Digestive Surgery

Dig Surg 2010;27:68–75
DOI: 10.1159/000268628

Published online: April 1, 2010

Liver Transplantation for Benign Hepatic Tumors: A Systematic Review

Giorgio Ercolani Gian Luca Grazi Antonio Daniele Pinna

Department of Surgery and Transplantation, Liver and Multiorgan Transplant Unit, Hospital Sant'Orsola-Malpighi, Bologna, Italy

Key Words

Orthotopic liver transplantation · Polycystic liver disease · Liver cell adenoma · Liver cell adenomatosis · Liver hemangioma · Hepatic epithelioid hemangioendothelioma · Caroli's disease and syndrome

Abstract

Orthotopic liver transplantation (OLT) has been performed for several benign hepatic tumors. Most of these diseases are usually managed conservatively, or treated by liver resection. OLT might be required when the lesions are symptomatic, diffuse in hepatic parenchyma, causing life-threatening complications or malignant transformation cannot be ruled out. Polycystic liver disease is the most common indication for OLT. We present a review of transplantable benign hepatic lesions to evaluate the need of OLT for these diseases, to summarize in which OLT is a good therapeutic option, and to show the early and long-term survival which might be expected.

Introduction

Benign liver tumors affect up to approximately 20% of the US population [1] and are the indication for hepatic resections in about 6% of patients [2]. No randomized clinical trials were found regarding elective surgery for benign liver tumors; most reported studies are retrospective or include case series with less than 60 patients [3]. For these reasons, no definitive conclusions concerning clinical practice can be drawn in the management of these lesions [3].

Orthotopic liver transplantation (OLT) has been reported in the treatment of several benign hepatic tumors; they are listed in table 1. In these cases, reasons for OLT were uncertain diagnosis or preneoplastic lesions with high risk of malignant transformation, association with metabolic diseases or Kasabach-Merritt syndrome, rupture or increased risk of life-threatening complications, abdominal encumbrance, or severe symptoms with discomfort. Published reports are limited and based on small case series; therefore, there is a lack of data regarding optimal indications for OLT. Liver transplantation is a definitive and curative therapy for benign hepatic tumors; however, due to the high morbidity, the still significant mortality and the shortage of donor grafts the indication for OLT remains far from being standardized in this population for whom conservative management and, in a few cases, surgical resection are the gold standard.

We reviewed the recent literature, and the results based on UNOS and ELTR data and tried to summarize accepted indications and long-term results. From 1989 to 2008, 394 liver transplantations were performed in the

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0253–4886/10/0271–0068$26.00/0

Accessible online at:
www.karger.com/dsu

Giorgio Ercolani, MD, PhD
Department of Surgery and Transplantation, Liver and Multiorgan Transplant Unit
Hospital Sant'Orsola-Malpighi
Via Massarenti, 9, IT–40138 Bologna (Italy)
Tel. +39 051 636 4810, Fax +39 051 304 902, E-Mail giorgio.ercolani@aosp.bo.it

Table 1. Benign liver tumors treated by liver transplantation from a review of the literature

Polycystic liver disease
Hepatic adenoma
Hepatic adenomatosis
Hepatic hemangioma
Hepatic epithelioid hemangioendothelioma
Caroli's disease and syndrome
Hepatic hydatid disease
Nodular regenerative hyperplasia
Lymphangiomatosis of the liver
Mesenchymal hamartoma
Focal nodular hyperplasia

Table 2. Number of most common benign hepatic tumors treated by liver transplantation in the USA [4] and Europe [5]

	UNOS database (394 cases)[a]	ELTR database (902 cases)[b]
Polycystic liver disease	301 (76.4%)	626 (69.4%)
Hepatic adenoma and adenomatosis	42 (10.6%)	61 (6.8%)
Hepatic cavernous hemangioma	15 (3.8%)	77 (8.5%)
Nodular regenerative hyperplasia	3 (0.7%)	34 (3.8%)
Others	33 (8.4%)	104 (11.5%)

[a] From 1989 to 2008. [b] From 1968 to 2008.

