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REVIEW ARTICLE

Liver cell adenoma and liver cell adenomatosis

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Abstract
During the last three decades liver cell adenoma and liver cell adenomatosis have emerged as new clinical entities in hepatological practice due to the widespread use of oral contraceptives and increased imaging of the liver. On review of published series there is evidence that 10% of liver cell adenomas progress to hepatocellular carcinoma, diagnosis is best made by open or laparoscopic excision biopsy, and the preferred treatment modality is resection of the liver cell adenoma to prevent bleeding and malignant transformation. In liver cell adenomatosis, the association with oral contraceptive use is not as high as in solitary liver cell adenomas. The risk of malignant transformation is not increased compared with solitary liver cell adenomas. Treatment consists of close monitoring and imaging, resection of superficially located, large (>4 cm) or growing liver cell adenomas. Liver transplantation is the last resort in case of substantive concern about malignant transformation or for large, painful adenomas in liver cell adenomatosis after treatment attempts by liver resection.

Key Words: *Liver cell adenoma, liver cell adenomatosis*

The prevalence of patients with liver cell adenoma is increasingly seen within hepatology practice due to the widespread use of oestrogen-based oral contraceptives, and due to the increased use of cross-sectional imaging for a variety of unrelated reasons. Consequently many lesions are identified as incidental findings in asymptomatic patients. The clinical significance and natural history of these incidental solid liver lesions is not fully understood, and there is a need for an optimal management strategy in such patients.

Liver cell adenoma is a benign neoplasm of the liver that has significant aetiological association with the oral contraceptive pill in young women. Liver cell adenoma secondary to oestrogen/progestogen ingestion is usually solitary, but some people may develop several adenomas disseminated throughout the liver. This latter condition is known as liver cell adenomatosis, does not have the strong association with oestrogen or anabolic steroid ingestion, and affects males more readily [1].

This article presents the current knowledge and optimal therapeutic strategies for patients with solitary liver cell adenoma and liver cell adenomatosis.

Background

Liver cell adenoma is the most important benign epithelial tumour of the liver, and has an estimated incidence of 3 per 1 000 000 per year [2]. The annual incidence is substantially higher with long-term oral contraceptive use, estimated at 3–4 per 100 000 [3], but may be less with newer oral contraceptives [4].

Liver cell adenoma was first described by Edmondson [5] in 1958 as an encapsulated liver tumour that does not contain bile ducts, when he identified two such lesions in 50 000 autopsies. In 1973, Baum [6] reported the important relationship between oral contraceptive use and the development of liver cell adenomas in seven patients. Several subsequent case series [7,8] in the 1970s supported the hypothesis of an association between the oral contraceptive pill and liver cell adenoma, and in 1976 Edmondson [9] published a case-control study giving further evidence of this association. The causal relationship between oral contraceptive medication and liver cell adenoma appears to be proportional to the hormonal dose and duration of medication [3,10,11], and is highest in women over 30 years of age after using oral contraceptives for more than 24 months. It is estimated the risk of developing an adenoma increases by a factor of 5 after 5 years, and by 25 after 9 years of oral contraceptive usage [11]. Regression of the tumour may occur after cessation of oral contraceptive usage [12], and there are reports of progression to hepatocellular carcinoma many years after stopping oral contraceptives [13–15]. Pregnancy appears to stimulate rapid

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growth in these lesions with risk of potentially fatal spontaneous rupture, and should be avoided in women of childbearing age [3].

Other possible aetiologies of liver cell adenoma include clomiphene [16], methyl testosterone [17], danazol [18], Klinefelter's syndrome [19], Types I, III and IV glycogen storage disease [20,21], and familial adenomatous polyposis [22].

Liver cell adenoma is usually a solitary nodule that may reach 30 cm in diameter. Macroscopically these lesions are smooth and soft on palpation, and range in colour from white to yellow to brown. On histological examination adenomas consist of cords of hepatocytes that have a high glycogen and fat content. The normal hepatic parenchymal architecture is lacking, with an absence of portal tracts and hepatic veins.

Liver cell adenomatosis is present in 10%–24% [23–25] of patients with liver cell adenoma and presents specific management difficulties. Liver cell adenomatosis was originally thought to affect males and females equally, but the most recent series report a female : male ratio of 7 : 1 and 15 : 1, respectively [26,27]. There is a strong association between liver cell adenomatosis and glycogen storage disease, but the association of liver cell adenomatosis and oral contraceptive or androgenic steroid use [1] is uncertain.

