year overall survival rate presented no significant difference between SLT and PLT, whereas 3- and 5-year overall survival rates were slightly, but significantly lower in SLT compared to the PLT group.

Current guidelines, published in 2020 (31), focus mainly on the optimal selection of patients with HCC for both deceased donor LT (DDLT) and living donor LT (LDLT). LT is recommended as a first-line option for HCC within Milan criteria, unsuitable for low-morbidity resection and ablation. In patients beyond Milan criteria, qualification for LT should be based on measurable pre-LT conditions including tumor size and number, tumor biology (including alpha-fetoprotein), probability of survival, transplant benefit, organ availability, waitlist composition and allocation priorities. In the case of LDLT, a combination of morphological and biological criteria should be employed to attempt to maximize recipient benefit while minimizing donor risk. The minimum acceptable recipient overall survival should be 60% at 5 years after LDLT, while estimated donor risk should be low aiming for zero donor mortality.

Interestingly, in the last decade recipients over 70 years with end-stage liver disease and HCC have become one of the fastest growing subgroup of patients undergoing liver transplantation [32]. It clearly highlights the progress transplant medicine has made over the years and the role it plays nowadays in cancer treatment.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most commonly reported primary liver tumor that accounts for 10–15% of all liver cancers. In general, CCA is the primary malignancy of the biliary tract. Based on its localization it is classified as either intrahepatic (IH CCA) or extrahepatic, with the second-order bile ducts serving as the separation point. Furthermore, extrahepatic cholangiocarcinoma has been divided into perihilar (pCCA) and distal extrahepatic cholangiocarcinoma at the level of the cystic duct [33].

Perihilar cholangiocarcinoma is the most common type of cholangiocarcinoma accounting for 50–67% of all cases [34]. The IH CCA incidence has increased over the past three decades while the incidence of perihilar and distal extrahepatic CCA has remained stable. The reasons for the observed trend remain unclear. There are several recognized risk factors of cholangiocarcinoma, including primary sclerosing cholangitis, liver fluke infection, hepatolithiasis, biliary malformation and, what is less obvious, cirrhosis and hepatitis C. Primary sclerosing cholangitis (PSC) is believed to be the most important risk factor, associated with a prevalence of cholangiocarcinoma of 5–15% [35, 36]. The lack of early symptoms of CCA and low specificity of diagnostic modalities are associated with extremely unfavorable prognosis in this primary liver tumor.

The treatment strategy of CCA is strongly associated with the primary localization of the tumor. Perihilar localization is observed to have slightly better prognosis compared to primary intrahepatic CCA, and in recent decades has been first introduced to indications for LT. In addition to LT, other new methods of management have been adopted to pCCA patients, including preoperative portal vein embolisation and biliary drainage, neoadjuvant chemotherapy and chemoradiation therapy [37]. The best long-term survival is observed in cases of surgical resection with negative surgical margins, but many patients are unresectable due to locally advanced or metastatic disease at diagnosis. Unresectable disease had earlier been approached only with non-curative treatment options with a zero 5-year survival rate. Since the late 1990s, pioneering liver transplantation (LT) had been performed as an option in patients with pCCA, with the aim of achieving negative resection margins. The initial results in unselected patients were disappointing [38]. Further attempts at Mayo Clinic led to the development of a protocol consisting of strict selection of patients and pretransplant multimodal chemoradiotherapy; this was associated with a great improvement in survivals (5-year OS greater than 80%) [39]. Mayo Clinic criteria for inclusion in the transplantation protocol were: pathologically confirmed hilar cholangiocarcinoma or CA19-9 >100 ng/ml in the presence of a radiographically malignant structure, tumor size <3 cm, absence of distant metastases on CT (and/or MRI) and isotope bone scan and no evidence of lymph node metastases. Neoadjuvant chemoradiatotherapy consisted of external beam radiation therapy together with intravenous fluorouracil, followed by intraluminal brachytherapy and oral Capecitabine while awaiting liver transplantation. Patients with a good response to neoadjuvant therapy were subsequently transplanted.

Since that time the Mayo Clinic Protocol has been adopted by other transplant centers worldwide, and nowadays relatively good outcomes are reported in LT for pCCA in highly selected patients, who all should undergo intensive pretransplant chemoradiotherapy. Compared with LT for other indications, however, an increased risk of late arterial and portal vein complications has been reported, most probably due to former radiation. In those cases graft loss can be avoided with close follow-up and prompt intervention for vascular complications [40]. Excellent long-term survival is achieved in patients with early-stage unresectable pCCA and patients with primary sclerosing cholangitis (PSC)-associated pCCA. Patient outcomes after LT for PSC-associated pCCA are superior to de novo pCCA. Thus, in a recent report from 2021, authors claim that liver transplantation together with aggressive neoadjuvant chemotherapy should be the treatment of choice for patients with pCCA arising in the setting of PSC [40, 41]. Current studies focus on the role of either strict selection of patients or the need for neoadjuvant chemoradiotherapy in treatment strategy of pCCA [41, 42]. In a recent report from an international, multicenter, retrospective cohort study, adjustments in neoadjuvant chemoradiotherapy, such as omitting radiotherapy, have been advocated [42]. Such changes may reduce the risk of hepatic vascular complications and further improve the outcome in patients with pCCA undergoing liver transplantation [43].

