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Updates on The Management of Hepatocellular Adenomas

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Benign liver neoplasm; Estrogen-dependent tumor; Molecular subtype; Malignant transformation; Tumor regression

Abbreviations:

HCA: Hepatocellular adenomas; OCP: Oral contraceptive pills; HCC: Hepatocellular carcinomas; HNF1-α: Hepatocyte nuclear factor 1-alpha; L-FABP: liver type fatty acid binding protein expression; A(SSA): Amyloid protein, CRP: C reactive protein; shHCA: Sonic hedgehog HCA; FNH: Focal nodular hyperplasia; LA: Liver adenomatosis; MODY3: Maturity-onset diabetes of the young

1. Abstract

1.1. Background and Aims: Hepatocellular adenomas are benign neoplasms mostly seen in women of childbearing age. This paper presents an updated synopsis on epidemiology, natural history, diagnosis, and management of hepatocellular adenomas with emphasis on individualized approaches derived from genetic profiling of the tumors and risk stratification.

1.2. Methods: We analytically reviewed the original articles, population-based studies, and guidelines published in the English language between January 1975 to December 2020. A management algorithm is formulated based on the research results. PubMed, Medline, and Google scholar search engines were used with the following Medical Subject Headings: "hepatocellular adenoma", "hepatic adenoma", "hepatic adenomatosis", "benign liver tumor", and "benign liver neoplasm".

1.3. Results: These tumors are rare with an incidence of 7 cases per 10 000 000 populations. Molecular subtype classification is based on the presence of inactivating mutations in hepatocyte nuclear factor 1-alpha, activating mutations in the beta-catenin gene, or alterations in the hedgehog pathway. Activating mutations of beta-catenin exon 3 increase the risk for progression to cancer, while activation of the sonic hedgehog pathway predisposes to intra-tumoral bleeding. Magnetic resonance imaging with hepato-specific contrast is the best imaging tool for diagnosis. Immunohistochemistry studies have a pivotal role in pathological classification. Progression to hepatocellular carcinoma is rare, mostly seen in older male patients or anabolic steroid users.

1.4. Conclusion: Management is individualized based on risk stratification. Surgical resection is recommended for male patients. In females, the molecular subtype, tumor size, menopausal status, and desire for pregnancy will determine the therapeutic plan. Surveillance is a valid option for smaller tumors without high-risk features. Surgical resection is indicated for tumors with high-risk features or larger tumors. Trans-arterial embolization, radiofrequency ablation, and microwave ablation have been used in selective cases.

2. Introduction

Hepatocellular adenomas (HCA) are benign liver neoplasms typically seen in women of childbearing age [1]. HCAs are classified into four subtypes with distinct genomic profiles and clinical behaviors [2]. Transformation to cancer may occur in tumors harboring high risk genetic mutations (variations) [3]. Radiological differentiation of these tumors from other liver lesions is challenging due to rarity and lack of characteristic features in most cases [4].

2.1. Epidemiology and Risk Factors

HCA's reported incidence is 7 cases per 10 000 000 populations with a breakdown of 13 cases per 10 000 000 in women (median age, 36.8) and 2 per 10 000 000 in men (median age, 52.3) [1]. Exposure to estrogen is one of the main risk factors. The incidence is higher in females. Long-term use of oral contraceptive pills (OCP), especially first-generation high dose estrogen pills, has been associated with 25 times higher risk of developing HCA [5]. A case control study on women taking modern low dose oral contraceptives showed a minimal increase in the risk of developing HCA (hazard ratio: 1.25) [6]. Anabolic steroid intake is a risk factor for hepatocellular adenoma formation and its progression to hepatocellular carcinomas (HCC) [7]. Glycogen storage diseases, obesity, diabetes mellitus, and dyslipidemia are also associated with a higher risk of HCA formation [3, 8] (Table 1).

