Chapter

Challenging Issues in Hepatic Adenoma

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Abstract

Hepatic adenoma is known as a benign lesion encountered mainly in female patients and classically linked to the administration of oral contraceptives. In the last decade, the risk factors for its occurrence have changed and so did the sex ratio. The histopathological classification of hepatic adenomas was found to be related with certain genetic mutations that determine the risk for malignancy. The diagnosis of hepatic tumor is correlated with clinical and imaging data in an effort not only to rule out other tumors but also to distinguish the subtype of adenoma, which is very important for the management of the patient. The ultimate diagnosis is established by pathologists by routine histopathological and specific immunohistochemical staining. There are two major issues that pathologists need to recognize: the presence of β-catenin gene mutation and/or malignant degeneration. The best imaging examination is considered to be MRI. However, along with MRI, ultrasound and computer tomography have proved themselves to be effective not only in evaluating the number, size, localization, and complications of hepatic adenomas, but also in identifying their subtype. A detailed presentation of characteristics of all groups of hepatic adenoma is provided. The means of management of hepatic adenomas are documented and decisional algorithm is explained, based on certain criteria.

Keywords: hepatic adenoma, hepatocellular adenoma, liver adenoma, adenomatosis, hepatectomy, laparoscopic hepatectomy, liver transplantation, liver imaging

1. Introduction

Hepatic adenoma (HA) is a rare, benign tumor of epithelial origin (2% of all liver tumors [1]) that develops usually in healthy liver [2] and is known to occur mainly in young female patients, having been linked to the prolonged use of oral contraceptives [3]. In Europe and North America, it has an incidence of 3/100,000/year [4]. Even though multiple hepatic adenomas have been described in the literature, this is a rare occurrence, most of the adenomas being solitary (70–80%), and thus, often asymptomatic unless they become complicated (voluminous adenomas causing upper quadrant pain and/or rupture of the tumor with hemoperitoneum and malignant transformation) [5]. Hepatocellular adenoma is a term sometimes used instead of hepatic adenoma, being correct in contradiction to liver adenoma

or liver cell adenoma, which are less desirable because these two can also include the bile duct adenoma [6]. Even though the prognosis of this type of tumor is not well established, it is important to differentiate it from other hepatic tumors since the hepatic adenoma has a particular therapeutic management. Differential diagnosis however can be challenging, but can be achieved preoperatively by imaging techniques. Positive diagnosis is a histopathological one and is often obtained postoperatively [7].

2. Epidemiology

The incidence of HA has increased in recent years, but at the same time, imaging techniques have improved, and therefore, this higher incidence might be explained by the better diagnostic techniques nowadays available. Also, in recent years, it seems to be a change in epidemiology, as more cases of HA in male patients are described, particularly in Europe and Asia. This may be caused by an increased incidence of obesity, another recognized risk factor of HA. Moreover, in recent years, more and more cases of malignant transformation of HA have been reported, and this also might be a result of improved histopathological diagnosis.

Although the link between HA and use or oral contraceptive in women of childbearing age is maintained, recent studies have shown other emerging important risk factors such as metabolic syndrome [8].

3. Risk factors

The most important risk factor seems to be the use of oral contraceptives. Hepatic adenoma used to be exceptionally rare before the age of oral contraceptives, but after these became popular as a contraceptive solution, more and more cases of HA were reported. In women who were long-time users of oral contraceptives, the incidence was 1 in 30–40,000, whereas in women who have never used oral contraceptives, the incidence was 1 in 1 million, which proves a strong link between these two. Hepatic adenomas in women with prolonged use of oral contraceptives tend to be more numerous, more voluminous, and with a higher risk of spontaneous rupture and bleeding [9–12].

Another important risk factor that became even more important than other known risk factors, such as glycogen storage diseases and diabetes mellitus type 2 alone, is the metabolic syndrome. Obesity is more and more prevalent in the general population, and thus, it became a more important risk factor in this pathology. Weight loss should be considered as the first therapeutic option in the management of HA in obese patients [13]. A recent study has proved that bariatric-induced weight loss results in significant regression of HA in severely obese women, which emphasizes the role of overweight in HA pathophysiology [14]. Even more so, patients with metabolic syndrome and hepatic adenomas seem to be associated with a higher rate of malignization [8]. The association between oral contraceptive use and metabolic syndrome on one hand and HA on the other tends to prove an important hormonal sensitivity of the tumor (obesity is associated with higher estrogen levels), and this is supported by the fact that adenomas may stop their evolution or even regress as a result of oral contraceptive cessation [15]. In spite of this, immunohistological studies failed to prove the direct effect of these hormones via steroid receptors in normal and adenomatous hepatic tissue, and so the mechanism by which high estrogen levels may cause an adenomatous transformation is still incompletely understood [16]. As a hyperestrogenic state, pregnancy has also been

incriminated as a risk factor, and there have been many reports of ruptured HAs in pregnant patients with a very high mortality for both mother and child [16–19].

Apart from estrogen, use of anabolic androgens has also been linked to a higher incidence in HAs, which is being proved not only in body builders but also in patients treated with steroids for Fanconi syndrome, aplastic anemia, etc. Cessation of steroid use has also been linked to regression in size of HAs [15].

Hepatic adenoma has also been linked to glycogen storage disease and hepatocyte nuclear factor 1A maturity onset diabetes of the young (HNF1A MODY). The incidence is 51% in patients with type I glycogen storage disease and 25% in those with type III glycogen storage disease (GSD) [8]. Hepatic adenoma in GSD occurs before the age of 20 years, is more common in males, and is typically multiple. Dietary therapy and correction of insulin, glucose, and glucagon levels have been proved to lead to regression of adenomas [15]. The mechanism by which GSD is involved in the development of HA is also unknown.

Finally, there seems to be a genetic predisposition, and nowadays, HAs are believed to result from specific genetic mutations involving TCF1 (transcription factor 1 gene), IL6ST (interleukin 6 signal transducer gene), and CTNNB1 (β catenin-1 gene) [20].

4. Pathology

HAs present as solitary lesions in most cases (70–80%), although multiple adenomas can exist of variable sizes. HAs usually occur in the right hepatic lobe. Macroscopically, HAs present as a smooth, tan-colored lesion, well demarcated from the normal hepatic tissue in spite of not having a capsule, often with areas of hemorrhage and necrosis (**Figure 1**). Large blood vessels that surround it are the source of hemorrhage in a complicated adenoma. The lack of a fibrous capsule means that the bleeding can extend into the liver parenchyma unrestricted.

Microscopically, adenomas are made of adenoma cells, which are typically larger than normal hepatocytes and contain glycogen and lipid inclusions (**Figures 2** and **3**). The nuclei are small and regular and mitoses are infrequent. The normal architecture of hepatic tissue is severely disrupted, with no portal tracts of bile ducts, while adenoma cells are disposed in trabeculae interspersed with arteries and thin-walled blood vessels and sinusoids. The absence of bile ducts is a notable feature that helps in the differential diagnosis of HA with non-neoplastic liver tissue and focal nodular hyperplasia. Kupffer cells may only rarely be present in HA.

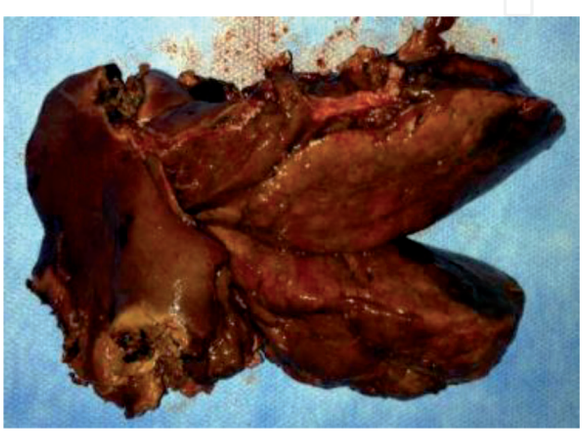


Figure 1.
Resected specimen after mesohepatectomy for a large IHA.

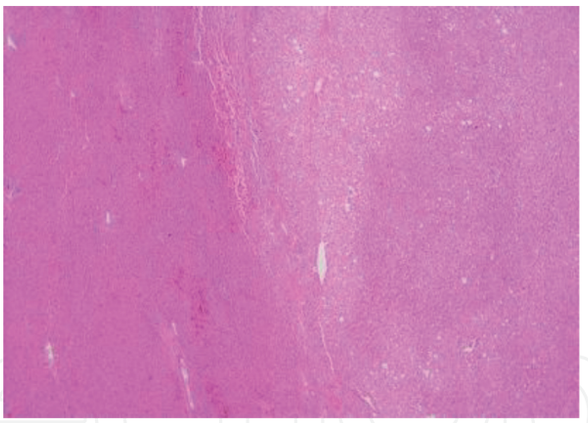


Figure 2.
Normal liver (left) and hepatocellular adenoma (right), HE ×40.

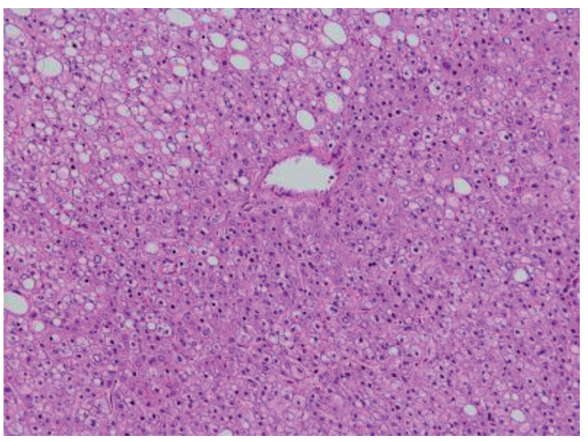


Figure 3.
Hepatocellular adenoma—benign hepatocytes (large, clear, and pale due to accumulation of glycogen) arranged in plates, cords, and sheets, HE ×200.

