World Journal of Hepatology

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World J Hepatol 2021 September 27; 13(9): 1098-1106

DOI: 10.4254/wjh.v13.i9.1098

ISSN 1948-5182 (online)

MINIREVIEWS

Liver transplantation for benign liver tumors

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Author contributions: Ostojic A, Mrzljak A and Mikulic D made contributions to the conception and design of the study, collection of data and in drafting and revising the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: None of the authors have any conflict of interest to disclose.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Croatia

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Abstract

Benign liver tumors are common lesions that are usually asymptomatic and are often found incidentally due to recent advances in imaging techniques and their widespread use. Although most of these tumors can be managed conservatively or treated by surgical resection, liver transplantation (LT) is the only treatment option in selected patients. LT is usually indicated in patients that present with life-threatening complications, when the lesions are diffuse in the hepatic parenchyma or when malignant transformation cannot be ruled out. However, due to the significant postoperative morbidity of the procedure, scarcity of available donor liver grafts, and the benign course of the disease, the indications for LT are still not standardized. Hepatic adenoma and adenomatosis, hepatic hemangioma, and hepatic epithelioid hemangioendothelioma are among the most common benign liver tumors treated by LT. This article reviews the role of LT in patients with benign liver tumors. The indications for LT and long-term outcomes of LT are presented.

Key Words: Benign liver tumor; Liver transplantation; Hepatic adenoma; Liver adenomatosis; Hepatic hemangioma; Hepatic epithelioid hemangioendothelioma

Core Tip: Liver transplantation (LT) is rarely performed for benign liver tumors. However, LT is a valid and efficient treatment option in selected patients with life-threatening complications or when surgical resection is impossible. The indications for LT for these lesions are still not well defined. This report focuses on the indications for LT and long-term LT outcomes in patients who underwent transplantation for benign liver tumors.

Citation: Ostojic A, Mrzljak A, Mikulic D. Liver transplantation for benign liver tumors. *World*

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 24, 2021
Peer-review started: February 24, 2021
First decision: May 3, 2021
Revised: May 12, 2021
Accepted: July 21, 2021
Article in press: July 21, 2021
Published online: September 27, 2021

P-Reviewer: Hong SK
S-Editor: Fan JR
L-Editor: Webster JR
P-Editor: Liu JH

J Hepatol 2021; 13(9): 1098-1106
URL: https://www.wjgnet.com/1948-5182/full/v13/i9/1098.htm
DOI: https://dx.doi.org/10.4254/wjh.v13.i9.1098

INTRODUCTION

Malignant liver disease, namely hepatocellular carcinoma, currently makes up between one quarter and one-third of liver transplantation (LT) indications worldwide [1]. Patients with benign liver tumors, on the other hand, only exceptionally undergo transplantation. According to large European and United States registries, transplantations for benign liver tumors make up 1% of all LTs performed in Europe and the United States[2,3].

Benign liver tumors are relatively common, occurring in up to 20% of the general population[4]. Most are treated conservatively, and liver resection (LR) is only required in a minority of patients[5]. Despite their relative frequency, due to the generally benign behavior, there are no standardized treatment guidelines.

LT is occasionally reported in the treatment of benign liver lesions; however, due to the morbidity of the procedure, shortage of donor liver grafts, and benign course of the disease in most patients, only very selected cases may qualify for LT. Some of the indications for LT in patients with benign liver tumors include diagnostic uncertainty and/or possible malignant transformation (MT), premalignant lesions, metabolic liver disease, complications such as rupture or hemorrhage, and significant patient symptoms due to the mass-effects of the tumor[6].

Most of the literature dealing with the topic is limited to case reports or small case series. Both deceased donor and living donor (LD) options of LT are performed for benign liver lesions. However, most of the allocation systems used across the world prioritize the patients for cadaveric LT on the basis of their model for end-stage liver disease (MELD) score[7]. Patients with benign liver lesions typically have low MELD scores and normal liver function. Therefore, LDLT is often the only option for a timely transplant before life-threatening complications develop. This is particularly the case in countries with low rates of cadaveric organ donation and advanced LDLT programs [8-10]. In this report we review the recent literature and analyze the most common indications and outcomes of LT in patients with benign liver tumors.