Table 1: Risk factors for HCA formation

Non modifiable Risk factors	Modifiable Risk factors
Female	Contraceptive pill intake
Glycogen Storage Disease	Anabolic steroid intake
	Obesity
	Dyslipidemia
	Diabetes Mellitus

2.2. Clinical Manifestations and Natural History

Most HCAs are detected incidentally. However, patients with larger tumors may experience abdominal pain, early satiety, other gastrointestinal symptoms, and a palpable abdominal mass. There are case reports of acute abdomen due to strangulation of large pedunculated HCAs or hemorrhagic shock due to tumor rupture and intraperitoneal bleeding [9, 10]. Malignant degeneration and rupture of the tumor leading to intra-abdominal hemorrhage are the two main complications. HCA may increase in size during pregnancy and regress after menopause. In a recent prospective population-based study, the researchers followed a cohort of 48 women with hepatocellular adenoma <5 cm in diameter, diagnosed by magnetic resonance imaging (MRI) during pregnancy. The tumors enlarged in 25% of these women with a median increase in the size of 13 mm [11]. In another observational study of 48 perimenopausal women with HCA, after a median follow-up time of 60.5 months, 43.5% of the lesions were not detectable, 33% were stable in size and 19.6% became smaller in comparison to the original size. HCA's median diameter after the observation period was 17.2 mm compared with 35.9 at the time of enrollment in the study [12].

transformation to hepatocellular carcinoma is a rare phenomenon. In a review of 1635 patients with HCA, 4.2% of tumors progressed to cancer. Clinical factors associated with progression to cancer were male gender, use of anabolic steroids, and glycogen storage disease [13]. In an observational study of 52 (44 females and 8 males) patients with histologically confirmed HCA, the cumulative 10- year risk for cancer formation in men was 60%. Men who developed HCCs were older than 50 at the time of diagnosis. None of the women in this cohort developed HCC [1]. Tumor hemorrhage and rupture is another life-threatening complication. In a multivariate analysis of 124 patients with HCAs, tumor size (OR, 7.8) and hormone use within the past 6 months (OR, 4.5) were the main risk factors. No tumor less than 5 cm in diameter was ruptured [14].

2.3. Pathological Subtypes

Current molecular and pathological subtyping of HCA was suggested in 2006 [2]. There are four subtypes based on inactivating mutations in the hepatocyte nuclear factor 1-alpha (HNF1-α), activating mutation in the β-catenin gene, or activation of inflammatory signaling pathways (Table 2) [15, 16].

Table 2: HCA subtype classification

HCA subtype	Frequency	IHC	Histological Features
H-HCA	35% - 40%	L-FACP under-expression in neoplastic cells Patchy CD34 expression	Steatosis Cellular atypia Lack of inflammatory cells and markers
B-HCA	15% - 20%	Strong glutamine synthase positivity Nuclear B-catenin over-expression	Steatosis Cellular atypia Lack of inflammaion pseudo acinar pattern
I-HCA	30% - 35%	Over expression of inflammatory markers (serum amyloid protein A and C reactive protein) CD34 positivity at pseudo portal tract area	Sinusoidal dilation Inflammatory infiltrates Area of peliosis with dialated sinusoidal spaces Thickened tortuous feeding vessels
U-HCA	10%	Non-specific mutations	No unique features

HNF1α inactivated (H-HCA): Somatic inactivating mutation of HNF1-α is detected in 35%-40% of HCAs. This mutation results in the production of nonfunctioning HNF1-α protein. HNF1-α protein is one of the critical factors for regulating glucose and lipid metabolism within the hepatocyte. The deficiency of this protein leads to intracellular deposition of fat [17]. HNF1-α mutations may be the primary event that results in the accumulation of estrogen metabolites and stimulation of hepatocyte proliferation [18]. The histological features of this subtype are steatosis, cellular atypia, and lack of inflammatory cells and markers. Immunohistochemistry (IHC) findings include decreased or absent liver type fatty acid binding protein expression (L-FABP) in neoplastic cells compared with background hepatocytes and patchy CD34 positivity (Figure 1).

