

Liver transplantation for benign liver tumors

Ostojić, Ana; Mrzljak, Anna; Mikulić, Danko

Source / Izvornik: **World Journal of Hepatology, 2021, 13, 1098 - 1106**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.4254/wjh.v13.i9.1098>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:105:650993>

Rights / Prava: [Attribution-NonCommercial 4.0 International/Imenovanje-Nekomercijalno 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2025-01-28**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



Liver transplantation for benign liver tumors

Ana Ostojic, Anna Mrzljak, Danko Mikulic

ORCID number: Ana Ostojic 0000-0003-4234-4461; Anna Mrzljak 0000-0001-6270-2305; Danko Mikulic 0000-0001-8103-6045.

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.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: Croatia

Ana Ostojic, Anna Mrzljak, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, Zagreb 10000, Croatia

Danko Mikulic, Department of Surgery, University Hospital Merkur, Zagreb 10000, Croatia

Corresponding author: Danko Mikulic, FEBS, MD, PhD, Surgeon, Department of Surgery, University Hospital Merkur, Zajceva 19, Zagreb 10000, Croatia. danko.mikulic@zg.t-com.hr

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

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

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

REFERENCES

- 1 **Adam R**, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A; All contributing centers (www.eltr.org); European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012; **57**: 675-688 [PMID: 22609307 DOI: 10.1016/j.jhep.2012.04.015]
- 2 **ELTR**. European Liver Transplant Registry (ELTR) Web site. [cited 1 February 2021]. Available from: www.eltr.org
- 3 **UNOS**. United Network of Organ Sharing (UNOS) database. [cited 1 February 2021]. Available from: www.unos.org
- 4 **Schwartz ME**, Roayaie S, Konstadoulakis MM, Gomatos IP, Miller CM. The Mount Sinai experience with orthotopic liver transplantation for benign tumors: brief report and literature review: case reports. *Transplant Proc* 2008; **40**: 1759-1762 [PMID: 18589189 DOI: 10.1016/j.transproceed.2008.02.076]
- 5 **Dimick JB**, Cowan JA Jr, Knol JA, Upchurch GR Jr. Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database. *Arch Surg* 2003; **138**: 185-191 [PMID: 12578418 DOI: 10.1001/archsurg.138.2.185]
- 6 **Ercolani G**, Grazi GL, Pinna AD. Liver transplantation for benign hepatic tumors: a systematic review. *Dig Surg* 2010; **27**: 68-75 [PMID: 20357454 DOI: 10.1159/000268628]
- 7 **Malinchoc M**, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]
- 8 **Lee JH**, Yoon CJ, Kim YH, Han HS, Cho JY, Kim H, Jang ES, Kim JW, Jeong SH. Living-donor liver transplantation for giant hepatic hemangioma with diffuse hemangiomatosis in an adult: a case report. *Clin Mol Hepatol* 2018; **24**: 163-168 [PMID: 28719965 DOI: 10.3350/cmh.2017.0002]