HEPATIC ADENOMA AND LIVER ADENOMATOSIS

Hepatic adenomas (HA) are rare benign tumors of the liver, with an incidence of 3-4 *per* 100000 women[11]. They predominantly occur in women of childbearing age, often in association with prolonged oral contraceptive use[12]. Since hormonal stimulation plays a significant role in the development of HA, anabolic steroid consumption is also a risk factor[13,14]. Other environmental factors associated with HA are obesity and non-alcoholic fatty disease of the liver (NAFLD)[15,16]. In recent years, due to low estrogen contraceptive formulations and an increasing prevalence of NAFLD and metabolic syndrome, the predominant etiology of HA is shifting from hormonal use towards metabolic liver disease[17]. Other genetic or developmental conditions associated with HA include glycogen storage diseases (especially Type 1a glycogenosis), maturity-onset diabetes of the young type 3, McCune-Albright syndrome, and abnormalities of hepatic vasculature such as absence of the portal vein and portosystemic venous shunts[18-21]. Liver adenomatosis (LA) is a particular entity, initially described by Flejou, defined as the presence of more than 10 adenomas in an otherwise normal liver[22]. However, during recent years, the term adenomatosis has been extended, and it is defined as a high number of liver tumors independent of an absence of underlying liver disease[23]. There are two types of LA. The massive type is characterized by an enlarged liver, deformed liver contour, and typically large and necrotic tumors. The second type is called multifocal, with preserved liver size and contour. This type has a less aggressive course, usually presenting with one or two larger adenomas that may cause complications[24].

Although usually asymptomatic, large-sized or multiple HA can present with abnormal liver function tests, abdominal pain and distention or signs of hemorrhage [25,26]. Hemorrhage is reported to occur in 20%-40% of adenomas, usually appearing in lesions larger than 5 cm[25-28]. It is usually intratumoral; however, the tumor can

also rupture, with resulting subcapsular or intraperitoneal hemorrhage.

MT is another potential complication of HA with an overall risk of about 5%. Male gender is a particular risk, while in women, MT is noted only in tumors larger than 7-8 cm. The existence of multiple lesions reportedly does not seem to confer a specific risk [26,29,30].

HA and LA do not constitute standard indications for LT and LT is only rarely performed. Larger adenomas and adenomas complicated by hemorrhage or MT should be treated with surgical resection. However, since both HA and LA can present with life-threatening complications not amenable to surgical resection due to size, number or localization, LT may be warranted. Sometimes progressive, symptomatic growth or MT occurs after previous hepatectomy, hastening LT. Underlying liver disease can also be the primary indication for LT, such as in glycogen storage disease or vascular malformations of the liver. According to the available literature, glycogen storage disease is considered a risk factor for MT of liver adenomas[31].

According to the 2018 European Liver Transplant Registry (ELTR) report, LA represents only 0.04% of all indications for LT in Europe. The outcomes are excellent, with 1- and 5- year survival rates of 88%[32]. In 2016, Chiche *et al*[33] analyzed 49 patients from the ELTR who underwent LT for LA between 1986 and 2013. Overall, 28 (57%) patients had the massive LA form, while 21 (43%) patients had the multifocal form. Sixteen patients had glycogen storage disease, and seven patients had underlying vascular disease, supporting the notion that the first definition of LA was too restrictive. Regarding the leading indications for LT, histologically proven MT (16 patients) and suspicion of MT (15 patients) were the primary indications, while only five patients underwent LT due to hemorrhage. Out of the 15 patients with a suspicion of MT, only one patient had hepatocellular carcinoma confirmed on the surgical specimen, making this indication debatable. In the analysis of risk factors for MT, age > 30 years and history of partial hepatectomy proved to be statistically significant. Based on the results of the study, Chiche *et al*[33] suggested that LT for LA should be considered when the patient has either a major criterion (histologically proven hepatocellular carcinoma) or at least 3 out of 5 minor criteria (more than two severe hemorrhages, more than two previous resections, beta-mutated or inflammatory adenomas, underlying liver disease - major steatosis or vascular abnormalities, age > 30 years)[33].

In conclusion, HA is only exceptionally accepted as an indication for LT. Also, multiple non-resectable adenomas in the context of LA are likely to remain stable and uncomplicated, so they do not require a major operation with inherent risks such as an LT, especially in the era of organ shortage. Exceptional circumstances when LT can be considered include treatment for an underlying disease such as glycogen storage disease or vascular malformations, multiple non-resectable adenomas in men, and cases with proven or suspected MT.

HEPATIC HEMANGIOMA

Hepatic hemangiomas (HH) are the most common primary tumors of the liver, with an incidence of 0.4%-20%[34]. They are most commonly found in women 30-50 years old (female-to-male ratio, 3:1), but they can be detected in all age groups[35]. Most hemangiomas are small in size (< 4 cm), solitary and asymptomatic[35,36]. HH that measure 10 cm and larger are called giant hemangiomas, and most of them are also asymptomatic[35,36]. Rarely, HH can present as multiple lesions, as a part of a systemic hemangiomatosis syndrome[37,38]. The diagnosis of hemangiomas is usually established incidentally on imaging studies, and owing to their benign course, HH are usually managed conservatively[34]. Larger hemangiomas can cause symptoms, usually abdominal pain or discomfort[37]. Occasionally, HH can present with hemorrhage or consumptive coagulopathy, a condition known as Kasabach-Merritt syndrome (KMS)[34]. HH treatment is rarely indicated, and therapeutic modalities include arterial embolization, surgical resection, and LT. Medical therapy with steroids, vincristine, interferon-alpha, antiplatelet agents, or sirolimus with high doses of propranolol is only indicated for HH that present with KMS[39,40]. However, there is no strong evidence in favor of any pharmacological agent[40]. Apart from KMS, indications for treatment of HH are rapidly growing tumors, persistent pain, hemorrhage, risk of rupture, and symptoms resulting from compression of adjacent organs and vessels[37].