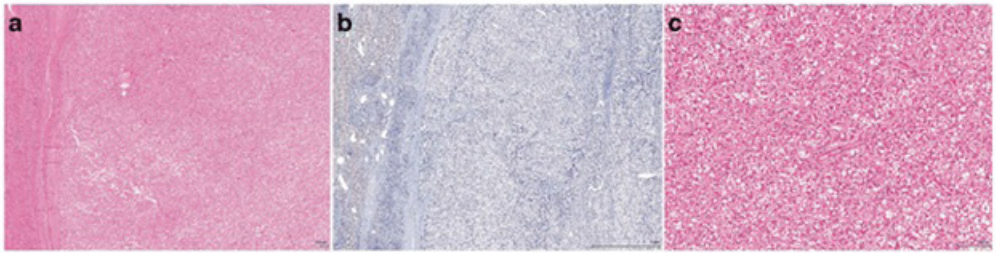

Figure 1: H-HCA. Steatosis in hematoxylin and eosin staining in low (a, x20) and high magnifications (c, x100. b, loss of LFABP expression. Image by Margolskee, et al. Hepatocellular adenoma classification: a comparative evaluation of immunohistochemistry and targeted mutational analysis. Diagn Pathol. 2016 Mar 9;11(1):27.

β-catenin-mutated type (B-HCA): Activation of β-catenin gene is seen in 15% to 20% of HCAs. This HCA subtype is more common in patients with glycogen storage disease and men taking anabolic steroids. β-catenin plays a significant role in hepatocyte development, proliferation, and regeneration. Activating mutations in β-catenin exon 3 increase the risk for transformation to HCC, while mutations in exon 7/8 are not associated with an increased risk of malignancy [3, 16]. IHC characteristics include strong glutamine synthase and nuclear beta-catenin expressions. Histological features are cellular atypia, steatosis, lack of inflammation, and pseudo acinar pattern (Figure 2).

Inflammatory type (I-HCA): 30% to 35% of HCAs are inflammatory HCAs. In the past, these tumors were known as telangiectasia focal nodular hyperplasia [19]. Tumors in this subtype are considered inflammation-induced hepatobiliary neoplasms. Mutations of the β-catenin gene are detected in 10% of I-HCAs. This subtype is more common in patients with metabolic syndromes such as alcoholism and obesity [3, 15]. Histological characteristics include sinusoidal dilatation, inflammatory infiltrates, peliosis areas with dilated sinusoidal spaces, and thickened tortuous feeding arteries. A prominent periductal inflammatory reaction is seen. IHC findings include CD34 positivity at the pseudo portal tracts and strong expression of inflammatory markers such as serum amyloid protein A (SSA) and C reactive protein (CRP). Glutamine synthetase expression is seen in I-HCA with the β-catenin mutation (Figure 3).

Unclassified type (U-HCA): This subtype accounts for 10% of HCAs. There is no specific genetic mutation or unique morphologic features. Tumors with activation of the sonic hedgehog pathway comprise 1/3 of this subtype.

Nault et al. suggested a new molecular classification system based on gene sequencing and expression analyses of 611 samples. In this system, HCAs with the activation of sonic hedgehog pathway are labeled sonic hedgehog subtype (shHCA). shHCA has a higher tendency to bleed. Tumors harboring activated b-catenin genes constitute two subtypes; b-catenin exon 7/8 activated and b-catenin exon 3 activated. Mutations of β-catenin in exon 3 increase the risk for malignancy, whereas mutations in exon 7/8 do not increase cancer risk [3].

Figure 2: B-HCA. a, Border of b-HCA (middle and right) with normal background liver(left). b strong glutamine synthase positivity (right). There is focal perivenular staining in the normal background liver (left). C, glutamine synthase overexpression (right panel) and β-catenin nuclear staining (left panel). Image by Margolskee, et al. Hepatocellular adenoma classification: a comparative evaluation of immunohistochemistry and targeted mutational analysis. Diagn Pathol. 2016 Mar 9;11(1):27.