- 9 **Zhong L**, Men TY, Yang GD, Gu Y, Chen G, Xing TH, Fan JW, Peng ZH. Case report: living donor liver transplantation for giant hepatic hemangioma using a right lobe graft without the middle hepatic vein. *World J Surg Oncol* 2014; **12**: 83 [PMID: 24708716 DOI: 10.1186/1477-7819-12-83]
- 10 **Di Sandro S**, Slim AO, Lauterio A, Giacomoni A, Mangoni I, Aseni P, Pirota V, Aldumour A, Mihaylov P, De Carlis L. Liver adenomatosis: a rare indication for living donor liver transplantation. *Transplant Proc* 2009; **41**: 1375-1377 [PMID: 19460563 DOI: 10.1016/j.transproceed.2009.03.021]
- 11 **Thomeer MG**, Broker M, Verheij J, Doukas M, Terkivatan T, Bijdevaate D, De Man RA, Moelker A, IJzermans JN. Hepatocellular adenoma: when and how to treat? *Therap Adv Gastroenterol* 2016; **9**: 898-912 [PMID: 27803743 DOI: 10.1177/1756283X16663882]
- 12 **Rosenberg L**. The risk of liver neoplasia in relation to combined oral contraceptive use. *Contraception* 1991; **43**: 643-652 [PMID: 1651205 DOI: 10.1016/0010-7824(91)90007-3]
- 13 **Nakao A**, Sakagami K, Nakata Y, Komazawa K, Amimoto T, Nakashima K, Isozaki H, Takakura N, Tanaka N. Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. *J Gastroenterol* 2000; **35**: 557-562 [PMID: 10905366 DOI: 10.1007/s005350070081]
- 14 **Socas L**, Zumbado M, Pérez-Luzardo O, Ramos A, Pérez C, Hernández JR, Boada LD. Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature. *Br J Sports Med* 2005; **39**: e27 [PMID: 15849280 DOI: 10.1136/bjism.2004.013599]
- 15 **Bunchorntavakul C**, Bahirwani R, Drazek D, Soulen MC, Siegelman ES, Furth EE, Olthoff K, Shaked A, Reddy KR. Clinical features and natural history of hepatocellular adenomas: the impact of obesity. *Aliment Pharmacol Ther* 2011; **34**: 664-674 [PMID: 21762186 DOI: 10.1111/j.1365-2036.2011.04772.x]
- 16 **Chang CY**, Hernandez-Prera JC, Roayaie S, Schwartz M, Thung SN. Changing epidemiology of hepatocellular adenoma in the United States: review of the literature. *Int J Hepatol* 2013; **2013**: 604860 [PMID: 23509632 DOI: 10.1155/2013/604860]
- 17 **Heinemann LA**, Weimann A, Gerken G, Thiel C, Schlaud M, DoMinh T. Modern oral contraceptive use and benign liver tumors: the German Benign Liver Tumor Case-Control Study. *Eur J Contracept Reprod Health Care* 1998; **3**: 194-200 [PMID: 10036602 DOI: 10.3109/13625189809167253]
- 18 **Reddy SK**, Kishnani PS, Sullivan JA, Koeberl DD, Desai DM, Skinner MA, Rice HE, Clary BM. Resection of hepatocellular adenoma in patients with glycogen storage disease type Ia. *J Hepatol* 2007; **47**: 658-663 [PMID: 17637480 DOI: 10.1016/j.jhep.2007.05.012]
- 19 **Wang DQ**, Fiske LM, Carreras CT, Weinstein DA. Natural history of hepatocellular adenoma