Presentation and diagnosis

Symptomatic patients usually present with right upper quadrant pain secondary to bleeding within the liver cell adenoma. At initial presentation these symptoms are often attributed to cholecystitis, the most common diagnosis in this patient population. Liver function tests may be abnormal secondary to necrosis or haemorrhage, and alkaline phosphatase is often elevated in those with liver cell adenomatosis. Some present with an acute abdomen and life threatening haemorrhage secondary to an uncontained rupture and bleeding into the peritoneal cavity, but most have a more indolent clinical presentation.

Some liver cell adenomas are picked up incidentally during imaging studies of the liver or noted during laparoscopic cholecystectomy. The differential diagnosis includes focal nodular hyperplasia, a benign liver lesion of vascular origin, and well-differentiated hepatocellular carcinoma. These two lesions can be difficult to differentiate from adenoma and remain the diagnostic challenge as they have different therapeutic implications. Patients with focal nodular hyperplasia are less likely to be symptomatic or have deranged liver function tests [28,29].

The ultrasonographic features of liver cell adenomas are non-specific and may appear iso-, hypo-, or hyperechoic. The classical appearance is of a well-demarcated hyper-echoic mass, but central necrosis or haemorrhage gives rise to heterogeneous echogenicity that simulates that of focal nodular hyperplasia [30]. The CT appearances of adenoma may be quite variable, but the classical lesion characteristics are best appreciated with multi-phase helical CT scanning. Liver cell adenoma shows early phase peripheral contrast enhancement and subsequent centripetal contrast enhancement [31]. The pattern of perfusion starting at the periphery can be demonstrated on angiography and has been used to differentiate liver cell adenomas from focal nodular hyperplasia where the vascular supply arises centrally from a feeding artery leading to rapid filling of the suprahepatic vein ('spoke wheel' appearance) [32].

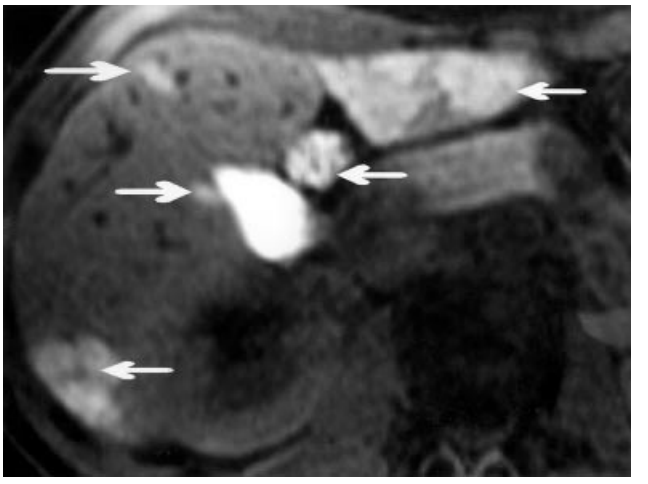

Figure 1. Teslascan MRI at 24 hours after injection: uptake of contrast in left lobe and lateral aspect of right lobe by multiple adenomas (arrows).

Magnetic resonance imaging has the optimal sensitivity for lesion detection, but again characterization of the lesion can be variable. Ultra-fast sequences with breath-holding and gadolinium contrast provide most information [27,33,34], and surveillance of patients with liver cell adenomatosis is highly effective using a delayed teslascan 24 hours after injection of gadolinium (see Figure 1). Even with these advances it may be impossible to differentiate liver cell adenoma from focal nodular hyperplasia or hepatocellular carcinoma, and a biopsy is then essential for histological clarification.

