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Hepatocellular adenoma management: advances but still a long way to go

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Hepatic Oncology

Practice points

- More than 80% of hepatocellular adenoma (HCA) developed in normal or occasionally steatotic liver occur in women taking oral contraceptives. Other factors include drugs, obesity, vascular disorders and genetic diseases, particularly MODY3, glycogenosis.
- HCA is not a single entity. Four major molecular subgroups of HCA were defined by: mutations inactivating HNF1A gene (H-HCA, 35% of the HCA); the inflammatory phenotype with mutations of different genes leading to STAT3 activation (IHCA, 50%); the activation of β -catenin by mutations in exon 3 (β -HCA, 15%); among β -HCA, half displayed both inflammatory and β -catenin-activated phenotypes (β -IHCA); and the remaining unclassified tumors (UHCA, 10%).
- The diagnosis of HCA is based on clinical, radiological and pathological data. MRI and/or immunohistochemistry are necessary to identify the two major subtypes.
- The two major risks are hemorrhage and hepatocellular carcinoma. To avoid these risks, large HCA (>5 cm) are resected. To avoid the risk of malignant transformation, smaller nodules are resected in men. In β -HCA and β -IHCA early resection or strict follow-up is recommended. There is no consensus concerning the best way to follow patients with nonresected HCA.
- In spite of the great progress made in the understanding of HCA, the management of HCA subtypes has not gained yet major recognition. There are several reasons for that, the major one being the lack of information of the natural history of the different subtypes in different etiological and clinical circumstances. To make progress in the management of HCA and propose guidelines, we need to collect data from different parts of the world, we need expert centers and we need a multidisciplinary approach including surgeons, radiologists, pathologists and molecular biologists.
- Medical treatment such as administration of the SRC inhibitor dasatinib or JAK1/2 inhibitor ruxolitinib may represent new options in the future.

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SUMMARY Hepatocellular adenomas (HCAs) are composed of four molecular subgroups: mutations inactivating the *HNF1A* gene; the inflammatory phenotype with mutations of different genes leading to STAT3 activation; the activation of β -catenin by mutations in exon 3; among β -HCA, half display both inflammatory and β -catenin-activated phenotypes; and the unclassified tumors. The identification of these subtypes by MRI and immunohistochemistry on tissue is considered as a major criterion to manage patients. Of particular relevance is the identification of the β -catenin-mutated group due to its high risk of malignant transformation. In spite of this progress, the classification has not gained recognition among surgeons. It is hoped that by working as a multidisciplinary team, including surgeons, radiologists, pathologists and molecular biologists, patients will be managed more rationally. In this article, we will present known and new data, well accepted and that which is still controversial. The progress made in the field of HCA in the last 12 years, whether in epidemiology, diagnosis (clinical, pathology, imaging) or management, is related in one way or another to molecular advances.

Molecular data

• The classification

Hepatocellular adenomas (HCAs) are defined as the monoclonal proliferation of well-differentiated hepatocytes arranged in sheets and cords and characterized by the absence of a portal triad and interlobular bile ducts [1]. HCA is not a single entity [2]. Four major molecular subgroups of HCA are defined by (Table 1): mutations inactivating *HNF1A* gene (H-HCA, 35% of the HCA) [3–8]; the inflammatory phenotype with mutations of different genes leading to STAT3 activation (IHCA, 50%) [9–11]; the activation of β -catenin by mutations in exon 3 (β -HCA, 15%) [12–15]; among β -HCA, half display both inflammatory and β -catenin-activated phenotypes (β -IHCA) [12–18]; and the remaining unclassified tumors (UHCA, 10%) [12–18].