Similarities with a well differentiated hepatocellular carcinoma (Edmonson I) makes the differential diagnosis a challenging one.

Based on an extensively characterized clinical, morphological, phenotypical, and genotypical profile, four distinct subtypes of HA have been identified [3, 21]:

1. Hepatocyte nuclear factor-1 (HNF-1)—mutated HAs (H-HA)

2. β-Catenin-mutated hepatic adenomas (β-HA)

3. Inflammatory hepatic adenomas (which harbor mutations involving the interleukin-6 signal transducer) (IHA)

4. Unclassified hepatic adenomas (U-HA).

Inflammatory and HNF1-mutated hepatic adenomas are the most frequent subtypes (80%).

The first group (H-HA) comprises 35–40% of all patients and almost exclusively includes women. It is related to the presence of transcription factor 1 gene mutations that inactivate hepatocyte nuclear factor 1α (HNF-1α). The nonfunctioning HNF-1α protein promotes lipogenesis and hepatocellular proliferation. Moreover, abnormal HNF-1α protein determines silencing of liver fatty acid-binding protein FABP1. FABP1 is a gene positively regulated by HNF-1α and expressed in normal

liver tissue, but in H-HA its downregulation results in impaired fatty acid trafficking in hepatocytes, which causes intracellular fat deposition [22]. H-HA is sometimes associated with maturity-onset diabetes of the young (MODY), type 3, and familial hepatic adenomatosis. Half of these patients have multiple HAs. More than 90% have a history of oral contraceptive use. The tumors are characterized by marked steatosis (**Figures 4**–**7**), a very low risk of complications, and a low risk of malignant transformation. On immunohistochemistry staining, H-HA is LFABP (liver fatty acid binding protein) negative, which is in contrast with normal expression in the surrounding nontumoral liver [21]. The sharp contrast between tumor and adjacent parenchyma in terms of steatosis and LFABP expression enables delineation of tumor borders which are often irregular and lobulated with often small HA foci in vicinity.

The second group comprises 10–15% of all patients, includes mainly men, and is characterized by the presence of mutations that activate β-catenin and cellular abnormalities. β-Catenin is encoded by catenin β 1 gene (CTNNB1) on chromosome 3p21 and represents an important downstream effector of the Wnt/β-catenin pathway. This pathway is important in liver embryogenesis, cell adhesion, growth, zonation, and regeneration [22]. An activating β-catenin mutation is also associated with specific conditions such as glycogen storage disorders or androgen administration. The phenotype is represented by cellular atypia with high nuclear-cytoplasmic ratio, nuclear atypia, and pseudoglandular growth pattern. It is identified by immunohistochemistry due to a strong expression of glutamine synthetase with or without aberrant cytoplasmic and nuclear expression of β-catenin. β-HA has the highest risk of malignant transformation than other HA subtypes, and it is very difficult to be distinguished from the well-differentiated hepatocellular carcinoma (HCC). Some risk factors are related to β-HA, such as male hormone administration, glycogenosis, and familial polyposis.

The third group (IHA) includes 50% of all patients and is most common in overweight women who suffer from metabolic syndrome or have had prolonged estrogen exposure. Patients with IHA demonstrate both serum and lesional indicators of an active inflammatory response. IHA is characterized histological by inflammation, marked sinusoidal dilatation or congestion, numerous thick-walled arteries, and ductular reaction (**Figures 8** and **9**). This subgroup was previously named 'telangiectatic focal nodular hyperplasia.' The extent of congestion, peliosis, and hemorrhage is different from case to case. Steatosis may be present in IHA but is not as extensive as in H-HA. In case of multiple tumors, the amount of steatosis

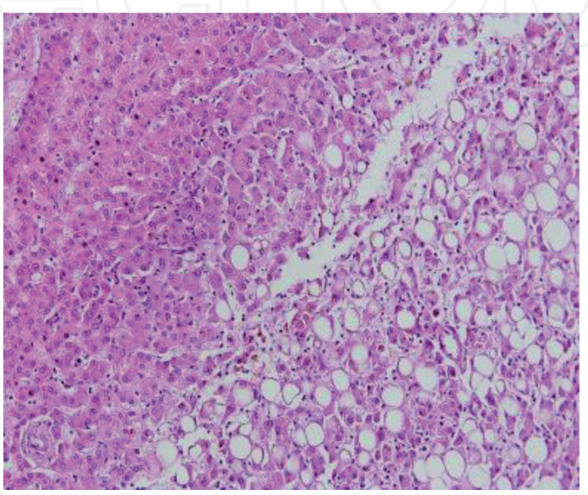


Figure 4.
Hepatocellular adenoma—HNF1 alpha mutated subtype—steatosis within the tumor, HE ×200.

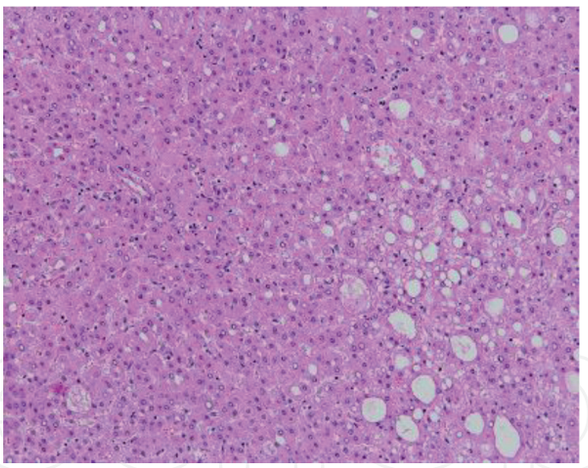


Figure 5.
Hepatocellular adenoma—HNF1 alpha mutated subtype—steatosis and pseudoglandular formations, HE ×200.

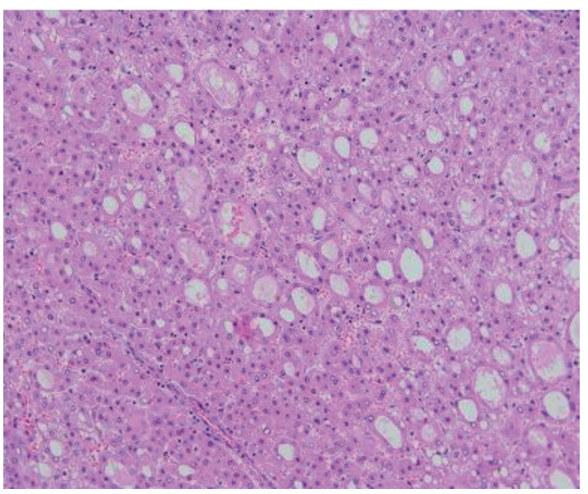


Figure 6.
Hepatocellular adenoma—HNF1 alpha mutated subtype—pseudoglandular formations and steatosis within the tumor, HE ×200.

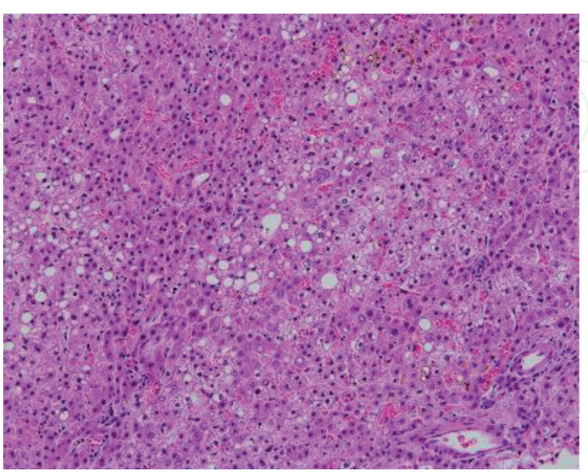


Figure 7.
Hepatocellular adenoma—steatosis within the tumor, HE ×200.

varies among the tumors in the same patient. Immunohistochemically, it is distinctive by a strong expression of inflammation-associated proteins such as serum amyloid A and C-reactive protein at mRNA and protein levels. The genetics of this

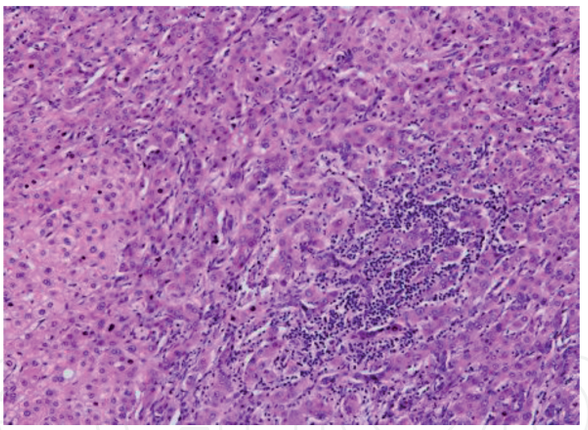


Figure 8.
Hepatocellular adenoma—inflammatory subtype, HE ×200.