Lesion biopsy

Percutaneous biopsy of a liver lesion is not to be recommended in young fit patients as this can induce bleeding and tumour dissemination, does not exclude malignancy if normal tissue is found, and may be inaccurate. In a study by Charny *et al.*, only 11 of 30 biopsies were accurate [35]. There are numerous case reports of women using oral contraceptives who develop hepatocellular carcinomas, but preoperative or operative liver needle biopsies reveal liver cell adenomas only [14,36–39] (Table I). Excision biopsy of liver lesions either by open surgery, or laparoscopically [40], is the gold standard method for diagnosis. Even with tumour tissue, accurate microscopic differentiation between benign liver cell adenomas and hepatocellular

Table I. Malignant transformation of liver adenomas

	Length of OC use	αFP	Liver biopsy	Specimen analysis/particularities
Davis M, 1975 [62]	2 years	normal	–	Well-differentiated hepatocellular carcinoma (HCC) in adenoma
Pryvor AC, 1977 [36]	12 years	normal	liver adenoma	Well-differentiated HCC in adenoma
Tesluk H, 1981 [14]	5 years	normal	liver adenoma	Adenoma regressed after OC stop, but did not disappear, 3 years later development of HCC.
Gordon SC, 1986 [15]	14 years	normal	–	Adenoma regressed after stop of OC; 5 years later development of HCC
Gyorffy EJ, 1989 [63]	19 years	initially normal, later on elevated	–	Initial percutaneous liver biopsy: liver adenoma Repeat biopsy 3 years later: HCC
Korula J, 1991 [37]	21 years	normal	liver adenoma	Well-differentiated HCC in adenoma
Ferrell DL, 1993 [38]	for 6 months, 5 years before presentation	unknown	liver adenoma	Well-differentiated HCC within multilobular adenoma
Herman P, 1994 [39]	15 years	unknown	–	Well-differentiated HCC in adenoma
	20 years	unknown	benign	Well-differentiated HCC in adenoma
Perret AG, 1996 [64]	3 years	normal	–	Disseminated foci of HCC in 14 cm multilobular adenoma
Ye MQ, 1999 [65]	25 years	normal	–	Well-differentiated HCC in adenoma

OC = oral contraceptives. HCC = hepatocellular carcinoma. αFP = α-fetoprotein.

carcinoma can be difficult. QBend 10- and erbB2-immunostaining [41,42], comparative genomic in situ hybridization [43], and fluorescence in-situ hybridization [44] may differentiate between hepatic adenoma and hepatocellular carcinoma but have not yet entered routine clinical practice.

Complications and management of solitary liver cell adenoma

Haemorrhage

This is a well-recognized complication of solitary liver cell adenoma [45–47] and is often the cause of pain in symptomatic patients. The morphology of adenomas with their extensive proliferation of blood-filled sinusoids, supplied by high-pressure arterial flow, and poor soft tissue support, makes them prone to bleed. The frequency of this complication is difficult to estimate, as this data is omitted in most case series, and many patients are advised to undergo resection of solitary liver cell adenoma at diagnosis to prevent a later presentation with tumour bleeding.

The risk of spontaneous bleeding into, or from, a ruptured adenoma, is likely to be between 20% and 40%. Selected series have demonstrated evidence of bleeding on microscopy in 4 of 10 patients [23], 3 of 15 patients on ultrasound, and 4 of 10 patients on contrast CT [28]. Most bleeding is contained and does not present a life-threatening event, but bleeding from a liver cell adenoma can be fatal [48], and in the series reported by Rooks, 6 of 79 patients (8%) with liver cell adenoma died due to bleeding [3].

It has been suggested that adenomas greater than 5 cm in diameter should be excised as they are at increased risk of bleeding [49]. However, Flowers [50] and Minami [51] reported patients with massive bleeding from adenomas of only 3.5 cm diameter, with one patient fatality in the postoperative period. In contrast, other patients with large adenomas have been observed for prolonged periods without evidence of bleeding. Currently there is no evidence to correlate risk of bleeding with size or number of liver cell adenomas.

There are numerous reports of bleeding liver cell adenomas during pregnancy and the puerperium, and women with known liver cell adenomas should be strongly advised not to become pregnant [3,52–59]. Excision of a liver cell adenoma has been successfully performed during the second trimester [52]. Given this risk and the unpredictable natural history of solitary liver cell adenoma with respect to bleeding, the majority of patients should be advised to undergo surgical resection.

Patients who present with bleeding or rupture will require surgical resection. However, the extent of resection and mortality can be reduced by delaying surgery to allow stabilization of the patient. Interventional radiological procedures such as hepatic artery embolization are a useful adjunct in this situation [60]. Depending on the severity of bleeding the options are emergency excision on presentation, elective excision after haemodynamic stabilization or conservative management with delayed excision [61].