USA for benign liver tumors (about 0.9% of all liver transplantations). The overall 1-, 3- and 5-year survival rates were 84.9, 81.2 and 75.9%, respectively [4]. From the European Liver Transplant registry during the period 1968–2008, 902 liver transplantations were performed (1.25% of all reported transplants) [5]. The numbers of most common hepatic lesions treated by OLT are reported in table 2.

Polycystic Liver Disease

Autosomal dominant polycystic disease is geneticall-ly heterogenous, with mutations in two distinct genes (PKD1 and PKD2) predisposing to combined polycystic liver and kidney disease, and mutation in a third gene, protein kinase C substrate 80K-H (PRKCSH), accounting for a rare isolated polycystic liver disease without renal involvement [6]. Hepatic cysts are rarely observed before puberty, are more prevalent in women and increase in number and size through the child-bearing years [6]. The severity of polycystic liver disease often correlates with the severity of renal cystic disease and degree of renal dysfunction [7, 8]. Most patients are asymptomatic; however, in a few patients massive and large cysts (liver cysts/parenchymal involvement >1) may cause abdominal pain, discomfort, and shortness of breath [6]. The most common complications are intracystic hemorrhage, infection, and posttraumatic rupture. Rarely, a patient may experience hepatic decompensation with ascites and encephalopathy. There are no effective medical treatments for symptomatic hepatic cysts. Radiologic cyst aspiration or sclerosis have been applied with various degrees of success and cyst recurrence [6]. Complete cyst fenestration by laparotomy or surgical resection have led to a complete, sustained resolution of symptoms but are associated with prolonged hospitalization and significant morbidity [9]. For this reason, cyst fenestration by laparoscopic approach is the preferred option with less morbidity and hospitalization even though a significant recurrence of symptoms has been reported [6].

Liver transplantation offers the best chance of definitive treatment in patients where the presence of massive and large cysts can cause life-threatening symptoms such as malnutrition, weight loss, asthenia, and reduction of oral intake. In cases of polycystic liver-kidney disease, whenever the above-mentioned symptoms are associated with renal failure requiring hemodialysis or with a glomerular filtration rate <30 ml/min, combined liver-kidney transplantation represents the optimal treatment giving distinct advantages [10–12]. In the USA, polycystic liver disease has been the main indication for OLT in 76% of transplanted patients with a benign tumor in the last 20 years, with 1-, 3- and 5-year survival rates of 82.5, 79 and 73.5%, respectively [4]. Similar results have been reported in Europe [5].

Since liver function is preserved until a late stage, and in a view of organ shortage, OLT remains controversial and the question of when OLT is appropriate is difficult. On the other hand, septic complications are frequent after transplantation in these patients and are the main cause of death. Postoperative mortality up to 20–30% was reported in earlier studies; except for a high postoperative risk, long-term results have been reported as satisfactory [1, 11, 13]. The increased risk of sepsis might have been

due to bacterial reservoirs in cysts and/or prolonged poor nutritional status, amplified by the immunosuppressive agents; total hepatectomy can be technically demanding with an increased amount of bleeding as a result of tight scar formation between the diaphragm, stomach, colon, spleen and cysts. Meticulous surgery, the application of the piggyback technique to avoid the use of venovenous bypass and the clamping of the portal vein at the very end of the hepatectomy are the key points in reducing postoperative morbidity and mortality [13].

A recent German study analyzed the quality of life after OLT and showed that most patients (91%) report an improvement in social status and better quality of life compared to before OLT; 78% of patients said they would opt for transplantation again [12].

OLT and/or combined liver-kidney transplantation are valid and curative therapies for polycystic liver and kidney disease in patients with defined criteria as mentioned above. Due to the absence of signs of liver failure, the model for end-stage liver disease (MELD) score is not representative for these patients. In the Eurotransplant area, the level of priority can be upgraded after a waiting time of 12 months [12]. These patients must be managed as a MELD exception or with additional points similar to the patients with hepatocellular carcinoma on cirrhosis. Anyway, the unreliable representation by the MELD score, the increased perioperative risk in patients with severe cachexia and malnutrition and the excellent long-term results after transplantation suggest the need for earlier referral to the waiting list for transplant.