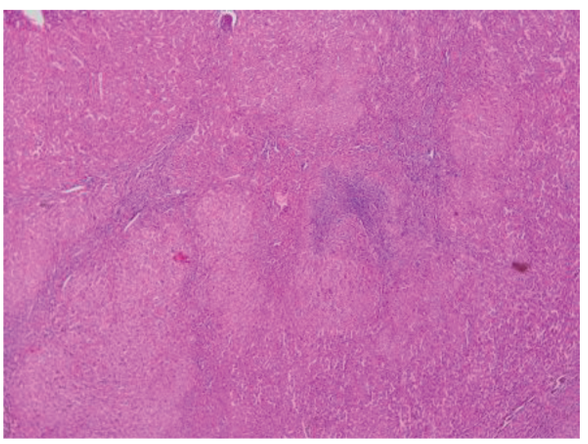


Figure 9.
Hepatocellular adenoma—inflammatory subtype, HE ×40, with sinusoidal dilatation and hemorrhage within the tumor.

group is related to activation of the JAK/STAT pathway underlined by mutations in different genes. In 60%, there are somatic gain-of-function mutations of the interleukin-6 signal transducer gene (IL6ST), which is located at chromosome 5q11 and encodes for glycoprotein 130. Gain-of-function mutations in glycoprotein 130 activate JAK–STAT-3 without interleukin-6 binding. The other 40% show overexpression of wild-type glycoprotein 130, which activates STAT-3 through an unidentified mechanism. Marked peliosis is probably caused by suppression of albumin gene, insulin-like growth factor gene IGF1, and/or transthyretin gene. Mutations of β-catenin may coexist in 10% of IHA (β-IHA). These patients may have signs and symptoms of systemic inflammatory syndrome, manifested as fever, leukocytosis, and elevated serum levels of CRP. Abnormal results of liver function tests may occur, with elevation of alkaline phosphatase and γ-glutamyl transferase. Systemic AA amyloidosis is a rare complication of HA which causes nephrotic syndrome with deteriorating renal function. Resection of the tumor is followed by improvement in renal function and a marked decrease of the serum concentrations of acute phase proteins [23].

The last group that is unclassified (UHA) accounts for 5–10% of adenomas. For this group, the genotype is unknown and the phenotype and immunohistochemistry—unspecific. In this group is also included HA that cannot be classified due to near-total necrosis or hemorrhage [21].

The first important thing for the pathologist is to correctly identify the β-catenin-activated HA and to decide when immunostaining is needed. Morphology

and additional immunohistochemical markers can discriminate between different types of HA in more than 90% of cases [24]. Identification of beta-catenin positive adenomas has important implications in the decision for surveillance and treatment of these patients. Even if very specific, nuclear β-catenin immunostaining is of low sensitivity in accurate detection of β-HA and β-IHA due to uneven staining distribution or focal nuclear staining. Therefore, additional molecular biology is required. It is recommended to perform glutamine synthetase (GS) staining on every single HA, because GS is one of the target genes in case of β-catenin activation, and it is usually diffusely and strongly expressed in β-catenin-activated HA. GS staining can also be patchy or diffuse but less intense and still be an indication of β-catenin-activating mutations, but in this case, a molecular analysis must be performed to confirm it.

The second important thing for the pathologist is to correctly recognize foci of HCC inside HA. The problem is to avoid overdiagnosis in case of mild or focal cellular atypia. Some HAs may look worrisome due to the presence of architectural distortion, thicker liver cell plates, extensive pseudogland formation, and decreased reticulin framework together with increased CD34 staining (**Figure 10**). These are called "atypical HA," "borderline lesions," and, recently, "well-differentiated hepatocellular neoplasms of uncertain malignant potential." Reticulin staining (**Figure 11**) is the most powerful tool to identify foci of definite malignant transformation, especially in association with architectural distortion, cellular atypia, and increased CD34 staining. Glypican 3 is also very useful when it is positive (**Figure 12**), but its negativity does not rule out malignancy [25]. In most cases of HA and occasionally in HCC, the CD34 staining intensity is variable in different areas and virtually all HCCs have homogenous CD34-positive staining intensity and density [26]. Total loss of reticulin network and diffuse increased CD34 expression, possible presence of glypican 3, and increased MIB1 staining are indications for HCC foci. HSP70 can be also useful. There is no specific phenotype of HCC developed from HA, but some observed that these HCC are often pigmented or cholestatic.

The pathologist needs enough samples, some of them at the junction with the nontumoral liver. For immunohistochemical results, it is mandatory to have a biopsy of the nontumoral liver for comparison.

Interestingly, certain magnetic resonance imaging (MRI) features seem to correlate with the histologic subtypes, suggesting that it may be possible to classify them by MRI [7]. HNF1-inactivated HA and inflammatory HA can particularly be diagnosed by radiologists with considerable accuracy.

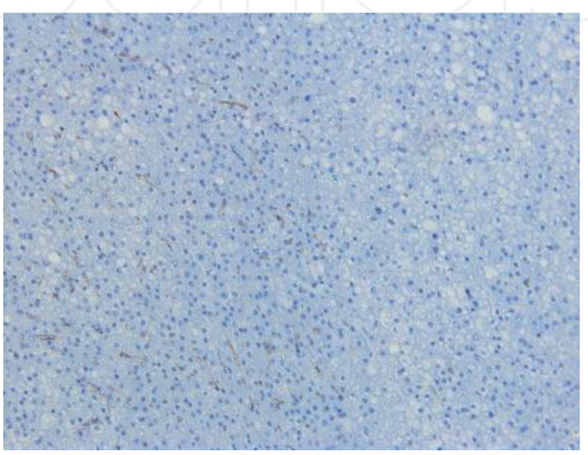


Figure 10.
Hepatocellular adenoma—CD34 immunohistochemical stain for endothelial cells, few sinusoids are seen in the tumor, ×200.

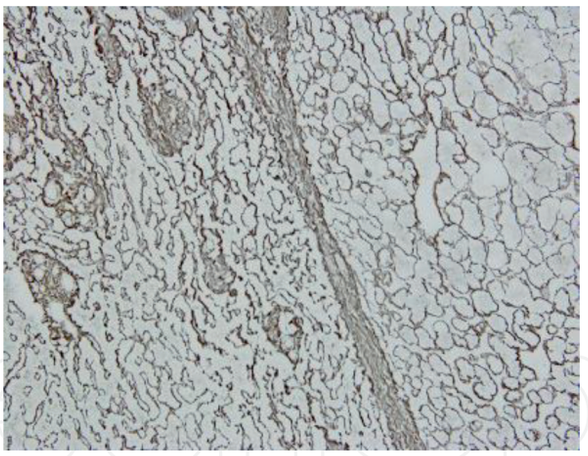


Figure 11.
Hepatocellular adenoma—reticulin stain—left normal liver and right hepatocellular adenoma—there is no loss of reticulin network, Gomori ×200.

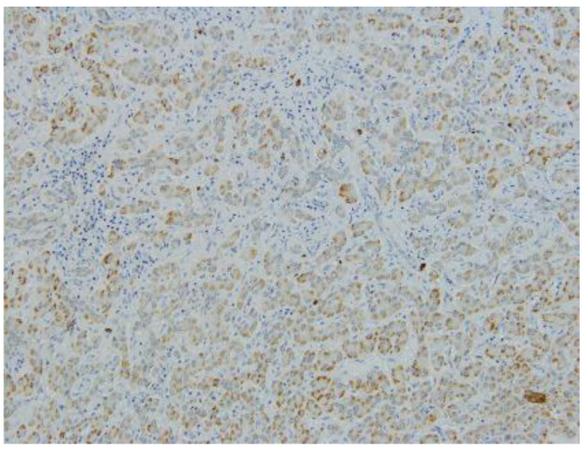


Figure 12.
Hepatocellular adenoma—HNF1 alpha mutated subtype—mild lipofuscin deposits revealed by glypican 3 immunohistochemical stain, ×200.

4.1 Adenomatosis

Adenomatosis is a distinct clinical entity and was first described in 1985 [27] and since then has been defined by the presence of more than 10 adenomas, involving both hepatic lobes, in the absence of glycogen storage diseases, prolonged use of steroids, or resolution with steroid cessation [28]. It is estimated that adenomatosis affects both men and women, and, unlike HA, is correlated with a higher risk of impaired liver function, manifested as an increase in serum alkaline phosphatase and GGT levels [27] and also with a higher risk of bleeding. Instead, the malignant degeneration does not correlate with the number of lesions. There are two different patterns of adenomatosis: (1) the massive pattern, which is defined by the existence of larger lesions, up to 10 cm, that often result in gross hepatomegaly with deformed contour of the liver and (2) the multifocal pattern, which is characterized by smaller lesions, with diameter less than 4 cm, that rarely deform the liver, but has a tendency to progress fast and become symptomatic [29]. The etiology of hepatic adenomatosis is suspected to be linked to congenital or acquired abnormalities of hepatic vasculature. In a study of 15 patients with adenomatosis, 5 had abnormalities in hepatic vasculature: congenital absence of portal vein, portal venous thrombosis with cavernous modification, and intrahepatic portosystemic shunts [1, 30].

The conditions that predispose to adenomatosis and evolution of the disease are poorly understood, since the medical literature reports only information in regard to individual cases or small case series, but some similarities with the HA are evident: the tendency toward hemorrhage (especially in adenomas larger than 4 cm) and the risk of malignant transformation. Adenomas in hepatic adenomatosis may be of inflammatory, hepatocyte nuclear factor 1 alpha mutated, or beta-catenin mutated subtype.

5. Signs and symptoms

Most commonly, HA goes unnoticed due to its lack of signs and symptoms, but when it does become symptomatic, it is either due to its increase in volume, tumor necrosis, or complications such as life-threatening intra-abdominal bleeding due to spontaneous rupture of the highly vascularized tumor. Sudden, severe pain with hypotension in a patient with HA indicates rupture into the peritoneum, an event associated with a mortality of up to 20 percent if not identified and/or treated accordingly [9, 31, 32]. The risk of bleeding is difficult to estimate overall, but it is quite high in patients with symptomatic HAs (25–64%). Tumor size that exceeds 35 mm has been associated with an increased risk of bleeding [33]. The risk of bleeding depends on the localization of the tumor. Exophytic lesions (protruding from liver) had the highest risk of bleeding (67%), followed by subcapsular ones (19%) and at last intrahepatic HA (11%). Lesions in segments II and III had more bleeds than those in the right liver (34% versus 19%). The visualization on imaging of peripheral or central arteries represents a risk of bleeding comparative with no visible vascularization in the lesion [33]. Also a long history of contraceptive use and recent hormonal use are risk factors for bleeding from HA. Young age seems to be associated with an increased incidence of HA rupture, independent of hormonal treatment duration, suggesting a need for careful surveillance or prophylactic treatment in this population [34]. Bleeding is graded as intratumoral (grade I), intrahepatic (grade II), or extrahepatic (grade III) and represents a potentially life-threatening complication in patients with HAs.