For years intrahepatic cholangiocellular carcinoma has been associated with extremely poor outcomes and considered as a contraindication for LT. Progress in chemotherapy and observational data of incidental transplantations in patients with IH CCA have recently intrahepatic HCC to another indications for LT. However, based on the first metaanalysis from 2021, the indications for LT in IH CCA are limited to a single tumor sized <2 cm and carefully selected patients with advanced IH CCA after neoadjuvant therapy [44, 45].

Hepatic epithelioid haemangio-endothelioma

Hepatic epithelioid haemangio-endothelioma (HEHE) is a very rare malignant tumor of vascular origin and uncertain biological behavior, predominantly effecting females. The degree of malignancy of HEHE is considered to be between that of hemangioma and that of hemangiosarcoma of the liver. Regar-

ding the multifocal growth, HEHE can often be misdiagnosed as a metastatic disease or multifocal HCC. Due to the rarity of the disease and unpredictable tumor behavior, optimal treatment has not been fully established. Treatment strategies are dependent on the clinical course of HEHE and include observation, anti-angiogenic drugs, radiotherapy/chemotherapy and surgical approach with hepatectomy in solitary lesions and liver transplantation (LT) in multifocal, diffuse, unresectable or recurrent tumors. Nowadays, in the case of unresectable intrahepatic disease, LT is regarded as a treatment of choice. Interestingly, the presence of metastasis is not a contraindication for LT since it has been observed not to influence survival [46, 47].

In a series of 110 patients with HEHE, who underwent LT between 1987 and 2005, reported by Rodriguez et al., the 5-year survival rate was 64% [48]. In 2006 Mehrabi et al. [49] reviewed 434 cases of HEHE. Liver transplantation was the most common treatment method in that group of patients (44.8%) and the reported 1-year and 5-year survival rates were 96% and 54.5% respectively. Favorable outcomes of LT performed in a series of 18 patients with HEHE were also reported in the report of Krasnodębski et al. [50]. Two of the 18 recipients had concomitant extrahepatic tumors. No disease recurrence was observed during a median follow-up of 65.9 months. The survival probability calculated using the Kaplan-Meier estimator after 1, 5, and 15 years was 94.0%, 82.6%, and 41.3%, respectively Fukuhara et al. suggested that adjuvant therapy performed in aggressive cases with vascular infiltration before disease recurrence might be beneficial and reported the use of the mTOR inhibitor everolimus in combination with tacrolimus to achieve not only immunosuppression, but also an antitumor effect after LT in the case of HEHE with massive vascular infiltration [51].

Hepatic adenoma

Hepatic adenoma (HA) is a benign liver tumor that most commonly occurs in women of reproductive age. The risk factors of HA development are oral contraceptives and some underlying liver diseases, including glycogen storage disease (GSD) and Abernethy malformation (absence of the portal vein). The clinical manifestation of HA varies from asymptomatic cases, through lesions accompanied with abdominal pain up to tumors leading to hepatomegaly or liver rupture with intraperitoneal bleeding. HA is associated with increased risk of HCC development, particularly in patients with glycogen storage disease. Treatment options depend on clinical presentation and range from regular follow-up imaging, withdrawal of hormone-containing pills to liver resection or, ultimately, liver transplantation. In patients with multiple HA and GDS the risk of HCC significantly increases. LT provides definitive prevention against HCC, corrects primary hepatic enzyme defect and most metabolic abnormalities observed in GSD patients [52].

Apart from single case reports, there are only two larger studies on liver transplantation for HA in literature. A European report from 2016, based on data from the European Liver Transplant Registry, identified 49 patients who underwent LT for adenomatosis in the years 1986–2013 [53]. The main indications for LT in this cohort of patients were suspicion or histologically proven HCC. A recent American report from 2022 analyzed data from the United Network for Organ Sharing (UNOS) database and identified 142 HA patients who underwent LT in years 1987–2022 in the United States. The most common indications for LT were suspected malignancy (39.7%), unresectable HA (31.7%), and increasing size of HA lesions (27.0%). Glicogen storage disease (GSD) was present in 53.1% of patients. LT in HA patients was associated with excellent long-term outcomes. The 1-, 3-, and 5-year patient survival rates were 94.2% , 89.7% and 86.3% respectively [54].

Conclusions

Since active or suspected malignancy has stopped being considered as a contraindication for organ transplantation, liver transplantation has gradually started playing a role in the treatment strategies of liver tumors. Nowadays LT is one of the major therapeutic approaches in primary liver cancers and in rare liver tumors. The majority of HCC cases, the leading histologic type of liver cancer, occur in cirrhotic liver and primary liver transplantation for HCC constitutes the leading histologic type of liver cancer and in most cases occurs in cirrhotic liver. Primary liver transplantation for HCC represents the ideal treatment because it targets both the tumor and the underlying liver disease. The outcomes of selected HCC patients treated with LT are comparable to patients without HCC, even when gradually expanded criteria are implemented. Unresectable pCCA, that had earlier been fatal in 100% of cases, is now associated with relatively good outcomes in carefully selected transplant patients, who undergo neoadjuvant chemoradiatotherapy. In particular, excellent long-term survival is achieved in patients with early-stage unresectable pCCA and patients with primary sclerosing cholangitis (PSC)-associated pCCA. Even IH CCA, associated with an extremely poor outcome and for years considered a strong contraindication for LT, has recently been introduced for LT in carefully selected patients after neoadjuvant therapy. Rare primary liver tumors, HEHE and AH, are also successfully treated with liver transplantation in unresectable intrahepatic lesions (HEHE) or suspected malignancy (AH). Due to the gradual progress in transplant medicine, further extension of indications for LT in primary liver tumors will certainly be observed.

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