Liver Cell Adenoma and Liver Cell Adenomatosis

Liver cell adenoma is increasingly seen due to the widespread use of estrogen-based oral contraceptives (incidence of 3 per 1,000,000 per year); it is often diagnosed as an incidental finding in asymptomatic patients [14, 15]. It has been rarely reported in association with anabolic steroid use, glycogen storage disease, or Klinefelter's syndrome [15]. Symptomatic patients usually present with right upper quadrant pain and normal liver function tests. Spontaneous bleeding is a well-recognized complication which is often the cause of pain; it appeared in 20–40% of patients, in particular when the lesion was >5 cm, and is associated with an 8% risk of death [15, 16]. Another serious complication is the risk of malignant transformation in about 5% of patients [16, 17]. This risk does not disappear even in the case of regression of the adenoma after oral contraceptive discontinuation, while there is no report of de novo adenoma after primary resection of solitary cell adenoma [15, 17]. Liver transplantation has been reported in the treatment of solitary giant adenoma [4, 5]. However, with the improvements of surgical techniques and perioperative management, postoperative morbidity has been reduced after liver resection and the mortality rate is around 1% even after major hepatectomies [17, 18]. Surgical resection is therefore the treatment of choice for solitary liver cell adenomas >5 cm or complicated by hemorrhage or malignant transformation, and OLT should be abandoned.

Multiple adenomas occur in 10–24% of all patients with liver cell adenomas, developing a new clinical entity known as 'liver cell adenomatosis' which was first described in 1985 by Flejou et al. [19]. The typical findings of liver adenomatosis are the presence of multiple adenomas (arbitrarily more than 3 or 10), no association with oral contraceptives, no history of glycogen storage disease, predominant in women and with unknown etiology [15, 20]. The disease is related to a vascular liver problem due to altered hepatic parenchyma associated with steatosis, but the etiopathogenetic mechanism remains unknown [20, 21]. The largest review was published in 2008 reporting clinical characteristics, pathologic findings and surgical management of 94 patients with liver adenomatosis [21]. Diagnosis has usually been based on symptomatic hepatic nodules causing upper right quadrant pain. Intratumoral or intraperitoneal hemorrhage can be present in 46–63% of patients and is much more frequent compared to patients with solitary liver adenoma [21]; malignant transformation is less frequent. The risk of complications seems to be related more to the diameter of the largest nodule than to the number of nodules [17]. CT scan or MRI is the most useful method for diagnosis and for the strict follow-up that is required in these patients. The management of liver adenomatosis remains problematic. OLT has been reported in 6% of published series of liver adenomatosis and in more than 5% of liver transplantations performed for benign liver tumors in the USA and Europe [4, 5]. Indications for OLT were the progressive, symptomatic growth of the remaining adenomas after previous hepatectomy or when malignancy could not be ruled out [15].

Observation and strict follow-up are the basic requirements for management of liver adenomatosis; surveillance programs should include regular (annual) CT or MRI scanning and frequent serum α-protein measurement. In most patients with tumors >5 cm or complicated by bleeding, or when malignant transformation

cannot be excluded, liver resection is the treatment of choice; it is associated with relief of symptoms and optimal long-term results [17, 21]. All technical achievements should be used, including portal vein embolization to increase remnant hemi-liver and two-stage hepatectomy, to allow even extensive resections and remove most nodules, especially the larger ones. After the initial surgical approach, around 25% patients need a second operation and 43% of the remaining adenomas continue to grow [21]. Thus, we believe that in rare progressive symptomatic forms with multiple growing adenomas and a history of repeated complications or partial resection of larger lesions or increased serum α-fetoprotein level with concern about malignant transformation, liver transplantation should be considered the last therapeutic option.

Liver Hemangioma

Cavernous hepatic hemangioma is the most frequent benign liver tumor with a prevalence in autopsy and imaging studies of up to 7% [22]. The majority of hepatic hemangiomas should be managed conservatively.

When surgical resection is indicated, enucleation offers greater preservation of functional liver parenchyma with fewer complications and should be considered the technique of choice [23, 24].