Malignant transformation in solitary liver cell adenoma

There are numerous reports of malignant transformation of liver cell adenoma to hepatocellular carcinoma [14,15,37–39,62–65]. Most reported cases are associated with oral contraceptive use for a prolonged period of time. α-fetoprotein levels are often within normal range in these patients and thus a poor indicator of tumour progression (Table I).

Most cases of hepatocellular carcinoma develop at the site of the liver cell adenoma lending support to the

Table II. Adenoma series

	Patients	Hepatocellular carcinoma	Male	Rupture	Bleeding	Oral contraceptive use
Weil R, 1979 [68]	8	0	1			
Kerlin P, 1983 [69]	23	2	2			19 : 23
Leese T, 1988 [24]	18	0				16 : 18
Flowers BF, 1990 [50]	6	0	1	2		5 : 5
Belghiti J, 1993 [70]	13	1				
Cherqui D, 1995 [28]	6	0		2	CT 3 : 6 MRI 3 : 5	5 : 6
Nagorney DM, 1995 [71]	24	2	2	2	2	9 : 22
Ault GT, 1996 [60]	11	3	1			9 : 10
DeCarlis L, 1997 [72]	19	2				17 : 19
Weimann A, 1997 [29]	44	3	1		6	
Ichikawa T, 2000 [73]	25	2	4		CT 11 : 44	12 : 21
Reddy KR, 2001 [74]	25	1		3		22 : 25
Charny CK, 2001 [75]	12	1	2			
Marini P, 2002 [61]	7	1		6	7	7 : 7

hypothesis of a progressive adenoma-carcinoma sequence. However, some pathologists debate the malignant potential of liver cell adenomas and consider them as the end-stage of hepatocyte proliferation induced by anabolic steroids [66]. The international working party of hepatocellular lesions takes a cautious view on the question of malignant potential of liver cell adenomas and states that 'malignant progression has been reported, but is rare' [67]. Of the 14 series on liver cell adenoma reported to date [24,28,29,50,60,61, 68–75], 10 series [29,60,61,69–75] have reported progression or *de novo* development of hepatocellular carcinoma within the liver cell adenoma and this occurs with a frequency of 1 : 12 to 1 : 9 (i.e. 8%–11%) (Table II). Five of the 10 series [60,67,69,70,73] specified follow-up ranging between 16–81 months. One patient died from progressive hepatocellular carcinoma 18 months following resection [69]. There have been no reports of recurrence or progression to liver cell carcinoma in the other patients.

There is a real risk of malignant transformation in the order of 10%, and this should be seriously considered when advising patients.

Tao states that oral contraceptive-induced liver cell adenomas are reversible if oral contraceptives are discontinued within a certain time period, and that after prolonged oral contraceptive usage dysplastic foci develop within the liver cell adenoma that progress to hepatocellular carcinomas [76].

Fully developed cancers have extensive genomic damage as the result of their genetic instability ('bystander effect') [77]. Pre-cancerous and benign tumours have less genetic alterations. Liver cell adenomas attracted the attention of genetic research in recent years to identify the initial critical genetic event in the development of hepatocellular carcinoma. Results are yet inconclusive and summarized in Table III.

The etiological role of oral contraceptives in inducing liver cell adenoma is beyond doubt, and many studies have shown regression and even complete resolution of adenomas after cessation of the oral contraceptive pill [90–97]. This observation is not consistent, as others have not noted any change in the size of existing liver cell adenomas after discontinuation of oral contraceptives [98,99]. It probably correlates with the observation that the detection of hormone receptors in liver cell adenomas varies between 26% and 73% [100,101]. Discontinuation of oral contraceptives before surgery is worthwhile, as this may facilitate adenoma regression and reduce the extent of liver resection.

It is important to note that even complete resolution of the adenoma does not prevent the late occurrence of hepatocellular carcinoma, as this has been observed 3–5 years after cessation of oral contraceptive usage and regression of the adenoma [14,15]. In contrast, there are no reports of *de novo* adenoma occurrence or formation of hepatocellular carcinoma after primary resection of solitary liver cell adenoma. This provides a strong argument in favour of liver resection as the primary treatment for solitary liver cell adenoma.