Hepatic adenomas are diagnosed when they cause epigastric or upper quadrant pain or during an imaging study done for unrelated ailments, and less commonly when an abdominal mass is palpated on clinical examination. When HA is sufficiently large and compresses bile ducts, jaundice may become another sign.

6. Diagnosis and differential diagnosis

There are no specific serologic markers or laboratory findings for HA, but certain findings can lead the diagnosis away from an adenoma and toward a liver cell carcinoma in case of an increased serum alpha-fetoprotein, or toward a metastasis in the case of increased serum tumor markers for digestive tract tumors [35].

The definite diagnosis in this pathology is naturally a histological one; however, obtaining it preoperatively means making a biopsy from a fragile and highly vascular tissue, with significant risk of bleeding. Having to deal with a benign lesion, and given the fact that the amount of tissue obtained is rarely enough or suitable for a diagnosis, this risk is not justified. Thus, the diagnosis of this tumor is based on analyzing a combination of epidemiologic and clinical data and imaging studies, but often the confirmation of the diagnosis is done by the pathologist, after the hepatic resection.

Usually a HA is suspected in a young adult with a singular and asymptomatic hepatic lesion, but a thorough differential diagnosis should be made and often this proves to be difficult. The differential diagnosis between adenomas and focal nodular hyperplasia is usually challenging, but can be done, most of the times, based on imaging characteristics.

6.1 Imaging in liver adenomas

Imaging in adenomas includes mostly ultrasound, contrast-enhanced ultrasound (CEUS), multislice computer tomography (MSCT), and magnetic resonance imaging (MRI) (**Figure 13**).

6.1.1 Ultrasound

The most accessible, cost-friendly, and probably responsible for most discoveries of asymptomatic HA is the ultrasound, even though it cannot distinguish it from other liver tumors. On gray scale ultrasound, HA is seen as a well-defined solid, echogenic mass, but sometimes as complex hyper/hypoechoic, heterogeneous mass with anechoic areas due to fat, hemorrhage, necrosis, and calcifications; a capsule may also be seen [36]. Color Doppler US can aid in the distinction from FNH in the absence of a central arterial signal, FNH having characteristic intratumoral and peritumoral vessels [37, 38]. Contrast-enhanced ultrasound with sulfur hexafluoride microbubbles (SonoVue or Lumason) greatly improves diagnosis as compared to US without contrast.

6.1.2 Computer tomography

One of the most accurate imaging tools in diagnosing a HA is contrast enhanced computed tomography (CECT), on which it appears as a well demarcated tumor, with characteristic peripheral enhancement during the early phase with subsequent centripetal flow during the portal venous phase. A heterogeneous consistency is usually a sign of necrosis, hemorrhage, or fibrosis [5].

Multiphasic computed tomography (CT) has a detection rate of 100% for adenomas, which is however different per type of examination: nonenhanced 86%, hepatic arterial-dominant phase (HAP) 100%, portal venous-dominant phase (PVP) 82%, and delayed 88%. Tumor margins are well defined by a low-attenuation pseudocapsule in 86% of adenomas and the surface appears smooth, without lobulated contour, in 95%. Tumor fat and calcifications are uncommon (7%, respectively 5%). Other than areas of fat, hemorrhage, or necrosis, the adenomas show homogenous enhancement, especially on PVP and delayed-phase scans [39].

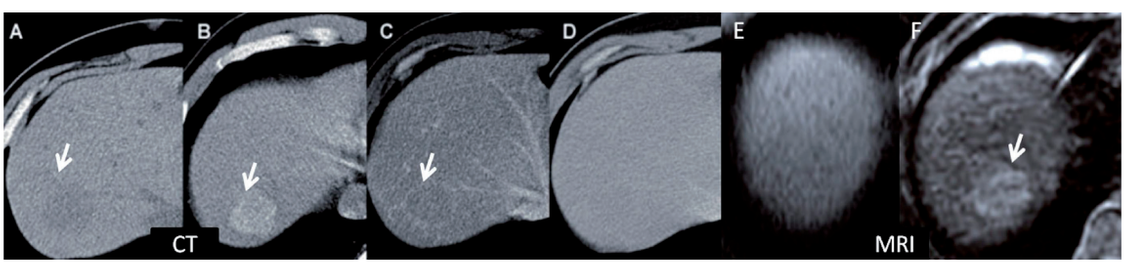


Figure 13.
HA located in segment VII as shown by imaging on NECT (A), CECT—arterial phase (B), portal venous phase (C), parenchymal phase (D), MRI T1w (E), and T2w (F). Atoll sign characterized by a hyper intense band in the periphery and isodensity in the center of the lesion with respect of the surrounding liver is relevant on CT in portal venous phase (C). A hyperintense rim in T2 wi is described in inflammatory adenoma (arrow in F).

MSCT technique: nonenhanced CT and enhanced triphasic CT: in arterial (30–35 s after the bolus tracker detection), portal venous (60–80 s after contrast medium injection), and equilibrium/late phases (after 3–5 min). 1.5 ml/kg of nonionic iodinated contrast material is injected into an antecubital vein with a rate of 3 ml/s using a power injector.

CT findings are depending on HA subtype. On nonenhanced CT (NECT), hemorrhage within tumor is seen on as hyperdense foci, intratumoral lipid as hypodense foci (negative density), and focal coarse calcifications are rarely seen (**Figure 14**). On contrast-enhanced (CECT), encapsulation is present in ~20% of HAs, best seen on the late phase (**Figure 14**). Hypervascularity is most intense and persistent in inflammatory subtype of HA (**Figure 15**).

CT is most useful in distinguishing a HA from other liver tumors or lesions: (1) focal nodular hyperplasia which has a characteristic central star-shaped hypodense scar, (2) hemangiomas with their peripheral enhancement on arterial phase and progressive centripetal fill-in pattern, (3) liver cell carcinoma which has a particular wash-in, wash-out pattern, and (4) singular liver metastases with no fat or hemorrhage.

6.1.3 Magnetic resonance imaging (MRI)

6.1.3.1 MRI technique

Unenhanced conventional sequences: T2w is useful in detection of focal liver lesions. T2* is important in the evaluation of iron content and chemical shift artifact sequences; T1 in/out of phase is important to delineate steatosis or intralesional lipomatous content; ssFSE short TE/long TE makes differentiation between cysts and solid mass; and diffusion is the most sensitive sequence for liver lesion detection.

Contrast enhanced T1: multiphase dynamic 3D acquisitions without and with intravenous injection of 0.1 ml/kgbw of extracellular or liver-specific contrast paramagnetic agents (Gd-EOB-DTPA) in arterial phase (AP): detection of hypervascular lesions, portal venous phase (PVP), late phase (LP), and hepatobiliary phase (HBP).

Imaging key features in HAs are: hypervascularity, fat content, hemorrhage, and encapsulation. MRI shows some elements better than CT (lipid and hemorrhage). HA shows no substantial uptake or retention in contrast enhanced MRI with Gadoxetate (Primovist). MRI features for adenomas are distinct from FNH. T1WI: mass with heterogeneous signal intensity; increased signal intensity (due to fat or recent hemorrhage); decreased signal intensity (necrosis, calcification, old hemorrhage) T1 + C: heterogeneous, hypervascular liver mass with foci of fat or hemorrhage in a young woman.

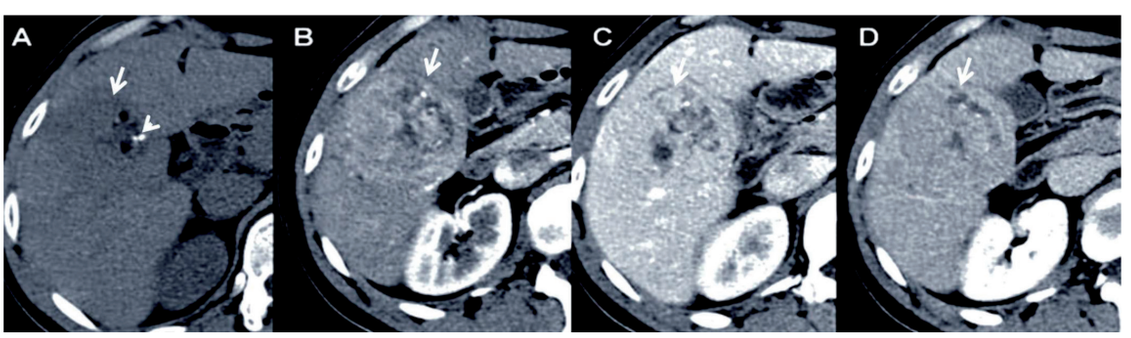


Figure 14.
NECT with large liver mass with central calcifications, small lipomatous inclusions, solid components and necrosis (A), CECT—arterial phase (B), portal venous phase (C), and parenchymal phase (D).