Liver transplantation has been reported in very rare cases of huge hemangiomas [25]. According to a recent review, only 12 cases have been reported in the English literature and most of them were associated with the presence of Kasabach-Merritt syndrome characterized by coagulopathy, thrombocythemia, hypofibrinogenemia and fibrinolysis [25, 26]. Only 3 patients received liver transplantation for hepatic hemangiomas in the last 9 years in the USA [4]. Thus, considering the high incidence of liver hemangioma in the healthy population, OLT seems to be a very rare indication and is required only in exceptional cases. It is interesting to note that deceased donor liver grafts even with giant hemangiomas have been used for orthotopic transplantation, in two cases after enucleation at the back-table and in another case with the hemangioma left in place [27].

Infant hepatic hemangioma is a clinically different entity which must be distinguished from hemangioma in adults. According to the Infant Hepatic Hemangioma Registry based in Boston, infants with the diffuse type hemangioma are at greatest risk of death. Infants with hemodynamically significant shunting are candidates for steroids. However, 10–20% of patients refractory to medical therapy develop life-threatening complications, IVC compression and respiratory distress; for these patients OLT is the only suitable therapeutic option [28].

Hepatic Epithelioid Hemangioendothelioma

Primary hepatic epithelioid hemangioendothelioma (HEH) is a rare soft tissue vascular tumor with an intermediate clinical course between benign hemangioma and malignant angiosarcoma, first described in 1984 by Ishak et al. [29]. No definitive etiology has been confirmed as a causative factor, even if several factors have been correlated to HEH such as vinyl chloride, asbestos, thorotrast, etc. [30]. In 2006, a review of 434 patients reported in the literature showed that HEHs have a heterogeneous presentation in young patients (mean age 41.7 years): multifocal in 81% of patients and unifocal involvement of the liver in the other 19%; they are asymptomatic in 25% of patients, with varying degrees of symptoms (pain, discomfort, weight loss) going up to portal hypertension and liver failure in the remaining; in 36% of patients, an extrahepatic involvement was documented, lung, lymph nodes and bone were the most frequent sites [30]. Definitive diagnosis can be made by association of clinical and radiologic signs, such as multiple low-density intrahepatic nodules at CT scan, a hypervascularized central lesion, focal calcification in a young patient with good condition. As the tumor originates from endothelial cells, it presents positive staining for factor VIII as well as for CD31 and CD34 [22]. FDG-PET scan can be useful in the staging of the disease, particularly before OLT [31]. More than 50% of untreated patients died, although a few patients have been reported to survive without any therapy; systemic or locoregional chemotherapy as well as radiotherapy have been reported without significant success [22, 30]. Liver resection was the first treatment in 9.4% of patients; this is an acceptable therapy whenever a curative resection can be performed irrespective of extrahepatic disease. However, palliative resection should be avoided since the remaining nodules showed a very aggressive behavior after partial hepatectomy, probably due to the hepatic regeneration stimulated by the resection [30]. Liver transplantation has been the most frequent therapeutic option (44.8% of patients) [30]. Long-term results were satisfying with 5- and 10-year overall survival rates of 83 and 74%. This data was confirmed by a recent multicenter study of the European Liver Transplant Registry [32]

which analyzed 59 patients who underwent OLT for HEH. About a quarter of the patients developed recurrence after a median time of 49 months, but aggressive treatment using anti-angiogenetic therapies or rapamycin-based immunosuppression significantly prolonged survival [30, 32]. The role of retransplantation in the case of allograft recurrent disease is questionable on the basis of 1 patient who was retransplanted for recurrent disease and died [33]. Except the two communications by Mehrabi and Lerut, there are only two old reviews with 36 and 13 OLT for HEH and a few case series [30, 32, 34, 35]. These studies confirm that lymph node invasion and minimal extrahepatic disease are not a contraindication to OLT. Only the presence of macrovascular invasion significantly affected long-term outcome [32]. The role of OLT is questioned on the basis that spontaneous long-term survivors have been reported, and because of the high percentage of extrahepatic disease and the risk of recurrent disease [30, 34, 35]. However, most of the published series reported satisfactory long-term results with 5-year survival close to 71% and 5-year disease-survival free over 65% [30, 32, 36]. From the data available in the literature, OLT should be proposed earlier in the disease course of HEH and, due to the incidence of extrahepatic disease and graft recurrence, anti-angiogenetic adjuvant treatment using anti-vascular endothelial growth factor should be introduced routinely; retransplantation could also be re-evaluated.