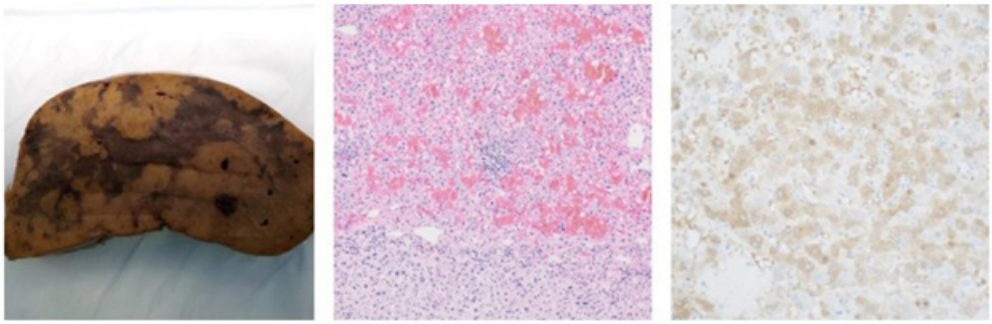

Figure 3: IHCA. Left, a cross-section of the tumor with areas of hemorrhage seen as dark red patches. Middle- sinusoidal dilatation and inflammatory infiltrate in hematoxylin and eosin staining. Right, cytoplasmic CRP expression is seen in IHC staining (Courtesy of Shaojun Liu MD PhD and Maria Isabel Fiel MD).

2.4. Imaging Characteristics

HCAs are commonly detected incidentally in the cross-sectional imaging studies performed for unrelated indications. The radiologist's main challenge is to differentiate HCAs from malignant tumors and other benign hepatic lesions such as Focal Nodular Hyperplasia (FNH) or hemangiomas. The imaging findings reflect histologic features. Increased vascularity, sinusoidal congestion, hypervascularity, and inflammatory infiltrate appear as hyperenhancing and steatotic areas as hypoenhancing after intravenous contrast administration. In general, there is heterogenous enhancement following intravenous contrast administration with a return to background liver signal intensity on delayed sequences on multiphasic helical Computed Tomography (CT) scan and MRI studies. Although hepatic adenomas are usually solitary, the presence of 2 or 3 lesions is common. Multiple adenomas are a common phenomenon and was reported in up to 48% of patients in some series, especially in cases with liver steatosis [20, 21].

2.4.1. Ultrasonography (US): Hepatic adenomas are occasionally detected in ultrasonic examinations of the liver. Intra-tumoral hemorrhage manifests as hyper or hypoechoic areas within the tumor. Calcifications in the necrotic areas of the tumor may appear as acoustic shadowing. The ultrasonographic findings are not characteristic for adenoma, and further cross-sectional imaging should be obtained [22].

2.4.2. CT Scan: HCAs are usually well circumscribed iso-dense lesions on non-contrast CT, portal venous phase, and delayed images; but may appear hypo or hyperdense based on the extent of steatosis in the background liver. HCAs are heterogeneous on non-contrast and contrast-enhanced CT scans due to areas of necrosis and hemorrhage. This feature is more obvious in larger tumors. On contrast-enhanced CT, the lesions are hypervascular in the arterial phase and become iso to hypoattenuating in the portal venous phase and delayed images. Central scar (stellate scar) and central artery within the scar are characteristic findings of FNH and are not seen in hepatic adenomas. Differentiating HCA from HCC is challenging as both lesions have similar imaging features, and HCA might progress to cancer. The presence of underlying cirrhosis, portal hypertension, and imaging evidence of invasion or lymph node enlargement are in favor of HCC [21, 22].