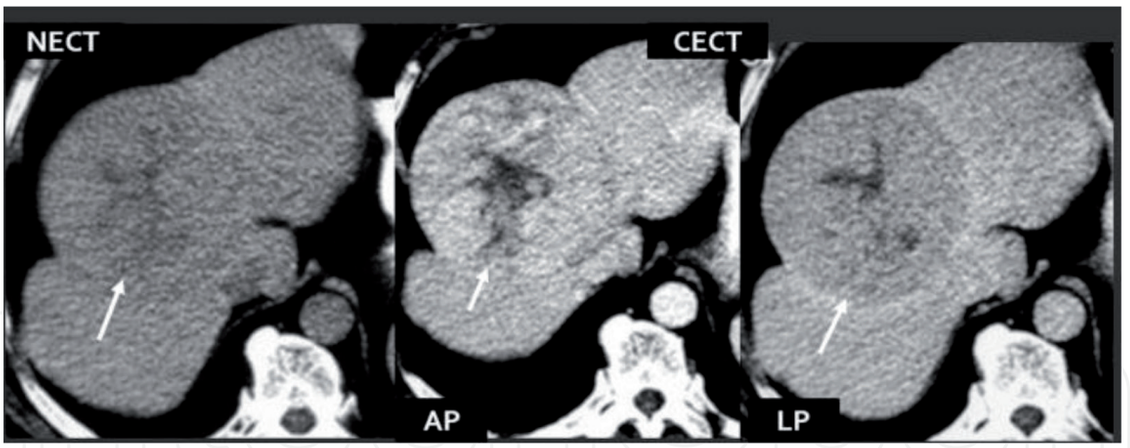


Figure 15.
CT evaluation: liver adenoma with central necrotic area and encapsulation (arrow).

6.1.3.2 MRI evaluation

Some MRI findings of HAs are similar to CT findings, but MRI is usually more sensitive in detecting fat from hemorrhage. The appearance of HAs on MRI is highly variable, especially in T1, but if contrast medium is used, then it may be better characterized, showing early arterial enhancement and becoming nearly isointense to liver on delayed images.

On T1-weighted images (T1wi), HA appears as a heterogeneous signal intensity mass. The increased signal of HA is due to fat and recent hemorrhage, and the decreased signal intensity is due to necrosis, calcification, or old hemorrhage. A fibrous pseudocapsule may be seen in HA as a hypointense rim. In T2wi, the mass appears heterogeneous; increased signal intensity corresponds to old hemorrhage or necrosis, and the decreased signal intensity is due to the fat or recent hemorrhage. The peripheral rim (fibrous pseudocapsule) in HA appears hypointense in liver parenchyma (**Figure 16**). After contrast injection (T1wi + C) in arterial phase, adenomas are heterogeneous hypervascular masses (inflammatory HA+++) and in delay phase a pseudocapsule, which is hyperintense comparative to the normal liver, can be seen. After Gadoxetate-enhanced MR (Gd-EOB-DTPA), in HA there is no substantial contrast uptake or retention on hepatobiliary phase [40].

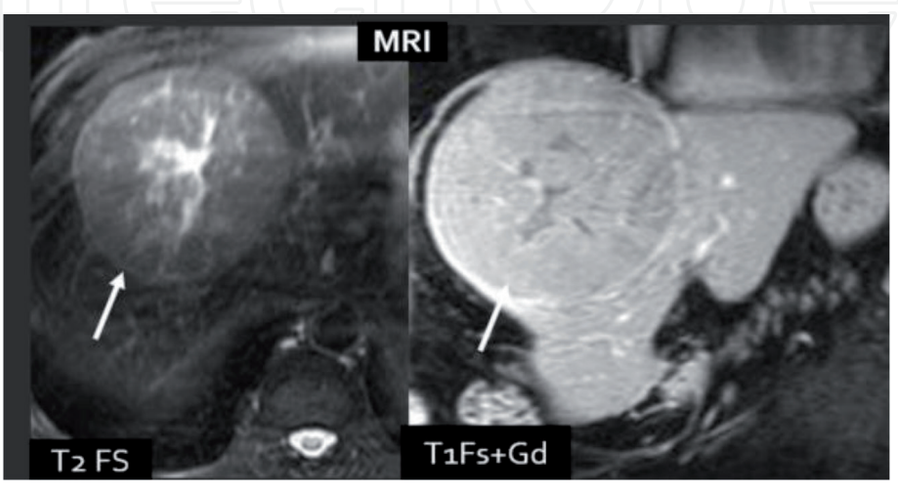


Figure 16.
MRI evaluation: liver adenoma with central necrotic area and pseudocapsule hyperintense to the surrounding liver (arrow).

MRI with hepatobiliary agents is an important tool not only in differential subtype definition but even in surveillance with early identification of complications and discovery of some signs of HA malignant degeneration [41]. Lesion enlargement and heterogeneity of signal intensity and of contrast enhancement are signs of malignant transformation [42].

Imaging recommendations: the best imaging tool is represented by Gadoxetate-enhanced MRI including multiphase and hepato-biliary phase acquisition [43]. The best sequence to evaluate fat into HA is T1wi with in and opposed TE.

6.1.3.3 Classification of HAs based on imaging examinations

MRI is the imaging modality of choice for characterization of HA subtypes [22]. Inflammation, abnormal rich vascularization, peliotic areas, and abundant fatty infiltration are pathologic findings differently present in the HA subtypes at multiparametric MRI [41].

HNF1A-mutated adenoma (H-HA): on MRI, the diffuse and homogenous fat deposition within HA-H determines a specific imaging pattern: on T1-weighted Gradient-Echo MR, it is hyper- or isointense, with diffuse signal drop-off with the use of chemical shift sequence (**Figure 17**). On T2-weight MR, images appears isointense to slightly hyperintense. Gadolinium-enhanced T1-weighted MR images show moderate enhancement in the arterial phase, with no persistent enhancement in the portal venous and delayed phases. Generally, its size is less than 5 cm, and there are minimal risks of bleeding and malignant transformation [22]. At multidetector CT, macroscopic fat deposits can be identified and establish the diagnosis of H-HA. On CEUS, it has iso- to moderately increased vascularity, mixed filling in the arterial phase after contrast and isoechoic appearance in the portal venous and delayed phases.

β-catenin-mutated hepatic adenoma (β-HA): there are no distinctive patterns established on MRI, multidetector CT, or CEUS, but they usually are hypervascular with evidence of hemorrhage or necrosis within tumor. Besides the fact that has the highest risk of malignant transformation (> 10%), it may mimic hepatocellular carcinoma with strong enhancement during arterial phase and with portal venous wash-out.

Inflammatory hepatic adenoma (IHA): includes those previously called "telangiectatic HA." It has specific patterns on MRI due to less fat content, sinusoidal dilation, peliotic areas, and abnormal vessels. On T1-weighted Gradient-Echo MR images, it is depicted as isointense or mildly hyperintense, without signal drop-off with the use of chemical sequence, and on T2-weighted MR images, it becomes bright (diffusely hyperintense). On Gadolinium-enhanced T1-weighted MR images, it shows intense enhancement during arterial phase that persists in

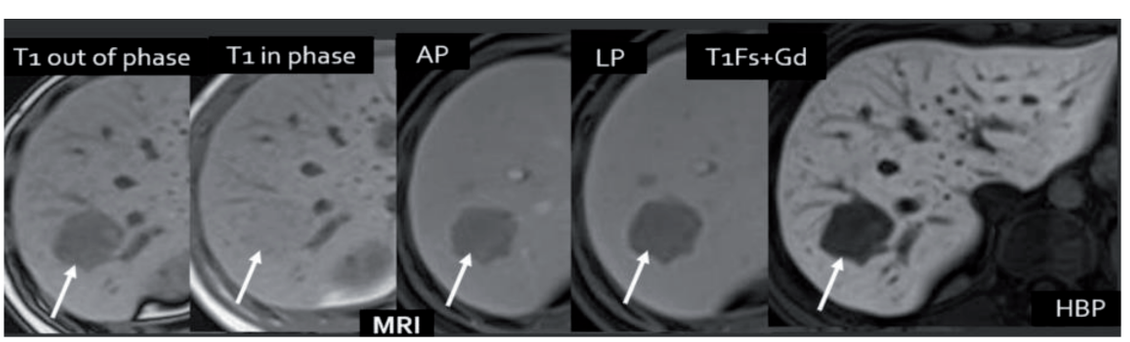


Figure 17.
HNF1A-mutated HA: diffuse lipid deposition within HA best seen using T1 with TE in and out of phase (arrow).

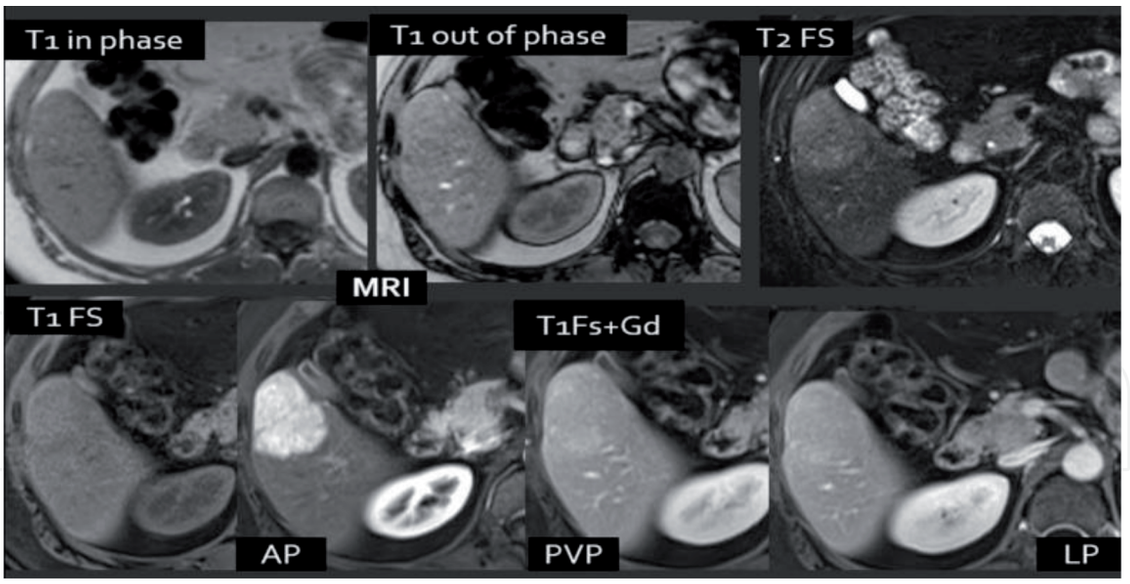


Figure 18.
Inflammatory liver adenoma: hyperintensity T2 wi and hypervascularity of the liver mass through the late AP, and discreetly hyperintense in portal and late phase.

the portal venous and delayed phases (**Figure 18**). The atoll sign is specific for IHA and may be due to sinusoidal dilatation. In up to 30% of cases, there is evidence of hemorrhage, and a 10% likelihood of malignant degeneration is estimated. At multidetector CT, IHA is depicted as heterogeneously hyperattenuating mass in NECT and in CECT shows enhancement features similar to those at MRI. At CEUS, it has arterial vascularity with centripetal filling, a sustained enhanced rim and central wash-out in the late venous phase.