Caroli's Disease and Caroli's Syndrome

Caroli's disease is a rare congenital disease characterized by gross segmental dilatation of the intrahepatic bile ducts causing a macroscopic appearance of intrahepatic multiple cysts; it is included in type IVa and V of Todani's classification for choledochal cysts and combined with polycystic renal disease in a few cases [37, 38]. It can be associated with hepatic fibrosis which is a different entity, named Caroli's syndrome [39]. Clinically, it is dominated by episodes of cholangitis which might become frequent with a dismal long-term outcome. Liver resection is the treatment of choice in the case of monolobar forms and absence of congenital hepatic fibrosis; conservative management with percutaneous or endoscopic drainage and stent or hepaticojejunostomy have failed in the definitive solution of symptoms and are considered palliative treatments [40]. Liver transplantation has been reported only in small case series and no clear guidelines are available [39, 40]. In a recent review of 110 liver transplantation for Caroli's disease or syndrome, the 5-year patient and graft survival were 86 and 71%, respectively [40]. Early postoperative outcome has been affected by a high incidence of septic and vascular complications; however, the long-term outcome in patients surviving more than 1 year after OLT was excellent [39, 40].

Since cholangitis is the principle cause of morbidity and mortality, OLT should be advocated earlier during the natural history of the 'diffuse type' of Caroli's disease with recurrent biliary infections and an aggressive management to prevent and treat septic complications both pre- and post-OLT is warranted to improve long-term results [39, 40]. Usually, these patients do not present symptoms of liver failure and are not represented by MELD score. In cases of Caroli's disease with recurrent cholangitis, an exception to MELD score and the use of an upgrade of priority after a few months on the waiting list should be considered. Liver transplantation is the treatment of choice even in patients with Caroli's syndrome when the association with congenital hepatic fibrosis can lead to develop signs of portal hypertension with ascites and esophageal varices. In patients with concomitant end-stage renal disease due to the polycystic kidney, combined liver-kidney transplantation is advisable.

Chronic episodes of cholangitis with formation of liver abscesses can be complicated by the occurrence of cholangiocarcinoma in 7% up to 14% of patients [40, 41]. The diagnosis of cholangiocarcinoma in these cases is quite difficult and no clear clinical or biochemical parameters seem to allow an early diagnosis; a precise timeline in relation to malignant degeneration is not yet defined. Liver transplantation as a preemptive therapy for the risk of cholangiocarcinoma in asymptomatic patients with Caroli's disease might be considered, but at the moment it is still debated.

Other Rare Indications for Liver Transplantation

Liver transplantation has rarely been performed for other benign hepatic tumors which are grouped together since there are only case reports or small case series reported in the literature.

Alveolar echinococcosis is an infectious disease caused by *Echinococcus multilocularis* which grows primarily in the liver of infected, generally young patients, developing as a tumor-like lesion. Without appropriate treatment, most patients die within 10 years [42]. Benzimidazole

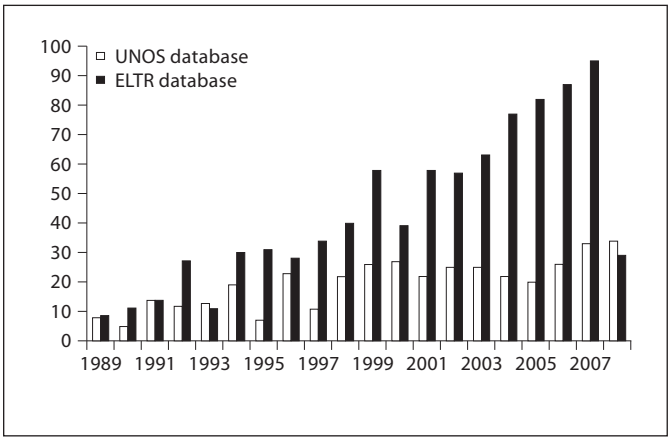

Fig. 1. Number/year of liver transplantation for benign hepatic tumors in the last 20 years in the USA and Europe.