Resection of solitary liver cell adenoma

Prevention of bleeding and/or malignant transformation is guaranteed with surgical resection, but there is morbidity and mortality associated with surgical resection. Depending on experience, the morbidity associated with liver resection for benign tumours ranges from 10% to 27%, and mortality from 0% to 3% [49,70].

Despite the risk associated with surgery, we strongly favour surgical resection of solitary liver cell adenoma for four reasons. Firstly, the risk of malignant transformation is substantial (around 10%), and regression of liver cell adenomas after stopping oral contraceptives does not prevent late malignant transformation. Secondly, bleeding or rupture of a liver cell adenoma is common and unpredictable, occurring in

Table III. Genome analysis of liver adenomas

	Analysis	Interpretation	Results
Brunt EM, 1992 [78]	Immunohistochemistry of c-erbB-2 oncopeptide	Over-expressed in epithelial neoplasms	Negative in 2/2 liver adenomas
Ding SF, 1992 [79]	Southern blot of DNA from liver adenoma and HCC in one patient		Chromosome 17p13 loss comprising the p53 tumour suppressor gene in hepatocellular carcinoma, but not in liver adenoma
Nasarek A, 1995 [80]	Fluorescence in-situ hybridization of chromosomes 1 and 8	Common aberrations in hepatocellular carcinomas (HCC)	Negative
Gaffey MJ, 1996 [81]	PCR of HUMARA gene	Detects x-chromosome inactivation	Clonality in 2/2 liver adenomas
Paradis V, 1997 [82]	PCR of HUMARA gene	Detects x-chromosome inactivation	Clonality in 6/7 liver adenomas
Strassburg CP, 1997 [83]	Northern and Western blot analysis of UGT1A locus		UGT1A-locus downregulated in liver adenoma and HCC
D'Errico AD, 1998 [84]	IHC of CK 8, 18, 7, 19	Hepatocellular differentiation CK 8, 18 Biliary differentiation CK 8, 18, 7, 19	CK 8, 18 positive in 10/10 liver adenomas CK 7, 19 negative in 10/10 liver adenomas
De Boer CJ, 1999 [85]	IHC for Ep-Cam	Marker of early neoplasia in adult cells	Negative in 2/2 liver adenomas
Libbrecht L, 2001 [23]	IHC for CK 7, 8, 18, 19, chromogranin A, OV-6 and neural cell adhesion molecule (NCAM) as markers for hepatic progenitor cells	Hepatic progenitor cells present in 5/10 adenomas	Hepatic progenitor cells have potential role in hepatocarcinogenesis
Tannapfel A, 2002 [86]	PCR and fluorescence in-situ hybridization FISH for INK4-ARF inactivation and microdeletion of $p14^{ARF}$ and $p16^{INK4a}$	INK4a-ARF (CDKN2A) locus on chromosome 9p21 encodes the tumour suppressor proteins $p14^{ARF}$ and $p16^{INK4a}$ and is frequently inactivated in many human cancers	Alterations of $p14^{ARF}$ and $p16^{INK4a}$ in 3/25 and 6/25 liver adenomas, respectively, not necessarily associated with malignancy
Takayasu H, 2002 [87]	IHC for β-catenin, PCR of β-catenin gene	Genes for β-catenin involved in Wnt pathway, Wnt pathway activated in HCC	Nuclear accumulation of β-catenin in 2/2 liver adenomas, β-catenin gene mutation in 1/1 liver adenoma
Torbenson M, 2002 [88]	IHC for β-catenin and PCR of cluster region of adenomatosis polyposis coli protein. Loss of heterozygosity analysis of chromosome 5q	Genes for β-catenin and APC involved in Wnt pathway, Wnt pathway activated in HCC	Nuclear accumulation of β-catenin in 7/15 liver adenomas No mutation of β-catenin- and APC-gene, no LOH of 5q
Chen YJ, 2002 [89]	Comparative genomic hybridization	Frequent gains on chromosomal arms 1q (50%), 17q (50%), 1p (38%) and 11q (38%)	Genome alterations of liver adenomas coincide with those of HCC

IHC = immunohistochemistry. PCR = polymerase chain reaction. CK = cytokeratins.