Unclassified hepatic adenoma (U-HA) does not fit other profiles of HA subtypes.

6.1.3.4 Differential imaging diagnostic of adenomas

Hepatocellular carcinoma (HCC) may be hard to distinguish on imaging or pathology. Biliary, vascular, nodal invasion and metastases of HCC typically occur in older, cirrhotic men [42, 45]. Adenoma occurs in young, healthy women.

Fibrolamellar HCC is shown as a large, lobulated mass with scar and septa inside. Vascular, biliary invasion and metastases are common.

Focal nodular hyperplasia (FNH) is depicted on MRI + C in arterial phase as a homogeneously enhancing mass and in all other phases as an isodense mass comparative to normal liver. In T2WI, a scar is typically seen as hyperintense. On delayed phase MR, FNH uniformly retains Gadoxetate [44, 45]. Gadoxetic acid-enhanced MRI can differentiate between HA and FNH with a high sensitivity and specificity [46].

Hypervascular metastases are usually multiple. The primary tumor (i.e., thyroid, breast, kidney, or endocrine) must be searched for. CT + C or MRI + C in arterial phase shows heterogeneous enhancement. In portal and delayed phases, hypervascular metastases may appear isodense, hypodense, or hypointense.

6.2 Nuclear medicine studies

Most HAs have a decreased uptake of Gallium and colloid, early and retained uptake of hepatobiliary agents, and no uptake on PET scanning.

If radiological studies cannot distinguish HA from HCC and FNH, a combination of radionuclide imaging, including technetium (99mTc)-sulfur colloid sulfur-colloid,

Ga, and technetium-99 pyridoxyl-5-methyltryptophan (PMT) uptake may help establish the correct diagnosis [47]. Most adenomas do not take up technetium Tc-99m sulfur colloid so they appear as a "cold" spot in the parenchyma of the liver. This examination is not particularly good in diagnosing an adenoma but in distinguishing one from a FNH, which shows equal or greater uptake of the radiolabeled agent compared with surrounding liver [48]. 99mTc-labeled DISIDA (dimethyliminoacetic acid) liver scintigraphy has also been used by some authors for diagnosis of HA [47].

Positron emission tomography (PET) scanning with fluorine-18-fluorodeoxyglucose (^{18}FDG) is useful in differentiating HAs from malignant tumors, because malignant tumors show uptake of ^{18}FDG but not benign tumors, with some exceptions like inflammation and abscess.

Although CEUS, CT, MRI, and nuclear studies help in characterization of hepatic lesions as adenomas, the findings sometimes are nonspecific, and biopsy and/or resection may still be necessary.

6.3 Detection of malignant transformation

The pathogenesis of malignant transformation of hepatocellular adenoma is still poorly understood. Some light was recently shed on the mechanisms of hepatocarcinogenesis, which suggest the importance of telomerase reverse transcriptase (TERT) promoter mutations beside the early event of β-catenin mutation. Apparently, only the β-catenin mutations that occur on exon 3 and not those on exon 7–8 are involved in malignant transformation of HA [49]. It still remains unclear if hepatocellular carcinoma emerges from hepatocellular adenoma or if the lesions are coincident. Malignant transformation of hepatocellular adenoma has been reported in 4% of women and 47% of men with HA [50]. The risk of malignancy is very high for β-HA, which is most frequently associated with glycogenosis type 1, androgenic hormone intake (many of these tumors expressing androgen receptors in men), and familial polyposis. It is important to remind that no HA subtype is devoid of risk of malignant transformation. Men are predisposed to hepatocellular carcinoma regardless of etiology, and for this reason, surgical treatment is strongly recommended for male patients diagnosed with HA. For women, an older age (50 years or older) or a younger age (15 years or less) is a risk factor for malignant degeneration that must be taken into account to refer these patients to surgeon for resection or at least to a hepatologist for very close and careful surveillance.

At present, no clinical assessment can distinguish between HA and degenerated HA, and no rules for surveillance of HA in both sexes are clearly defined according to subtypes. The methods and the periodicity of following these patients are variable. Radiological assessments could include CEUS, multidetector raw CT, and dynamic MRI. CEUS allows more sensitive recognition and specific exclusion of malignancy compared with CT and dynamic MRI and has the advantage that can be repeatedly performed without the risk associated with allergic reactions or radiation exposure. Moreover, MRI has the disadvantage that cannot be performed everywhere in the world because the technical skills and expertise are very much geographically dependent. Two main features must be taken into consideration at reassessment of these patients with HA: the size of the tumor and, more important, the hemodynamic changes that precede the tumor growth [50]. Malignant degenerations are considered when the tumor was first iso-attenuated when compared with normal liver during the nonenhanced and delayed phases and appeared homogenous in the early phase but, at a later examination, it becomes enhanced in the early phase and hypo-attenuated in the delayed phase. Also, the presence of a nodule within a nodule during the arterial phase is known as a sign of malignancy. β-HA often has cytological atypia and pseudoglandular pattern, and it is sometimes almost impossible to identify HCC.

7. Management and current guidelines

The surgeons must be convinced that HA subtypes are important for the management of the patients. From now on, a diagnosis of HA cannot be conceived without group classification. The number and location of HA play a great role in management, but various clinical conditions such as age, sex, etiology, background liver, or comorbidities must be taken into consideration. Other aspects also play a role in decision making, like where the patient lives, the degree of his/her anxiety, and cost of surveillance. The management of patients with HA must be planned by a complex team formed by surgeons, hepatologists, pathologists, radiologists, gastroenterologist, molecular biologists, and geneticists.

There are no clear guidelines for the management of HA, because the treatment depends on many factors such as HA size, number, localization, gender, age, presence of symptoms, and complications.

In young women treated with contraceptive pills, asymptomatic lesions under 5 cm in diameter should be kept under close observation with CT/CEUS repeated every 6 months [51] and repeated alpha-feto-protein, all the while ceasing to use contraceptive pills [52]. Any modification in imaging suggesting a malignant transformation or an increase in the serum tumor marker should lead to liver resection. There are some authors who advocate resection of adenomas of any size given their risk of malignization and bleeding, if the resection can be performed with acceptable risk. The facts that surgical excision guarantees a definitive diagnosis and long-term cure favor the universal indication of surgery for HA [53].

7.1 Surgical resection

The indications for surgery in nonemergent cases are: HA > 5 cm, female patients taking oral contraceptives with HA > 3 cm [47], HA with growing size, HA with HCC or dysplastic foci, β-catenin-activated HA, imaging features of malignant transformation, increased serum alpha fetoprotein, HA in males regardless of the tumor size, HA in GSD, symptomatic patients, or when malignancy cannot be excluded [54]. The type of resection depends mainly on number, size, histological type, and localization of HA. The resection techniques vary from simple enucleation to liver transplantation [55]. Liver resection for HA can be anatomic or nonanatomic. Anatomic resections reported in the literature for HA refer to minor hepatectomies that imply the removal of the tumor with one or two segments of the liver [56], but also major hepatectomies like left and right hemihepatectomy, mesohepatectomy [57], and left or right extended hepatectomy [26, 58]. Nonanatomical resections are wedge resections [59]. Enucleation seems to be a choice for such benign tumor, but is not advisable due to the risk of remnant tumor that can cause tumor recurrence or, worse, malignant degeneration, especially for β-catenin HA. It was speculated that the classical 1 cm oncological safety margin could be lowered to 0.5 cm for HA. The safety margin at the edge of resection is mandatory, if any suspicion of HCC exists.

Surgery in elective cases is less than 1% and most tumors can be operated laparoscopically, with significant advantages [59–61]. A better cosmetic result, a shorter hospitalization (4 days) with early return to normal life, and a lower incisional rate are the main advantages that laparoscopy has comparative with open approach. However, laparoscopy should be performed only in specialized centers with extensive experience in both hepatic and laparoscopic surgery. The first non-anatomical laparoscopic liver resection for HA reported by Ferzli et al. [62] in 1995 was followed one year later by the first anatomic laparoscopic resection for HA performed by Azagra et al. [63]. Pure laparoscopic procedure can be performed for HA with no mortality and reduced morbidity even in

hemodynamic stable patients with ruptured HA [61]. Moreover, some surgeons consider laparoscopic surgery the standard of care for the treatment of HA [59]. Hand-assisted or "hybrid" techniques are also optional approaches [64] and the parietal incision is later used for specimen retrieval. In pure laparoscopic surgery, the specimen is retrieved through a Pfannenstiel incision even when the tumor is as large as 180 mm [61].

Pringle maneuver can be of great use to minimize the intraoperative blood loss and it is used by surgeons both in laparotomy and laparoscopy. Some authors consider it unnecessary for laparoscopic left lateral sectionectomy [60]. Instead, others perform the maneuver for both atypical and anatomical resections. Laparoscopy is restricted by the localization of HA involving segments VII and VIII. The half-Pringle maneuver was associated for right posterior sectionectomy and resulted in less bleeding [65].