seems to be effective in prolonging survival. Liver resection is the treatment of choice, and can be useful in the early phase of the disease. However, half the patients develop severe complications such as liver abscesses, recurrent cholangitis, secondary biliary cirrhosis, or Budd-Chiari syndrome [42, 43]. In these cases, liver transplantation remains the only option. In 2003, a review reported the results of 47 OLTs performed in Europe (mainly in France in Besançon). In half the patients, additional resective procedures were required, such as diaphragm resection and adrenalectomy; 10 patients required reoperation mainly for hemoperitoneum. Early postoperative outcome was affected by severe septic complications and 5-year survival was 58% [43]. Interestingly, only 2 of the 47 OLTs were performed after 2000. It seems that the introduction of benzimidazole therapy and a better patient selection has dramatically reduced the need for liver transplantation for this indication to only extremely selected cases.

Nodular regenerative hyperplasia (NRH) is an uncommon disease characterized by the presence of multiple, small non-fibrotic nodules (<1 cm) probably due to vascular abnormalities which are the main cause of intrahepatic non-cirrhotic portal hypertension [44]. It has been associated with several diseases including Budd-Chiari syndrome, myeloproliferative disorders, and connective-tissue disease. A few cases of liver transplantation have been reported in the literature [26, 44]; in most patients, successful long-term outcome was achieved. Recurrent NRH has been reported in the graft, but only rarely was retransplantation needed. NRH has also been described as a complication of immunosuppression using azathioprine, living donor transplantation using small-for-size grafts, and recipients receiving OLT for biliary diseases [26].

Despite the good long-term results, OLT should be considered a reasonable indication only for patients with end-stage disease when NRH is associated with severe symptoms of portal hypertension.

Hepatic lymphangiomatosis is a rare disease characterized by abnormal lymphatic proliferation causing intrahepatic cystic or cavernous lesions in the liver, spleen, and lungs which may cause organ dysfunction by compression or replacement of adjacent parenchyma. Four cases of liver transplantation have been reported; all of them were women and in 3 cases the long-term outcome was successful [45].

Other rare indications for liver transplantation for benign hepatic tumors massively involving the liver and usually associated with other hepatic diseases were inflammatory pseudotumors, mesenchymal hamartoma, and focal nodular hyperplasia [46–48].

Discussion

Liver transplantation is a rare indication for benign hepatic tumors; ELTR and UNOS data show that only 1% of transplants were performed for this indication with satisfying long-term results [4, 5]. In 70% of cases, polycystic liver disease with severe malnutrition and impairment of quality of life was the most common indication associated or not with renal transplantation for the presence of renal failure due to polycystic kidney disease. The remaining 30% were performed for different types of benign hepatic lesions (table 1).

In the last few decades, the total number of OLTs performed for benign liver tumors per year has been constant, with a slight increase in Europe (fig. 1). In fact, most benign lesions do not require any treatment and should be managed conservatively. Nowadays, whenever these tumors become symptomatic, or malignant transformation cannot be ruled out, liver resection is the gold standard since even extended hepatectomy can be performed with acceptable risks thanks to the improvements in technique and perioperative management in the tertiary referral centers for hepatobiliary surgery.

However, when benign tumors present life-threatening complications and are not amenable to liver resection due to their intrahepatic diffusion and extent or because of functional impairment, liver transplantation may be considered as a valid therapeutic option before patients become too sick.

Acknowledgments

We thank Drs Massimo Del Gaudio, Matteo Ravaioli, Matteo Cescon, Matteo Zanello and Alessandro Cucchetti for their contribution to this article, and the UNOS (United Network for Organ Sharing) and ELTR (European Liver Transplant Registry) for making their data available.