- formation in glycogen storage disease type I. *J Pediatr* 2011; **159**: 442-446 [PMID: 21481415 DOI: 10.1016/j.jpeds.2011.02.031]
- 20 **Kawakatsu M**, Vilgrain V, Belghiti J, Flejou JF, Nahum H. Association of multiple liver cell adenomas with spontaneous intrahepatic portohepatic shunt. *Abdom Imaging* 1994; **19**: 438-440 [PMID: 7950822 DOI: 10.1007/BF00206934]
 - 21 **Pupulim LF**, Vullierme MP, Paradis V, Valla D, Terraz S, Vilgrain V. Congenital portosystemic shunts associated with liver tumours. *Clin Radiol* 2013; **68**: e362-e369 [PMID: 23537576 DOI: 10.1016/j.crad.2013.01.024]
 - 22 **Flejou JF**, Barge J, Menu Y, Degott C, Bismuth H, Potet F, Benhamou JP. Liver adenomatosis. An entity distinct from liver adenoma? *Gastroenterology* 1985; **89**: 1132-1138 [PMID: 2412930]
 - 23 **Fruio N**, Chiche L, Bioulac-Sage P, Balabaud C. Hepatocellular adenomatosis: what should the term stand for! *Clin Res Hepatol Gastroenterol* 2014; **38**: 132-136 [PMID: 24126236 DOI: 10.1016/j.clinre.2013.08.004]
 - 24 **Chiche L**, Dao T, Salamé E, Galais MP, Bouvard N, Schmutz G, Rousselot P, Bioulac-Sage P, Ségol P, Gignoux M. Liver adenomatosis: reappraisal, diagnosis, and surgical management: eight new cases and review of the literature. *Ann Surg* 2000; **231**: 74-81 [PMID: 10636105 DOI: 10.1097/0000658-200001000-00011]
 - 25 **Cho SW**, Marsh JW, Steel J, Holloway SE, Heckman JT, Ochoa ER, Geller DA, Gamblin TC. Surgical management of hepatocellular adenoma: take it or leave it? *Ann Surg Oncol* 2008; **15**: 2795-2803 [PMID: 18696154 DOI: 10.1245/s10434-008-0090-0]
 - 26 **Dokmak S**, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D, Bedossa P, Belghiti J. A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. *Gastroenterology* 2009; **137**: 1698-1705 [PMID: 19664629 DOI: 10.1053/j.gastro.2009.07.061]
 - 27 **van Aalten SM**, de Man RA, IJzermans JN, Terkivatan T. Systematic review of haemorrhage and rupture of hepatocellular adenomas. *Br J Surg* 2012; **99**: 911-916 [PMID: 22619025 DOI: 10.1002/bjs.8762]
 - 28 **Marini P**, Vilgrain V, Belghiti J. Management of spontaneous rupture of liver tumours. *Dig Surg* 2002; **19**: 109-113 [PMID: 11978996 DOI: 10.1159/000052022]
 - 29 **Stoot JH**, Coelen RJ, De Jong MC, Dejong CH. Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. *HPB (Oxford)* 2010; **12**: 509-522 [PMID: 20887318 DOI: 10.1111/j.1477-2574.2010.00222.x]
 - 30 **Farges O**, Dokmak S. Malignant transformation of liver adenoma: an analysis of the literature. *Dig Surg* 2010; **27**: 32-38 [PMID: 20357449 DOI: 10.1159/000268405]
 - 31 **Calderaro J**, Labruno P, Morcrette G, Rebouissou S, Franco D, Prévot S, Quaglia A, Bedossa P, Libbrecht L, Terracciano L, Smit GP, Bioulac-Sage P, Zucman-Rossi J. Molecular characterization of hepatocellular adenomas developed in patients with glycogen storage disease type I. *J Hepatol* 2013; **58**: 350-357 [PMID: 23046672 DOI: 10.1016/j.jhep.2012.09.030]