30%–50% of such lesions. This bleeding is unrelated to lesion size or site, and may be fatal. Thirdly, it may be impossible to differentiate on radiology alone between an adenoma and a well-differentiated hepatocellular carcinoma. This necessitates resection and histological analysis to reassure patient and clinician. Finally, surgical resection provides a guaranteed long-term cure and no risk of tumour recurrence. Given these facts, surgical resection is presently the optimal treatment for all patients that present with solitary liver cell adenoma.

Liver cell adenomatosis

The same recommendation cannot be made for those who present with multiple adenomas within the liver. The clinical entity of liver cell adenomatosis was first proposed by Flejou *et al.* in 1985, who described 5 patients with multiple adenomas of the liver and collated this experience with 8 similar previous case reports. The characteristic features of liver cell adenomatosis proposed at that time were (a) arbitrarily more than 10 tumor nodules in the liver, (b) equal male/female distribution, (c) no association with oral contraceptives, (d) increased levels of serum alkaline phosphatase and γ-glutamyl transpeptidase [1].

Multiple adenomas occur in approximately 10%–24% of all patients with liver cell adenomas [23–25], and the reason for this remains obscure. Given the disparate and extensive distribution of lesions in liver cell adenomatosis, these patients present a more difficult management problem, as targeted adenoma excision as for solitary liver cell adenoma is not a practical option. Chiche *et al.* have suggested two distinct patterns of disease with liver cell adenomatosis [26]. The 'massive type' presents with gross hepatomegaly, a deformed liver contour, and contains many large tumour nodules ranging from 2–10 cm in diameter. The massive type may be rapidly progressive and presents a particular therapeutic challenge. The 'multifocal type' contains many adenomas up to 4 cm in diameter but the liver contour is not deformed or enlarged. These patients are unlikely to have symptoms and appear to have a less aggressive clinical course.

Risk of bleeding

As with solitary liver cell adenoma, patients with liver cell adenomatosis frequently present with right upper abdominal pain attributed to bleeding into the adenoma. As these patients have multiple lesions the risk of bleeding is substantially higher, occurring in 46% of patients in the series by Flejou *et al.* [1]. As it is not possible to resect all adenomatous lesions (except by liver transplantation), prophylactic liver resection to prevent bleeding must be targeted to those lesions at greatest risk of causing life-threatening haemorrhage. Large lesions >4 cm in diameter, and sub-capsular lesions that may bleed into the peritoneal cavity, should be considered for resection to prevent bleeding [102]. Of the 81 patients with liver cell adenomatosis described, 15 (18%) have presented with intra-abdominal bleeding [26,69,103–105], and two patients died on presentation from intraperitoneal haemorrhage [26,106].

Risk of malignancy

Chiche *et al.* challenge the malignant potential of adenomas in patients with liver cell adenomatosis [26], primarily as data in this regard are scant. However, six patients with undisputable liver cell adenomatosis are known to have undergone malignant transformation [24,25,27,107,108], with four of the six patients male. The original observation that liver cell adenomatosis affected men and women equally is no longer valid, as the majority of affected individuals (74%) to date are female [26]. Thus, male sex may be a risk factor for malignant transformation in liver cell adenomatosis. The 81 liver cell adenomatosis patients currently documented in the literature have an average documented follow-up of 57 months (range 3–180 months), at which time-point 41 patients have stable disease, 34 patients have progression of disease with increased size and/or number of lesions, and 6 (7%) have developed malignancy. At present there is no evidence to suggest that the risk of malignant transformation is increased in liver cell adenomatosis compared with that of solitary adenoma.

Liver transplantation for liver cell adenomatosis

The only potential cure for liver cell adenomatosis is liver transplantation, and therefore some have advised organ transplantation for this condition [69,70,109,110]. The benefit of liver transplantation to prevent bleeding or cancer in these young patients has to be balanced against the potential risk of transplantation. Perioperative mortality of liver transplantation is less than 1%, and 5- and 8-year survival are about 66% and 61% respectively. Most deaths (65%) occur within the first 6 months [111].

In the longer term, up to 11.5% of liver recipients have been reported to develop *de novo* tumours on immunosuppression [112], renal failure occurs in 10% after 10 years [113], and hypertension in more than 50% [114]. The rate of leakage or stenosis of the biliary anastomosis varies between 15% and 33% [115]. Rejection occurs in 3%–5% [116,117].