References

1 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. Transpl Proc 2008;40:1759–1762.
2 Dimick JB, Cowan JA, Knol JA, et al: Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database. Arch Surg 2003;138:185–191.
3 Colli A, Fraquelli M, Massironi S, Colucci A, Paggi S, Conte D: Elective surgery for benign liver tumors. Cochrane Database Syst Rev 2009:2:1–17.
4 UNOS database, based on OPTN data as of May 15, 2009 (www.unos.org).
5 ELTR database, update to December 31, 2008 (www.eltr.org).
6 Everson GT, Taylor MR, Doctor RB: Polycystic disease of the liver. Hepatology 2004;40:774–782.
7 Gabow PA, Johnson AM, Kaehny WA, et al: Risk factors for the development of hepatic cysts in autosomal dominant polycystic kidney disease. Hepatology 1990;11:1033–1037.
8 Perrone RD, Ruthazer T, Terrin NC: Survival after end-stage renal disease in autosomal dominant polycystic kidney disease: contribution of extrarenal complications to mortality. Am J Kidney Dis 2001;38:777–784.
9 Que F, Nagorney DM, Gross JB, Torres VE: Liver resection and cyst fenestration in the treatment of severe polycystic liver disease. Gastroenterology 1995;108:487–494.
10 Cavallari G, Nardo B, Montalti R, et al: Combined liver-kidney transplantation: experience at Bologna's transplant center. Transpl Proc 2004 36:541–542.
11 Ueno T, Barri Y, Netto G, et al: Liver and kidney transplantation for polycystic liver and kidney-renal function and outcome. Transplantation 2006;82:501–507.
12 Kirchner G, Rifai K, Cantz T, et al: Outcome and quality of life in patients with polycystic liver disease after liver or combined liver-kidney transplantation. Liver Transpl 2006;12:1268–1277.
13 Lerut J, Ciccarelli O, Rutgers M, et al: Liver transplantation with preservation of the inferior vena cava in case of symptomatic adult polycystic disease. Transpl Int 2005;18:513–518.
14 Rosenberg L: The risk of liver neoplasm in relation to combined oral contraceptives use. Contraception 1991;43:643–652.
15 Barthelmes L, Tait I: Liver cell adenoma and liver cell adenomatosis. HPB (Oxford) 2005;7:186–196.
16 Cho SW, Marsh JW, Steel J, et al: Surgical management of hepatocellular adenoma: take it or leave it? Ann Surg Oncol 2008;15:2795–2803.
17 Dokmak S, Paradis V, Vilgrain V, et al: A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. Gastroenterology 2009;137:1698–1705.
18 Cescon M, Vetrone G, Grazi GL, et al: Trends in perioperative out come after hepatic resection: analysis of 1,500 consecutive unselected cases over 20 years. Ann Surg 2009;249:995–1002.
19 Flejou JF, Barge J, Menu Y, et al: Liver adenomatosis. An entity distinct from liver adenoma? Gastroenterology 1985;89:1132–1138.
20 Cliché L, Dao T, Salamè E, et al: Liver adenomatosis: reappraisal, diagnosis, and surgical management. Ann Surg 2000;231:74–81.
21 Vetelainen R, Erdogan D, De Graaf W, et al: Liver adenomatosis: re-evaluation of aetiology and management. Liver Int 2008;499–508.
22 Bioulac-Sage P, Laumonier H, Laurent C, Blanc JF, Balabaud C: Benign and malignant vascular tumors of the liver in adults. Semin Liver Dis 2008;28:302–314.
23 Erdogan D, Busch O, Delden O, et al: Management of liver haemangiomas according to size and symptoms. J Gastroenterol Hepatol 2007;22:1953–1958.
24 Herman P, Costa M, Machado M, et al: Management of hepatic hemangiomas: a 14-year experience. J Gastrointest Surg 2005;9:853–859.
25 Ferraz A, Sette M, Maia M, et al: Liver transplant for the treatment of giant hepatic hemangioma. Liver Transpl 2004;10:1436–1437.
26 Lerut J, Weber M, Orlando G, Dutkowski P: Vascular and rare liver tumors: a good indication for liver transplantation? J Hepatol 2007;47:454–475.
27 Ortiz WA, Kelly D, Winans C, et al: Expanding the donor pool: safe transplantation of a cadaveric liver allograft with a 10-cm cavernous hemangioma – a case report. Liver Transpl 2006;12:687–689.
28 Christison-Lagay E, Burrows P, Alomari A, et al: Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. J Pediatr Surg 2007;42:62–68.
29 Ishak KG, Sesterhenn IA, Goodman ZD, et al: Epithelioid haemangioendothelioma of the liver. A rare hepatic tumor. Hum Pathol 1984;15:839–853.
30 Mehrabi A, Kashfi A, Fonouni H, et al: Primary malignant hepatic epithelioid hemangioendothelioma. A comprehensive review of the literature with emphasis on the surgical therapy. Cancer 2006;107:2108–21.
31 Nguyen BD: Epithelioid haemangioendothelioma of the liver with ^{18}F-FDG PET imaging. Clin Nucl Med 2004;29:828–830.