 - 32 **Adam R**, Karam V, Cailliez V, O Grady JG, Mirza D, Cherqui D, Klempnauer J, Salizzoni M, Pratschke J, Jamieson N, Hidalgo E, Paul A, Andujar RL, Lerut J, Fisher L, Boudjema K, Fondevila C, Soubrane O, Bachellier P, Pinna AD, Berlakovich G, Bennet W, Pinzani M, Schemmer P, Zieniewicz K, Romero CJ, De Simone P, Ericzon BG, Schneeberger S, Wigmore SJ, Prous JF, Colledan M, Porte RJ, Yilmaz S, Azoulay D, Pirenne J, Line PD, Truneka P, Navarro F, Lopez AV, De Carlis L, Pena SR, Kochs E, Duvoux C; all the other 126 contributing centers (www. eltr.org) and the European Liver and Intestine Transplant Association (ELITA). 2018 Annual Report of the European Liver Transplant Registry (ELTR) - 50-year evolution of liver transplantation. *Transpl Int* 2018; **31**: 1293-1317 [PMID: 30259574 DOI: 10.1111/tri.13358]
 - 33 **Chiche L**, David A, Adam R, Oliverius MM, Klempnauer J, Vibert E, Colledan M, Lerut J, Mazzafero VV, Di-Sandro S, Laurent C, Scuderi V, Suc B, Troisi R, Bachelier P, Dumortier J, Gugenheim J, Mabrut JY, Gonzalez-Pinto I, Pruvot FR, Le-Treut YP, Navarro F, Ortiz-de-Urbina J, Salamé E, Spada M, Bioulac-Sage P. Liver transplantation for adenomatosis: European experience. *Liver Transpl* 2016; **22**: 516-526 [PMID: 26919265 DOI: 10.1002/lt.24417]
 - 34 **European Association for the Study of the Liver (EASL)**. EASL Clinical Practice Guidelines on the management of benign liver tumours. *J Hepatol* 2016; **65**: 386-398 [PMID: 27085809 DOI: 10.1016/j.jhep.2016.04.001]
 - 35 **Bahirwani R**, Reddy KR. Review article: the evaluation of solitary liver masses. *Aliment Pharmacol Ther* 2008; **28**: 953-965 [PMID: 18643922 DOI: 10.1111/j.1365-2036.2008.03805.x]
 - 36 **Gandolfi L**, Leo P, Solmi L, Vitelli E, Verros G, Colecchia A. Natural history of hepatic haemangiomas: clinical and ultrasound study. *Gut* 1991; **32**: 677-680 [PMID: 2060877 DOI: 10.1136/gut.32.6.677]
 - 37 **Bajenaru N**, Balaban V, Săvulescu F, Campeanu I, Patrascu T. Hepatic hemangioma -review-. *J Med Life* 2015; **8** Spec Issue: 4-11 [PMID: 26361504]
 - 38 **Keegan MT**, Kamath GS, Vasdev GM, Findlay JY, Gores GJ, Steers JL, Plevak DJ. Liver transplantation for massive hepatic haemangiomas causing restrictive lung disease. *Br J Anaesth* 2001; **86**: 431-434 [PMID: 11573537 DOI: 10.1093/bja/86.3.431]
 - 39 **Warren D**, Diaz L, Levy M. Diffuse Hepatic Hemangiomas Successfully Treated Using Sirolimus and High-Dose Propranolol. *Pediatr Dermatol* 2017; **34**: e286-e287 [PMID: 28730754 DOI: 10.1111/pde.13219]
 - 40 **O'Rafferty C**, O'Regan GM, Irvine AD, Smith OP. Recent advances in the pathobiology and management of Kasabach-Merritt phenomenon. *Br J Haematol* 2015; **171**: 38-51 [PMID: 26123689]