HH are a sporadic indication for LT. Based on the ELTR data, only 71 patients with HH were transplanted from 1988 to 2016, and HH represents 0.1% of all indications for

LT[32]. HH is an even less frequent indication for LT in the United States, with only 25 patients having been transplanted from October 1988 through January 2013[41]. Patients diagnosed with HH who underwent LT have 1-year and 5-year survival rates of 80%-87.8% and 74.8%-77%, respectively[32,41].

To the best of our knowledge, only 18 reports (17 case reports and 1 case series) have been published in the English literature regarding LT for HH (Table 1)[42-59]. According to a recent systematic review that included 15 of the previously mentioned studies, patients' mean age was 39.93 ± 8.7 years. Abdominal distention, respiratory distress, upper abdominal pain, excessive bleeding, and coagulopathy were the most commonly reported symptoms. Twelve patients received grafts from a cadaveric donor, while four patients received LD grafts. All patients had abnormal liver function tests before LT, and they returned to normal within a few days postoperatively. Finally, all patients were alive 90 d after LT. One patient required re-transplantation following an acute liver rejection episode, and one patient was re-operated due to abdominal bleeding[60].

In summary, despite the high incidence of HH, LT is a very rare indication for HH. However, in unresectable HH or HH with life-threatening complications, LT can be considered a safe treatment option.

HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare vascular tumor of the liver with an estimated incidence of less than 0.1 *per* 100000[61]. HEHE is usually diagnosed in adulthood with a mean age at diagnosis of 41.7 years (age range; 30-40 years), and a female predominance (female-to-male ratio 3:2)[62,63]. The etiology of HEHE is not well understood, although several factors have been implicated, including vinyl chloride and asbestos[63]. The hallmark of HEHE is its borderline behavior, described as the aggressiveness of the tumor graded between hemangioma and hepatic hemangiosarcoma. Tumors are often multiple or diffuse throughout the liver. Additionally, HEHE can metastasize beyond the liver. Mehrabi *et al*[63] conducted an extensive review of the literature that included 434 HEHE patients. In that study, 81% of patients had multifocal tumors while a solitary tumor was present in the remaining 19% of patients. Extrahepatic disease (EHD) was diagnosed in 36% of the patients[63]. Lungs, regional lymph nodes, peritoneum, bone, spleen, and diaphragm were the most common extrahepatic sites[63,64]. HEHEs tend to have a heterogeneous clinical presentation, ranging from asymptomatic tumors to lesions causing hepatic failure. The most frequent symptoms are right upper quadrant or epigastric pain (60%–70%), weight loss (20%), impaired general condition (20%), and jaundice (10%)[65]. Definitive diagnosis is often made through a synthesis of radiological signs and clinical features such as occurrence in young adults and longstanding clinical history[64]. Fluorodeoxyglucose-positron emission tomography imaging can be helpful in the staging of the disease before LT[66]. However, histologic examination of appropriate tissue obtained by biopsy is required for correct diagnosis. The most common misdiagnoses include angiosarcoma, cholangiocarcinoma, metastatic carcinoma, and hepatocellular carcinoma (sclerosing variant)[67].

Owing to the rarity and inconsistent behavior of these tumors, the treatment algorithm for HEHE is not standardized. The primary treatment modality is surgery, including LR and LT. It should be noted that HEHE is unresectable in most cases due to its nature, so LT is reserved for patients with multiple or diffuse tumors and/or EHD[67]. Chemo and radiotherapy regimens and transcatheter arterial chemoembolization are other therapeutic options[63,67]. In the previously mentioned study by Mehrabi *et al*[63], most patients had undergone LT (44.8%) followed by no treatment in 24.8%, chemotherapy or radiotherapy in 21%, and LR in 9.4%[63]. Surgical resection and LT had the best survival rates, with 5-year survival rates of 54.5% and 75%, respectively. 5-year survival rates were 30% after chemo or radiotherapy and 4.5% after no treatment[63]. A multicenter ELTR study which analyzed 59 patients who underwent LT for HEHE confirmed excellent results for LT[68]. Moreover, it was concluded that EHD presence is not necessarily a contraindication to LT[68]. In 2010, Grotz *et al*[69] analyzed overall survival (OS) and disease-free survival (DFS) in patients with HEHE treated with LR or LT. In both groups, there were 11 patients with comparable results. LR was associated with a 5-year OS of 86% and DFS of 62%, while LT was associated with a 5-year OS of 73% and DFS of 46%[69]. In a recent study, Noh *et al*[70] evaluated the management and prognosis of 79 HEHE patients from the Surveillance, Epidemiology and End Results program during the study period from