32 Lerut J, Orlando G, Adam R, et al: The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma. Report of the European Liver Transplant Registry. Ann Surg 2007;246:949–957.
33 Demetris AJ, Minervini M, Raikow RB, et al: Hepatic epithelioid haemangioendothelioma: biological questions based on pattern of recurrence in an allograft and tumor immunophenotype. Am J Surg Pathol 1997;21: 263–270.
34 Lauffer JM, Zimmermann A, Krahenbuhl, et al: Epithelioid haemangioendothelioma of the liver. A rare hepatic tumor. Cancer 1996; 78:2318–2327.
35 Maklouf HR, Iashak KG, Goodman ZD: Epithelioid haemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer 1999;85:562–582.
36 Ben-Haim M, Roayaie S, Ye M, et al: Hepatic epithelioid haemangioendothelioma: Resection or transplantation, which and when? Liver Transpl Surg 1999;6:526–531.
37 Caroli J, Couinaud C: Une affection nouvelle, sans doute congénitale, des voies biliaires: la dilatation kystique unilobaire des canaux hépatiques. Sem Hop Paris 1958;14: 496–502.
38 Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K: Congenital bile ducts cysts: classification, operative procedures and review of 37 cases, including cancer arising from choledochal cyst. Am J Surg 1977;134: 263–269.
39 Habib S, Shakil O, Couto O, et al: Caroli's disease and orthotopic liver transplantation. Liver Transpl 2006;12:416–421.
40 De Kerckhove L, De Meyer M, Verbaandert C, et al: The place of liver transplantation in Caroli's disease and syndrome. Transpl Int 2006;19:381–388.
41 Chapman RW: Risk factors for biliary tract carcinogenesis. Ann Oncol 1999;10(suppl 4):308.
42 Xia D, Yan L, Zeng Y, et al: Orthotopic liver transplantation for incurable alveolar echinococcosis: report of five cases from West China. Transpl Proc 2005;37:2181–2184.
43 Bresson-Hadni S, Koch S, Miguet JP, et al: Indications and results of liver transplantation for *Echinococcus* alveolar infection. Lang Arch Surg 2003;388:231–238.
44 Krasinkas AM, Eghtesad B, Kamath P, Demetris AJ, Abraham SC: Liver transplantation for severe intrahepatic non-cirrhotic portal hypertension. Liver Transpl 2005;11: 627–634.
45 Ra S, Bradley R, Fishbein M, Busuttil R, Lu D, Lassman C: Recurrent hepatic lymphangiomatosis after orthotopic liver transplantation. Liver Transpl 2007;13:1593–1597.
46 Herraiz A, Torres-Quevedo R, Pallardo J: Transplante hepatico en pacientes con lesiones hepaticas benignas. Cir Esp 2008;84:60–66.
47 Hernandez JC, Alfonso C, Gonzales L, et al: Solid mesenchymal hamartoma in an adult: a case report. J Clin Pathol 2006;59:542–545.
48 Fujita S, Mekeel KL, Fujikawa T, et al: Liver-occupying focal nodular hyperplasia and adenomatosis associated with intrahepatic portal vein agenesis requiring orthotopic liver transplantation. Transplantation 2006;81: 490–491.