- DOI: [10.1111/bjh.13557](https://doi.org/10.1111/bjh.13557)]
- 41 **Sundar Alagusundaramoorthy S**, Vilchez V, Zanni A, Sourianarayanane A, Maynard E, Shah M, Daily MF, Pena LR, Gedaly R. Role of transplantation in the treatment of benign solid tumors of the liver: a review of the United Network of Organ Sharing data set. *JAMA Surg* 2015; **150**: 337-342 [PMID: [25714928](https://pubmed.ncbi.nlm.nih.gov/25714928/) DOI: [10.1001/jamasurg.2014.3166](https://doi.org/10.1001/jamasurg.2014.3166)]
 - 42 **Klompemaker IJ**, Sloof MJ, van der Meer J, de Jong GM, de Bruijn KM, Bams JL. Orthotopic liver transplantation in a patient with a giant cavernous hemangioma of the liver and Kasabach-Merritt syndrome. *Transplantation* 1989; **48**: 149-151 [PMID: [2501918](https://pubmed.ncbi.nlm.nih.gov/2501918/) DOI: [10.1097/00007890-198907000-00035](https://doi.org/10.1097/00007890-198907000-00035)]
 - 43 **Mora A**, Cortés C, Roigé J, Noguer M, Camps MA, Margarit C. [Orthotopic liver transplant for giant cavernous hemangioma and Kasabach-Merritt syndrome]. *Rev Esp Anestesiología Reanimación* 1995; **42**: 71-74 [PMID: [7899656](https://pubmed.ncbi.nlm.nih.gov/7899656/)]
 - 44 **Tepetes K**, Selby R, Webb M, Madariaga JR, Iwatsuki S, Starzl TE. Orthotopic liver transplantation for benign hepatic neoplasms. *Arch Surg* 1995; **130**: 153-156 [PMID: [7848084](https://pubmed.ncbi.nlm.nih.gov/7848084/) DOI: [10.1001/archsurg.1995.01430020043005](https://doi.org/10.1001/archsurg.1995.01430020043005)]
 - 45 **Brouwers MA**, Peeters PM, de Jong KP, Haagsma EB, Klompemaker IJ, Bijleveld CM, Zwaveling JH, Slooff MJ. Surgical treatment of giant haemangioma of the liver. *Br J Surg* 1997; **84**: 314-316 [PMID: [9117293](https://pubmed.ncbi.nlm.nih.gov/9117293/)]
 - 46 **Chui AK**, Vass J, McCaughan GW, Sheil AG. Giant cavernous haemangioma: a rare indication for liver transplantation. *Aust N Z J Surg* 1996; **66**: 122-124 [PMID: [8602810](https://pubmed.ncbi.nlm.nih.gov/8602810/) DOI: [10.1111/j.1445-2197.1996.tb01132.x](https://doi.org/10.1111/j.1445-2197.1996.tb01132.x)]
 - 47 **Longeville JH**, de la Hall P, Dolan P, Holt AW, Lillie PE, Williams JA, Padbury RT. Treatment of a giant haemangioma of the liver with Kasabach-Merritt syndrome by orthotopic liver transplant a case report. *HPB Surg* 1997; **10**: 159-162 [PMID: [9174860](https://pubmed.ncbi.nlm.nih.gov/9174860/) DOI: [10.1155/1997/10136](https://doi.org/10.1155/1997/10136)]
 - 48 **Russo MW**, Johnson MW, Fair JH, Brown RS Jr. Orthotopic liver transplantation for giant hepatic hemangioma. *Am J Gastroenterol* 1997; **92**: 1940-1941 [PMID: [9382077](https://pubmed.ncbi.nlm.nih.gov/9382077/)]
 - 49 **Kumashiro Y**, Kasahara M, Nomoto K, Kawai M, Sasaki K, Kiuchi T, Tanaka K. Living donor liver transplantation for giant hepatic hemangioma with Kasabach-Merritt syndrome with a posterior segment graft. *Liver Transpl* 2002; **8**: 721-724 [PMID: [12149767](https://pubmed.ncbi.nlm.nih.gov/12149767/) DOI: [10.1053/jlts.2002.33689](https://doi.org/10.1053/jlts.2002.33689)]
 - 50 **Ferraz AA**, Sette MJ, Maia M, Lopes EP, Godoy MM, Petribú AT, Meira M, Borges Oda R. Liver transplant for the treatment of giant hepatic hemangioma. *Liver Transpl* 2004; **10**: 1436-1437 [PMID: [15497149](https://pubmed.ncbi.nlm.nih.gov/15497149/) DOI: [10.1002/lt.20250](https://doi.org/10.1002/lt.20250)]
 - 51 **Meguro M**, Soejima Y, Taketomi A, Ikegami T, Yamashita Y, Harada N, Itoh S, Hirata K, Machara Y. Living donor liver transplantation in a patient with giant hepatic hemangioma complicated by Kasabach-Merritt syndrome: report of a case. *Surg Today* 2008; **38**: 463-468 [PMID: [18560973](https://pubmed.ncbi.nlm.nih.gov/18560973/) DOI: [10.1007/s00595-007-3623-4](https://doi.org/10.1007/s00595-007-3623-4)]