Of the 17 cases of liver transplantation for liver cell adenomatosis in the literature [24,27,108,118–120], outcome and survival are known for 10 patients (see Table IV). Average length of follow-up is 87 months (36–145 months). There was one death in the immediate postoperative period, and three patients have developed hepatocellular carcinomas in the transplanted liver or developed lung metastasis

Table IV. Results of liver transplantation for liver adenomatosis

	Age (years)/ Sex	Indication	Interval diagnosis—transplantation	Previous liver surgery	αFP	Survival	Status
Leese T, 1988 [24]	21/M		unknown	unknown		unknown	unknown
	14/M		5 years	left lobectomy	$\times 10^5$	13 months	alive
Tepetes K, 1995 [119]	10/F		3 years	explorat.laparotomy × 2		65 months	alive
	17/F		2 years	portocaval shunt		145 months	alive
	20/F		5 years	segmentectomy		101 months	alive
	31/F		2 years	segmentectomy		130 months	alive
	35/F		15 years	explorat.laparotomy × 2		36 months	alive
	43/F		6 months	trisegmentectomy		10 days	died of necrotizing pancreatitis
	46/F		1 year	trisegmentectomy		12 years	died of HCC 12 years after transplantation
Chiappa A, 1999 [120]	44/F	Progression of adenomatosis—liver failure	13 months	wedge excision of one adenoma	Normal	unknown	unknown
Grazioli L, 2000 [27]	36/M		unknown	unknown	Normal	unknown	unknown
	35/F		unknown	unknown		unknown	unknown
	19/F		unknown	unknown		unknown	unknown
	43/F		unknown	unknown		unknown	unknown
	46/F		1 year	trisegmentectomy		12 years	died of HCC 12 years after transplantation
Penna C, 2001 J Chir [118]	20/M	Progression liver adenomatosis—malignancy	5 years		Elevated	10 years	live
Yunta PJ, 2001 [108]	23/F	Progression liver adenomatosis—malignancy	diagnosis after transplantation		Elevated	27 months	alive with HCC in transplant liver

[27,108]. Two of these three patients did not have any evidence of malignancy in their native liver. Hepatocellular carcinoma in the transplanted organ became apparent 9 and 12 years after liver transplantation. This casts considerable doubt on the indication for transplantation in liver cell adenomatosis to prevent malignant transformation, as malignant progression can still occur despite transplantation.

Management of liver cell adenomatosis

Given the morbidity and mortality associated with liver transplantation, current world experience would support a more conservative approach as the optimal initial management strategy. Patients should be entered into a surveillance program that includes regular (annual) CT or MRI scanning, and frequent serum alpha-fetoprotein measurement to detect progression of disease (increased lesion size) and/or malignant transformation.

All female patients should be advised to stop hormone medication (e.g. oral contraceptives, hormone replacement therapy), and also ensure that they prevent further pregnancies. Patients presenting with intraperitoneal bleeding require laparotomy and resection of the bleeding tumour.

Those who have the massive form of liver cell adenomatosis may have a preponderance of large lesions within a single lobe, and are best managed by hemi-hepatectomy. Patients with multifocal liver cell adenomatosis should be monitored with regular liver imaging. Progression of disease with large subcapsular adenomas (>4 cm), concern of malignant transformation, and increasing symptoms are indications for resection in multifocal liver cell adenomatosis. Resection is the preferable option unless technically impossible. Orthotopic liver transplantation should be considered only as a last resort. Indications where transplantation is considered may include rise in serum alpha-fetoprotein, concern about malignant transformation on imaging, and symptomatic patients with marked hepatomegaly and a history of repeated adenoma complications [24,26].

Conclusion

Liver cell adenoma is the most important benign tumour of the liver because of its frequency and potential for complications which are life threatening: bleeding and malignant transformation. Despite significant progress in imaging, definite diagnosis is by excision biopsy.

Discontinuation of oral contraceptives is often associated with regression of the adenoma, but there is still a risk of malignant transformation. Because of the risks of bleeding and malignant transformation surgical excision is the preferred treatment option for solitary liver cell adenomas.

Liver cell adenomatosis provides a clinical challenge. Symptomatic tumours, which are accessible to surgery, should be resected. The role of transplantation remains unclear. Other treatment modalities such as embolization of bleeding tumours and radiofrequency ablation may be useful adjuncts in selected cases.

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