Total vascular exclusion of the liver is routinely recommended in high dorsal resections for HA [66].

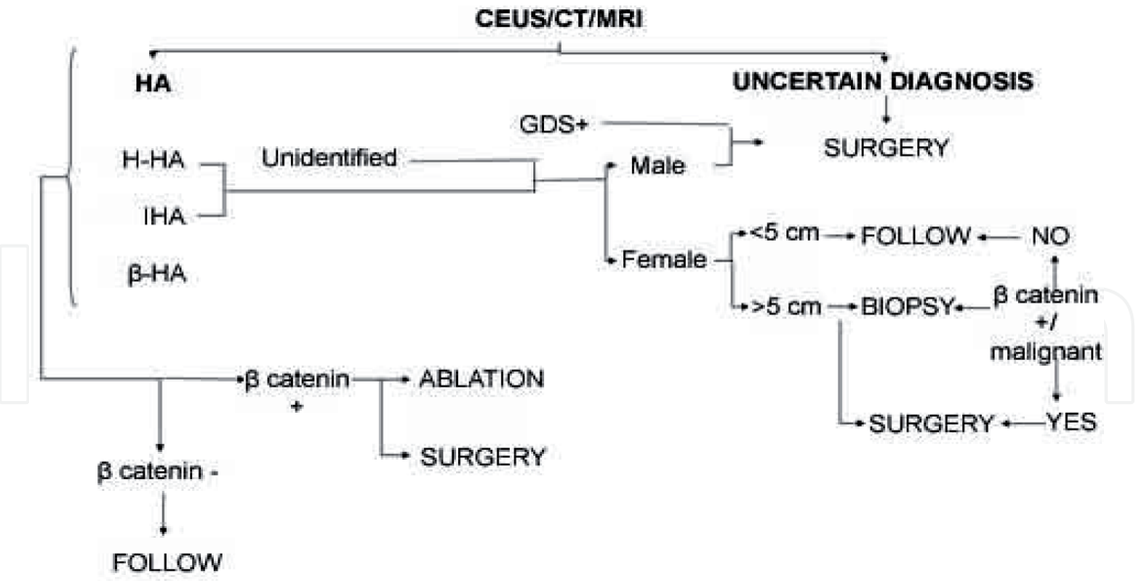
Intraoperative blood transfusion is rarely needed and generally is performed in case of ruptured bleeding adenoma. Conversion of laparoscopy to laparotomy should be considered just in case of too much bleeding and difficulties for the anesthesiologist to stabilize the patient.

The high rates of mortality and morbidity previously reported after liver resection for bleeding HA are recently denied by new evidences [30]. Emergency resection of ruptured HA has a mortality rate of 5–10%, whereas elective surgery has a mortality rate of less than 1% [67]. These results are explained nowadays by the availability of improved hemostatic techniques, excellent anesthesia support, and postoperative intensive care. In the past, in the presence of signs of hemorrhagic shock, the mortality was as high as 20% for resection [68]. At present, the mortality for such patients trends toward zero. Nonsurgical strategies such as arterial embolization or gauze packing have been recommended in order to stabilize the patient and delay resection to an elective setting. There are situations when intraperitoneal bleeding from a ruptured adenoma is self-limited and a laparotomy is done just for biopsy. A recent bleeding adenoma does not necessarily need resection. After this acute bleeding, some of these tumors regress, others are stationary, and few rebleed. Transarterial embolization (TAE) can not only stabilize the patient but also obtain complete avoidance of surgical intervention. Sometimes, repeated embolization is needed to achieve hemostasis. However, liver resection remains the best means to achieve hemostasis and also to obtain a thorough histology.

7.2 Liver transplantation

Liver transplantation is an extraordinary choice in a few selected patients, with multiple HAs, giant HAs [69], or recurrent adenomas that are not technically resectable [70]. Those HAs considered unresectable are either in close proximity to major vascular structures or the liver hilum or less than 20% of viable hepatic parenchyma remains after resection. Liver transplantation for recurrent HA is a more technically demanding procedure if compared to the cases with chronic liver disease due to the presence of postoperative adhesions that must be divided before reaching the liver and also due to difficulties in liver implantation when at least a major hepatic vein and hepatic pedicle are absent after major hepatectomy [70]. Transplanted liver is generally harvested from a cadaveric donor but living liver transplantation has also been reported [71]. Due to an expanding armamentarium and experience in angiographically controlling bleeding from a ruptured HA, liver transplantation as an ultimate life-rescue therapy remains exceptionally rare, being reported for spontaneous intra-partum rupture of hepatocellular adenoma [72] (**Algorithm 1**).

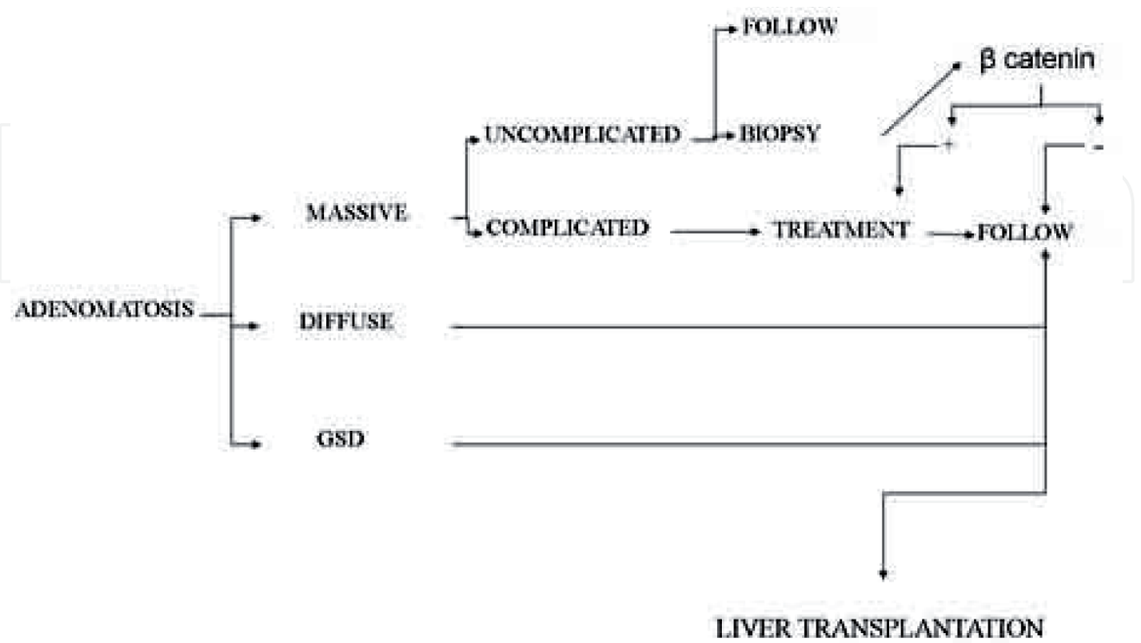
Algorithm 1. Management in hepatic adenoma.



7.3 Management of liver adenomatosis

The management of cases with liver adenomatosis is cumbersome. All women with adenomatosis must discontinue exogenous hormone therapy and should avoid pregnancies. In the massive pattern of adenomatosis, if larger lesions comprise a single lobe, a hemihepatectomy or more limited hepatic resection (**Figure 19**) could be a wise choice. Laparoscopic left lateral sectionectomy can be a good approach for those patients expecting a future liver transplantation [73] (**Algorithm 2**).

Algorithm 2. Management in liver adenomatosis.



Even the resection of only the complicated nodule (i.e., hemorrhagic liver nodule) seems appropriate as the first step toward enlisting for liver transplantation. Multiple resections are the preferable options in patients with liver

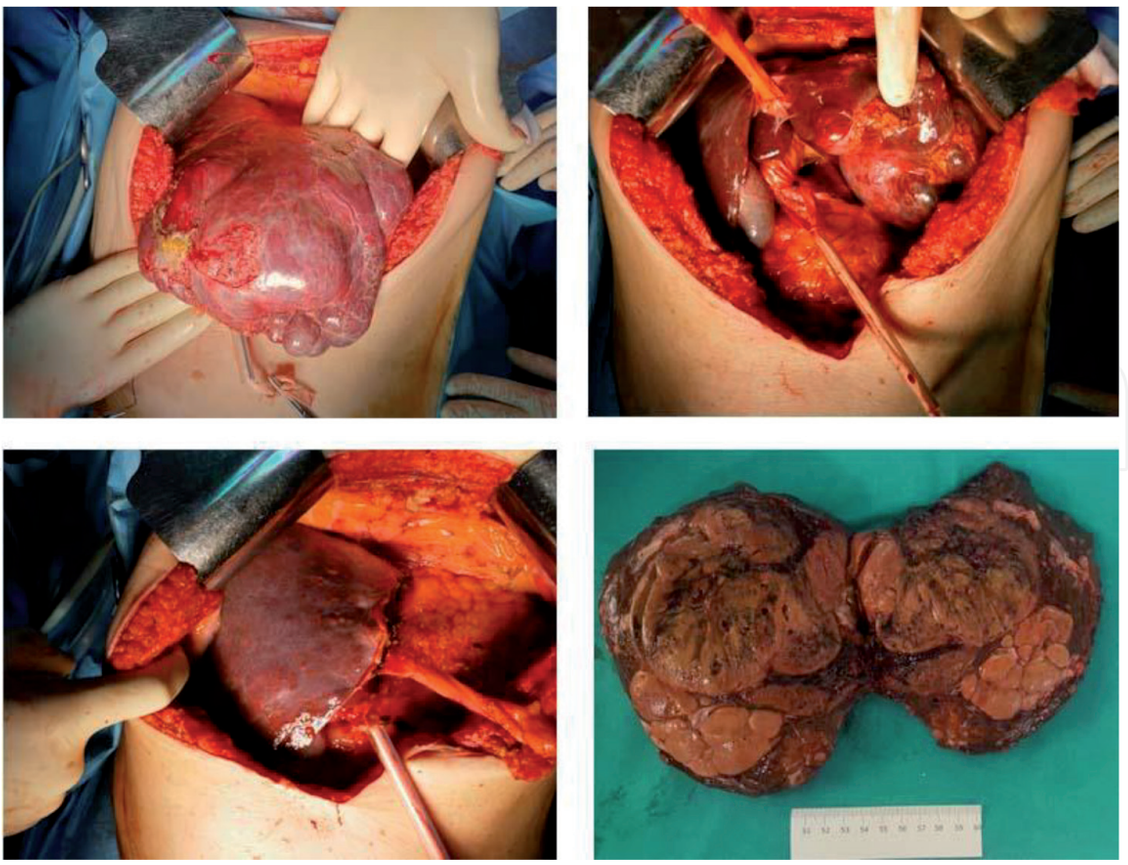


Figure 19.
Upper left: massive liver adenomatosis that deforms the contour of the left lateral sector. Upper right: a left lateral sectionectomy is planned and a cotton loop around hepatic pedicle is placed for Pringle maneuver. Lower left: intraoperative aspect after left lateral sectionectomy. Lower right: sectioned surgical specimen with evidence of the largest HA.