2.4.3. MRI: MRI with intravenous and hepato-specific agents is the best imaging modality for differentiating HCAs from other solid liver lesions and identifying the subtype. Adenomas are usually heterogeneous due to increased signal intensity in fat or blood areas and decreased intensity associated with necrosis, old blood, or calcifications. A peripheral rim of enhancement is detected in 1/3 of the cases due presence of a fibrous capsule. HCAs are most often hyperintense in comparison to the background liver on the T2 sequences. L-FABP–negative HCAs show a diffuse decrease in signal intensity on opposed-phase images due to diffuse steatosis within the tumor. The "atoll sign" is as a rim of T2 hyperintensity and central hypointensity. This finding is characteristic of I-HCAs and was detected in 43% of I-HCAs in a retrospective study of 48 histologically confirmed HCAs (Figure 4) [4, 22]. A vaguely demarcated scar, strong arterial enhancement, and delayed washout after gadolinium injection are reported features in B-HCA. However, MRI features overlap between various HCA subtypes, and many tumors lack characteristic findings [4,23].

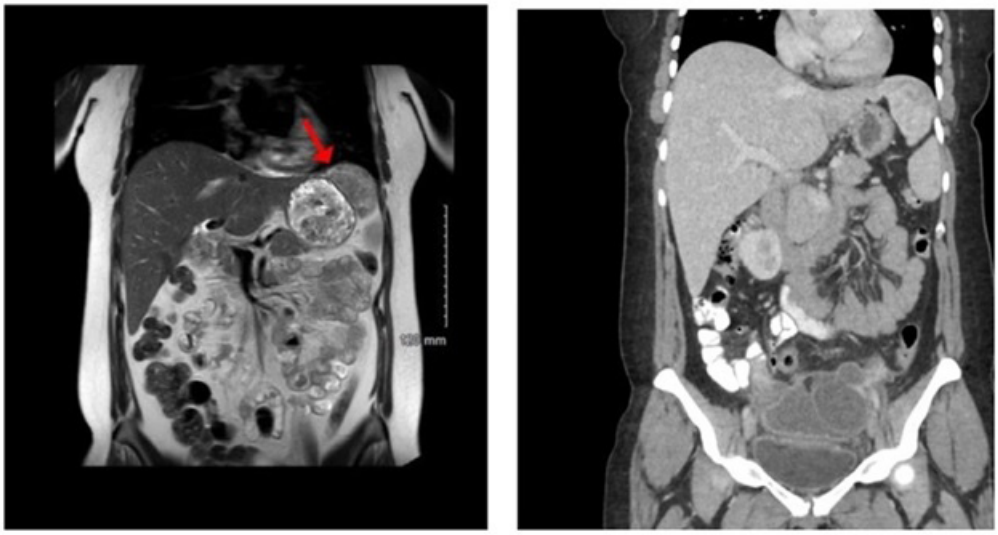

Figure 4: Left, MRI of the abdomen without and with contrast, Pedunculated I-HCA appears as a heterogeneous mass attached to the left lobe of the liver with a narrow pedicle (red arrow). The mass is hyperintense on T2 sequences. Right, Coronal CT scan with contrast: I- HCA appears as a heterogeneous mass attached to the left lobe of the liver.

2.4.4. Management: The latest EASL clinical practice guidelines on the management of benign liver tumors suggest a care plan based on the patient's gender and tumor size. Lifestyle changes to correct metabolic syndromes such as obesity, hyperlipidemia, diabetes is encouraged [24]. Bariatric surgery is a valid option to lose weight in morbidly obese patients [25]. Oral contraceptives and anabolic steroids should be discontinued (Figure 5).