 - 52 **Aseni P**, Lauterio A, Slim AO, Giacomoni A, Lamperti L, De Carlis L. Life-saving super-urgent liver transplantation with replacement of retrohepatic vena cava by dacron graft. *HPB Surg* 2010; **2010** [PMID: [20811479](https://pubmed.ncbi.nlm.nih.gov/20811479/) DOI: [10.1155/2010/828326](https://doi.org/10.1155/2010/828326)]
 - 53 **Vagefi PA**, Klein I, Gelb B, Hameed B, Moff SL, Simko JP, Fix OK, Eilers H, Feiner JR, Ascher NL, Freise CE, Bass NM. Emergent orthotopic liver transplantation for hemorrhage from a giant cavernous hepatic hemangioma: case report and review. *J Gastrointest Surg* 2011; **15**: 209-214 [PMID: [20549381](https://pubmed.ncbi.nlm.nih.gov/20549381/) DOI: [10.1007/s11605-010-1248-1](https://doi.org/10.1007/s11605-010-1248-1)]
 - 54 **Unal E**, Francis F, Aquino A, Xu R, Morgan G, Teperman L. Liver transplant for mixed capillary-cavernous hemangioma masquerading as hepatocellular carcinoma in a patient with hepatocellular carcinoma. *Exp Clin Transplant* 2011; **9**: 344-348 [PMID: [21967263](https://pubmed.ncbi.nlm.nih.gov/21967263/)]
 - 55 **About I**, Capdeville J, Bernard P, Lazorthes F, Boneu B. [Unresectable giant hepatic hemangioma and Kasabach-Merritt syndrome]. *Rev Med Interne* 1994; **15**: 846-850 [PMID: [7863122](https://pubmed.ncbi.nlm.nih.gov/7863122/) DOI: [10.1016/s0248-8663\(05\)82844-9](https://doi.org/10.1016/s0248-8663(05)82844-9)]
 - 56 **Yildiz S**, Kantarci M, Kizrak Y. Cadaveric liver transplantation for a giant mass. *Gastroenterology* 2014; **146**: e10-e11 [PMID: [24269562](https://pubmed.ncbi.nlm.nih.gov/24269562/) DOI: [10.1053/j.gastro.2013.08.001](https://doi.org/10.1053/j.gastro.2013.08.001)]
 - 57 **Lange UG**, Bucher JN, Schoenberg MB, Benzing C, Schmelzle M, Gradistanac T, Strocka S, Hau HM, Bartels M. Orthotopic liver transplantation for giant liver haemangioma: A case report. *World J Transplant* 2015; **5**: 354-359 [PMID: [26722664](https://pubmed.ncbi.nlm.nih.gov/26722664/) DOI: [10.5500/wjt.v5.i4.354](https://doi.org/10.5500/wjt.v5.i4.354)]
 - 58 **Martínez-González MN**, Mondragón-Sánchez R, Mondragón-Sánchez A, Gómez-Gómez E, Garduño-López AL, Bernal-Maldonado R, Oñate-Ocaña LF, Ruiz-Molina JM. [Cavernous hemangioma of the liver and hepatic hemangiomatosis. Indications and results of the surgical resection]. *Rev Gastroenterol Mex* 2003; **68**: 277-282 [PMID: [15125330](https://pubmed.ncbi.nlm.nih.gov/15125330/)]
 - 59 **Eghlimi H**, Arasteh P, Azade N. Orthotopic liver transplantation for Management of a Giant Liver Hemangioma: a case report and review of literature. *BMC Surg* 2020; **20**: 142 [PMID: [32600292](https://pubmed.ncbi.nlm.nih.gov/32600292/) DOI: [10.1186/s12893-020-00801-z](https://doi.org/10.1186/s12893-020-00801-z)]
 - 60 **Prodromidou A**, Machairas N, Garoufalia Z, Kostakis ID, Tsaparas P, Paspala A, Stamopoulos P, Sotiropoulos GC. Liver Transplantation for Giant Hepatic Hemangioma: A Systematic Review. *Transplant Proc* 2019; **51**: 440-442 [PMID: [30879561](https://pubmed.ncbi.nlm.nih.gov/30879561/) DOI: [10.1016/j.transproceed.2019.01.018](https://doi.org/10.1016/j.transproceed.2019.01.018)]
 - 61 **Hertl M**, Cosimi AB. Liver transplantation for malignancy. *Oncologist* 2005; **10**: 269-281 [PMID: [15821247](https://pubmed.ncbi.nlm.nih.gov/15821247/) DOI: [10.1634/theoncologist.10-4-269](https://doi.org/10.1634/theoncologist.10-4-269)]
 - 62 **Makhlouf HR**, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. *Cancer* 1999; **85**: 562-582 [PMID: [10091730](https://pubmed.ncbi.nlm.nih.gov/10091730/) DOI: [10.1002/\(sici\)1097-0142\(19990201\)85:3<562::aid-cnrc7>3.0.co;2-t](https://doi.org/10.1002/(sici)1097-0142(19990201)85:3<562::aid-cnrc7>3.0.co;2-t)]