adenomatosis, unless technically impossible or unsafe. Radiofrequency ablation or embolization in these patients was successful in some authors' experience [74]. Liver adenomatosis becomes an indication for liver transplantation if there is evidence of malignant transformation or complications [75]. Observing these changes is possible only if patients are carefully followed on a regular basis with imaging. Liver transplantation should be considered as the last resort for patients with adenomatosis. Patients with GSD should undergo transplantation earlier than other patients with HA because the literature considers this underlying disease as a risk factor for malignant transformation of adenomas [72]. Like in transplantation for HCC, imaging diagnosis of vascular invasion should be considered an absolute contraindication to transplantation. So all the efforts are directed to early diagnose a malignant transformation of HA, and any suspicion of malignancy has to be rapidly confirmed by biopsy. Discussion with the patients with liver adenomatosis about liver transplantation must be initiated when a major criterion or at least 3 minor criteria are identified. The only major criterion is the histological proof of malignancy in at least one adenoma. The minor criteria are: (1) more than 2 serious (life-threatening) hemorrhages, (2) more than 2 previous hepatectomies, (3) β mutated or inflammatory adenomas, (4) underlying liver disease (major steatosis and vascular abnormalities), and (5) age > 30 years [72] (**Figure 20**).

7.4 Alternative treatment of HA

Other options of treatment include: transarterial embolization or ablation and radiofrequency ablation. TAE is considered as a safe and effective mini-invasive

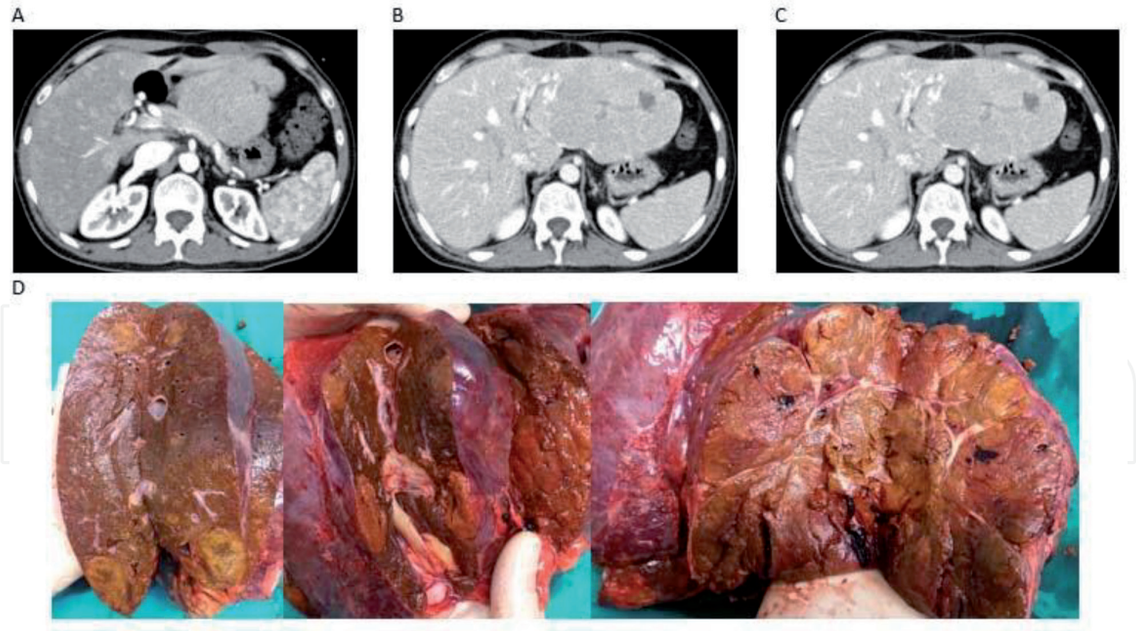


Figure 20.
Liver adenomatosis with a voluminous adenoma of the left liver in a 47-year-old male patient who had a liver transplantation. A-C. CECT of the liver with adenomatosis. D. Total hepatectomy specimen with numerous adenomas of various sizes, a voluminous adenoma in the left liver, and blood clots due to intratumoral bleeding.

procedure to be used in both elective and emergency conditions. For small lesions, TAE can achieve complete resolution and thus avoidance of liver surgery entirely. TAE may be also used as means to shrink the tumors to a size that renders them approachable for subsequent surgical resection [76]. TAE can reduce the size of large adenomas, multiple adenomas, or adenomas that are in a surgical inaccessible localization alleviating the symptoms and reducing the risk of perioperative bleeding. It has a low rate of complications (8%). These complications associated with TAE include post-embolization syndrome, temporary renal failure, and cyst formation [77]. One pyogenic abscess after TAE was also reported as a complication after TAE for a large HA. No sufficient data exist until now to conclude that TAE reduces the risk of hemorrhage or malignant transformation of residual HA, despite reports of a reduction in tumor size.

Radiofrequency ablation has its shortcomings, such as the need of many sessions in order to destruct the tumor completely, but it may be a very good option for tumors that cannot be operated [78].

Medical treatment such as administration of the SRC inhibitor dasatinib or JAK1/2 inhibitor ruxolitinib could be a new alternative in the future [79].

7.5 Management of pregnant patient

Pregnancy is no longer considered a contraindication in hepatocellular adenoma less than 5 cm. Given the fact that the HA behaves as a hormone-dependent tumor that seems to grow or regress according to estrogen level increase or decrease, respectively, it is advised that patients with adenomas who contemplate pregnancy firstly resolve the liver tumor prior to remaining pregnant [80]. If HA was diagnosed in a fertile but nonpregnant woman, and if the tumor is greater than 5 cm or she has experienced adenoma-related complications, resection is indicated before pregnancy. If HA is incidentally identified during pregnancy, the best management varies from case to case. For the smaller lesions, a conservatory approach is feasible on the condition of ultrasound follow-up every 6 weeks.

Adenomas greater than 5 cm that are discovered during pregnancy need individualized approach. Surgery is recommended during second trimester to minimalize the risks for both the mother and the fetus. Radiofrequency has been an option performed during the first and second trimester [18]. Angioembolization poses the radiation risk to the fetus early in pregnancy and must be avoided in the first trimester.

Pregnancy induces not only an increased level of endogenous hormones but also an increased liver vascularity that puts the patient at risk for adenoma rupture especially in the third trimester [81]. However, a ruptured HA discovered during pregnancy should be immediately resected by laparotomy or laparoscopy [28, 82, 83].

7.6 Follow-up of the patients

The great majority of nonresected uncomplicated HA remains stable, in few cases disappear, and in general do not grow. There is an observation that IHA may disappear more rapidly.

The follow-up of the patients with H-HA and IHA with complete resection can be stopped few years after surgery. In case of incomplete resection and with no significant change in HA size during the first years, the follow-up must be continued but at longer intervals.

Instead, the patients with β-HA resected or RF ablated must be followed-up very closely with AFP serum level check and repeated alternating imaging (US, CEUS, CT, and MRI) in order to early diagnose a possible recurrence and, in a much worse scenario, a possible malignancy with the same positioning in the liver [84].

8. Conclusions

The incidence of hepatic adenoma has increased lately as a result of more frequent imaging investigations performed for reasons not necessarily related to the presence of this benign tumor. The classical profile of the patient with adenoma has changed as a result of the emergence of new risk factors. As a result of research into phenotype, genotype, and imaging and the correlations of these results with clinical data, it is advisable that the diagnosis of hepatic adenoma include the subgroup of classification, which indicates the appropriate management of the case. The means of fitting the liver adenoma into the four subgroups are primarily imagistic, of which MRI has an essential role. In the case of insufficient data for the correct and complete diagnosis of hepatic adenoma, tumor biopsy is needed percutaneously or after tumor resection. Management of hepatic adenoma may mean on the one hand careful monitoring to recognize one of the two worrisome complications—hemorrhage and malignancy—and on the other hand, the treatment of the tumor, which may be asymptomatic or symptomatic, uncomplicated or complicated. In the elective cases, surgical resection remains the gold standard with a clear tendency toward laparoscopic approach in specialized centers, but in emergency cases caused by adenoma rupture, interventional arteriography has gained a net advantage over surgery. For rare cases of recurrent or extremely bulky hepatic adenomas, for which surgery is not feasible, but also for cases of liver adenomatosis on certain criteria, liver transplantation from cadaveric or living donor has become a reality. Careful monitoring of post-treatment patients should be continued and adapted according to the therapeutic outcomes and histopathology of the hepatic adenoma.

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