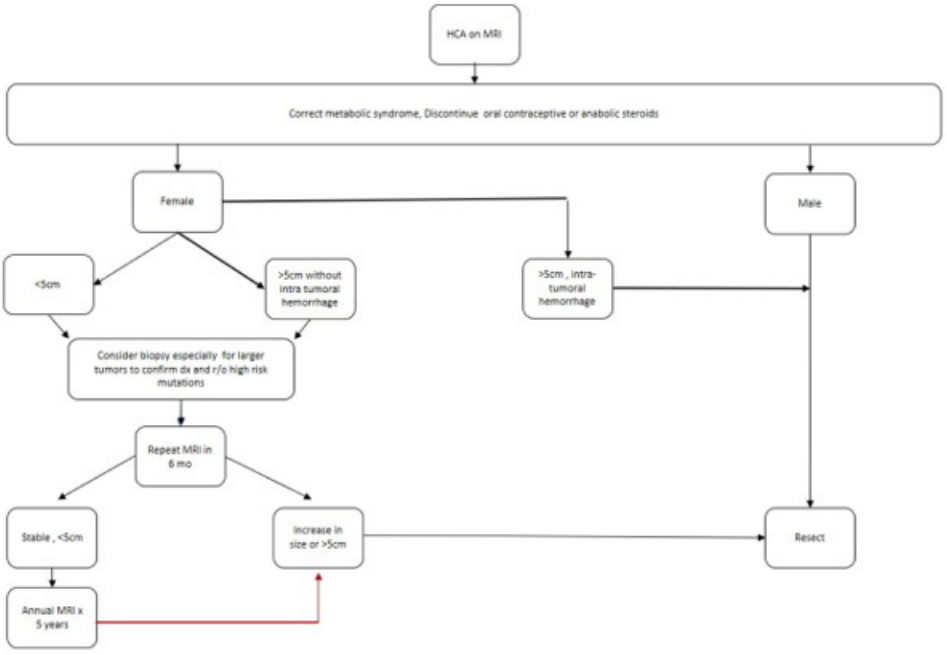

Figure 5: HCA management flowchart. High-risk features include activating mutation in β-catenin or sonic hedgehog pathway

Contrast enhanced MRI is the imaging modality of choice. In men, surgical resection of any HCA is recommended due to the higher risk for malignant degeneration [3]. In women, 6 months of observation is recommended. If the tumor increases in size (≥ 20%) or remains more than 5cm in diameter on the follow-up MRI study, surgical resection is advised. Women with tumors < 5cm in diameter will undergo surveillance by annual MRI [24]. In a retrospective review of MRI and CT scan studies of 44 patients with liver adenoma or adenomatosis who underwent imaging surveillance, maximum regression of the tumors was detected within 5 years and the tumor stabilized afterward [26]. The interval between follow-up MRIs can be increased to biannual after 5 years. Surveillance could be discontinued after menopause as the tumor's natural course is to regress or remain stable after menopause. In perimenopausal women, watchful waiting is a valid option as 2/3 of tumors either decrease in size or disappear in 5 years [12]. EASL guidelines do not recommend a routine biopsy of HCAs, except for situations when the diagnosis is in doubt. We advocate for more liberal use of image-guided biopsies, especially for larger tumors. MRI features of HCA are nonspecific, and there is overlap between various subtypes. There is a growing list of IHC protein markers for high-risk mutations within HCAs [27]. The information obtained by IHC staining of the biopsy specimens will help to customize the management plan for individual patients. The safety of percutaneous liver biopsy was evaluated in a retrospective review of medical records of 1398 patients who underwent image-guided percutaneous liver biopsies over 20 years. Significant complications occurred in 12 patients (1%), including 3 cases of death due to hemorrhage. Other complications included bile leak and visceral perforation. The patients who suffered from major bleeding after liver biopsy had multiple medical co-morbidities and were coagulopathic [28]. The safety and accuracy of transcutaneous image-guided biopsy of HCA was reviewed in a retrospective study of 61 biopsy-proven HCAs. One patient had a major hemorrhage requiring transfusion. The biopsy results were discordant with the final diagnosis in 10% of cases. The tumor was upgraded to well differentiated HCC or downgraded to FNH in follow-up investigations, including repeat biopsy, surgical resection, or MRI imaging [29]. These findings highlight the significance of risk-benefit analysis before pursuing liver biopsy.