- 63 **Mehrabi A**, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler MW, Schmidt J. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. *Cancer* 2006; **107**: 2108-2121 [PMID: [17019735](#) DOI: [10.1002/encr.22225](#)]
- 64 **Gurung S**, Fu H, Zhang WW, Gu YH. Hepatic epithelioid hemangioendothelioma metastasized to the peritoneum, omentum and mesentery: a case report. *Int J Clin Exp Pathol* 2015; **8**: 5883-5889 [PMID: [26191313](#)]
- 65 **Lerut JP**, Weber M, Orlando G, Dutkowski P. Vascular and rare liver tumors: a good indication for liver transplantation? *J Hepatol* 2007; **47**: 466-475 [PMID: [17697721](#) DOI: [10.1016/j.jhep.2007.07.005](#)]
- 66 **Nguyen BD**. Epithelioid hemangioendothelioma of the liver with F-18 FDG PET imaging. *Clin Nucl Med* 2004; **29**: 828-830 [PMID: [15545895](#) DOI: [10.1097/00003072-200412000-00019](#)]
- 67 **Virarkar M**, Saleh M, Diab R, Taggart M, Bhargava P, Bhosale P. Hepatic Hemangioendothelioma: An update. *World J Gastrointest Oncol* 2020; **12**: 248-266 [PMID: [32206176](#) DOI: [10.4251/wjgo.v12.i3.248](#)]
- 68 **Lerut JP**, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D, Boleslawski E, Burroughs A, Sellés CF, Jaecck D, Pfitzmann R, Salizzoni M, Söderdahl G, Steininger R, Wettergren A, Mazzaferro V, Le Treut YP, Karam V; European Liver Transplant Registry. The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma: report of the European liver transplant registry. *Ann Surg* 2007; **246**: 949-57; discussion 957 [PMID: [18043096](#) DOI: [10.1097/SLA.0b013e31815c2a70](#)]
- 69 **Grotz TE**, Nagorney D, Donohue J, Que F, Kendrick M, Farnell M, Harmsen S, Mulligan D, Nguyen J, Rosen C, Reid-Lombardo KM. Hepatic epithelioid haemangioendothelioma: is transplantation the only treatment option? *HPB (Oxford)* 2010; **12**: 546-553 [PMID: [20887322](#) DOI: [10.1111/j.1477-2574.2010.00213.x](#)]
- 70 **Noh OK**, Kim SS, Yang MJ, Lim SG, Hwang JC, Cho HJ, Cheong JY, Cho SW. Treatment and prognosis of hepatic epithelioid hemangioendothelioma based on SEER data analysis from 1973 to 2014. *Hepatobiliary Pancreat Dis Int* 2020; **19**: 29-35 [PMID: [31822393](#) DOI: [10.1016/j.hbpd.2019.11.006](#)]
- 71 **Rodriguez JA**, Becker NS, O'Mahony CA, Goss JA, Aloia TA. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: the UNOS experience from 1987 to 2005. *J Gastrointest Surg* 2008; **12**: 110-116 [PMID: [17710508](#) DOI: [10.1007/s11605-007-0247-3](#)]
- 72 **Lai Q**, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M, Mazzaferro V, Pascher A, Remiszewski P, Isoniemi H, Pirenne J, Foss A, Ericzon BG, Markovic S, Lerut JP; European Liver Intestine Transplant Association (ELITA). Hepatic Epithelioid Hemangioendothelioma and Adult Liver Transplantation: Proposal for a Prognostic Score Based on the Analysis of the ELTR-ELITA Registry. *Transplantation* 2017; **101**: 555-564 [PMID: [28212256](#) DOI: [10.1097/TP.0000000000001603](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