Table 1 List of the reported cases of liver transplantation for hepatic hemangioma

Ref.	Age (yr)/sex	Indication for LT	Type of donor	Follow-up	Condition
Klompmaker *et al*[42], 1989	27/M	KMS	LD	3 yr	Alive
Mora *et al*[43], 1995	42/F	KMS, respiratory distress	CD	16 d	Alive
Tepetes *et al*[44], 1995	4 wk/M	KMS	NA	8 d	Died, graft mal-function
Brouwers *et al*[45], 1997	4 cases	Pain (n = 2). Rupture (n = 1). KMS (n = 1)	NA	1 mo, 1 yr, 4 yr, 9 yr	Alive (n = 3). Died (n = 1)
Chui *et al*[46], 1996	33/F, 43/F	Bleeding (n = 1). Abdominal discomfort (n = 1)	CD	18 mo, 14 mo	Alive (n = 2)
Longeville *et al*[47], 1997	47/M	KMS	CD	12 mo	Alive
Russo *et al*[48], 1997	43/F	Huge mass	CD	14 d	Alive
Kumashiro *et al*[49], 2002	48/F	KMS, acute liver failure	LD	15 d	Alive
Ferraz *et al*[50], 2004	28/F	KMS, respiratory distress	CD	30 mo	Alive
Meguro *et al*[51], 2008	45/F	KMS	LD	10 mo	Alive
Aseni *et al*[52], 2010	46/M	Pulmonary embolism	CD	25 mo	
Vagefi *et al*[53], 2011	39/F	KMS	CD	NA	Alive
Unal *et al*[54], 2011	56/F	Upper abdominal pain	CD	6 mo	
Zhong *et al*[9], 2014	27/F	Diffuse mass	LD	50 mo	Alive
Yildiz *et al*[56], 2014	44/F	KMS, respiratory distress	CD	1 mo	Alive
Lange *et al*[57], 2015	46/F	Huge mass, portal vein thrombosis, ascites	CD	7 wk	Alive
Lee *et al*[8], 2018	51/F	Rapid growing tumor	LD	16 mo	Alive
Eghlimi *et al*[59], 2020	38/M	Huge mass	CD	8 mo	Alive

LT: Liver transplantation; M: Male; F: Female; LD: Living donor; CD: Cadaveric donor; KMS: Kasabach-Merritt Syndrome; NA: Non applicable.

1973 to 2014. Based on their results, patients who underwent surgical treatment (LR or LT) had significantly higher 5-year survival than those who underwent non-surgical treatment (88% *vs* 49%). In multivariate analysis, surgical therapy was the only independent prognostic factor for survival[70]. In the 2007 HEHE-ELTR report, the recurrence rate of HEHE after LT was 25%, while in the US survey that included 110 adults, the recurrence rate was 11%[68,71]. 149 patients from the ELTR registered between 1984 and 2014 were analyzed in order to identify the risk factors for post-LT recurrence of HEHE. Macrovascular invasion (HR 4.8), pre-LT waiting time of 120 d or less (HR 2.6), and hilar lymph node invasion (HR 2.2) were significant risk factors for recurrence, while EHD was confirmed not to be a risk factor[72]. A HEHE-LT score that stratified patients' risk of tumor recurrence was developed using these three risk factors. Patients with a score between 0 and 2 had a significantly better 5-year DFS than patients with a score of 6-10 (93.9% *vs* 38.5%; $P < 0.001$)[72]. This score can be used in the post-LT follow-up to decide on minimization and type of immunosuppression as well as for imaging surveillance. Furthermore, this study emphasizes the importance of routine extensive lymphadenectomy during LT. Also, mandatory waiting time should be set up in order to gain a better insight into the tumor biology and avoid futile LT[72].

CONCLUSION

In conclusion, LT is rarely indicated for the treatment of benign liver tumors, mainly due to their benign nature. Most of the complications resulting from benign liver tumors can be managed with radiological intervention or surgical resection. However, when benign liver tumors present with life-threatening complications or MT cannot be ruled out, and tumors are unresectable, LT is a reasonable and safe treatment option.

Due to their rarity, there are no standardized transplantation guidelines for benign liver tumors. Considering satisfying long-term results, studies from Europe and the United States strengthen the role of LT for benign liver tumors. Finally, a worldwide registry of patients transplanted for benign liver tumors with details about patients' history, imaging studies, and the surgical pathology would help to define precise LT criteria for this rare indication.

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