Surgical resection has traditionally been performed in an open fashion. Laparoscopic liver resection is gaining popularity and is offered in many hepatobiliary centers. The minimally invasive surgical approach's advantages are reduced bleeding, decreased postoperative pain, reduction in postoperative morbidities, and shorter hospital stays [30]. The robotic platform is also gaining popularity among hepatobiliary surgeons and is expected to offer similar advantages [31]. Arterial embolization is an option in emergency cases with ruptured adenoma to avoid emergency hepatectomy [10]. Radiofrequency and microwave tumor ablation techniques have been used for tumors less than 4 cm in diameter, centrally located unresectable tumors, or surgically unfit patients [32, 33].

2.5. HCA and Pregnancy

Pregnancy is not discouraged. The tumor enlarges in 25% of cases during pregnancy. Women with larger tumors or tumors with high-risk features are encouraged to undergo surgical resection before a planned pregnancy. The second trimester is the safest time for the mother and the baby for elective surgery [34]. There are reports of trans-arterial embolization of large HCAs in the third trimester with satisfactory results Pregnant patients with HCAs should have an ul-

trasound of the liver every 3 months during pregnancy.

2.6. Liver Adenomatosis

Liver Adenomatosis (LA) is a rare condition and is characterized by 10 or more HCAs. The adenomas are heterogeneous, and the same liver may harbor different subtypes of HCA. The background liver parenchyma is either normal or abnormal such as in glycogen storage disease or portal vein agenesis. Liver adenomatosis occurs in sporadic or familial forms with a germline inactivating mutation in HNF1A. The latter mutation is seen in patients with Maturity-Onset Diabetes of the Young (MODY3). An observation study of 40 patients with LA (excluding glycogen storage disease) reported 3% malignant transformation and 15% intra-tumoral hemorrhage during a median follow up of 10 years. 15% of the patients in this cohort had mixed liver adenomatosis. Most of the complications happened after age 40 [35]. The management algorithm is the same as solitary HCAs. The patient will be encouraged to stop oral contraceptives and other forms of sex hormone intake. Surgical resection is recommended for tumors larger than 5 cm in diameter or smaller tumors with increased risk of hemorrhage or malignancy such as shHCA subtype or in tumors with activating mutations of β-catenin in exon 3. Liver transplantation may be considered in patients with unresectable tumors but is rarely indicated [36].

2.7. Future Directions

There are several unanswered questions about HCA that will guide future research efforts. The molecular pathways that lead to progression to cancer provide potential targets for oncological treatments [37]. Predicting these tumors' natural course will allow the physician to tailor the management plan and avoid over or under treatment. Further research will enable us to accurately classify these tumors in a non-invasive manner and provide safer and less morbid treatment options.

3. Conclusion

HCAs are benign liver neoplasms with heterogeneous features. There are 4 subtypes, including H-HCA (35%-40%), B-HCA (15% to 20%), I-HCA (30%-35%), and U-HCA (10%). Progression to cancer and tumor hemorrhage are the two main complications. Activating mutations at β-catenin exon 3 and activation of the sonic hedgehog pathway will predispose to malignant transformation and intra-tumoral bleeding, respectively. Immunohistochemical staining is essential for subtype classification. Malignant transformation is rare and exclusively seen in male patients. MRI with hepatobiliary contrast is the best imaging study to characterize these tumors; however, imaging features are nonspecific in many cases. These tumors increase in size during pregnancy and regress after menopause. Patients with glycogen storage disease have a higher risk of developing HCAs and subsequent cancer. The management algorithm is individualized based on risk stratification, molecular subtype, and tumor genotype. Male patients should undergo surgical resection. In females, the tumor's molecular subtype and size and the patient's hormonal status will determine the management plan. Surgical resection is recommended for any tumor with high-risk features. For tumors smaller than 5 cm without high- risk features, surveillance with annual MRI is appropriate. For tumors 5cm or larger, an initial period of observation is advised before surgical resection. Ablative therapies have been used for patients with smaller tumors who are not good surgical candidates or when the tumor's central location prohibits surgery. Further research will advance our understanding of the genetic and environmental factors involved in these tumors' development and progression and identify the candidate genes and molecular pathways for targeted therapies.

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