• New data

Whole-exome sequencing of HCA revealed the high genetic diversity of these tumors, and the genes recurrently mutated in hepatocyte benign tumorigenesis and in the subsequent malignant transformation [9]. Among the genes mutated, a recurrent somatic mutation in *FRK* was identified leading to an activation of the FRK kinase activity and to constitutive STAT3 activation associated with the inflammatory phenotype of HCA. Overall, the gene mutations identified in IHCA activate the STAT3 pathway to cause a common inflammatory phenotype within the tumors. By integrating all of the ‘omics data with the clinical and pathological features of these tumors, the mutational spectrum of inflammatory HCA is composed of mutations in genes *IL6ST* (26% of HCA), *FRK* (5%), *STAT3* (2%), *GNAS* (2%) and *JAK1* (1%). Nowadays, inflammatory driver gene mutations remain to

be identified in 18% of IHCA. Moreover, 10% of the HCA remain unclassified and in these cases additional specific genetic or epigenetic defects remain to be identified.

Exome sequencing has revealed, in addition to exon 3 mutations of *CTNNB1*, possible mutations located in exon 7 and in exon 8 [9]. Because those exon 7/8 mutations lead to low activation of the Wnt/ β -catenin pathway, all HCAs with *CTNNB1* exon 7 and exon 8 mutations were previously considered as unclassified or inflammatory HCA; and they were further classified for all analyses in the β -HCA or β -IHCA molecular subgroups. *CTNNB1* exon 3 and exon 7/8 mutations were mutually exclusive; *CTNNB1* exon 7 and exon 8 mutations are rarely involved in HCA transformed in HCC as well as in classical HCC, suggesting that these genes are not significantly involved in the malignant transformation process. In accordance with this low activation of the β -catenin pathway, immunohistochemical analyses of these cases revealed a faint patchy glutamine synthase expression without nuclear staining of β -catenin. All these results showed that *CTNNB1* exon 7/8 mutations weakly activate β -catenin *in vivo* in HCA.

Interestingly, the methylome analysis distinguished perfectly the five molecular groups of HCA [9], and identified genomic clusters of hypomethylation at gene family loci showing a close relationship between epigenetic changes, gene mutations and phenotypes of the tumors. A set of liver-specific genes, hypermethylated and downregulated specifically in H-HCA, were also identified.

Accumulation of chromosome aberrations is a typical feature of malignant transformation of HCA. Here, in hepatocellular tumors, somatic-activating *TERT* promoter mutations

Table 1. Hepatocellular adenoma and its subtypes: differential diagnosis, etiology and pathology.

	H-HCA	IHCA	β-IHCA	β-HCA	UHCA
HCA without specific etiology					
Sex mainly women [†] in all subtypes	Rare in man	Both sexes	Both sexes	Both sexes	Rare in man
Obesity plays a role in all subtypes		Major role	Major role		
HCA with specific etiology					
Both sexes (except POCS)	MODY3, FAP, vascular diseases [‡]	GSD, FAP, vascular diseases [‡] , POCS	GSD	GSD, male hormones, vascular diseases [‡]	GSD
Pathology (with/without specific etiologies)					
	Steatosis [§]	Sinusoidal dilatation, inflammation, thick arteries, DR [¶]	As IHCA	No specific characteristics [#]	No specific characteristics [#]
IHC (tumor)	Lack of LFABP	Expression of CRP	Expression of CRP, GS strong/diffuse or patchy ^{††} , β-cat nuclear staining ^{††} , Risk of malignancy	GS strong/diffuse or patchy ^{††} , β-cat nuclear staining ^{††} , Risk of malignancy	No specific characteristics
Differential diagnosis (imaging and if necessary biopsy): focal nodular hyperplasia and hepatocellular carcinoma.					
Risk of malignancy: male sex, β-catenin mutation (requires biopsy), increase in size (imaging); imaging criteria, some etiologies (GSD, liver vascular diseases, male hormones).					
Arguments suggesting borderline lesions or HCC foci (require biopsy): cytological and architectural abnormalities (atypia, loss of reticulin, pseudo glands, etc...), positivity of HSP70, GPC3, CD34. In full blown HCC, it is almost impossible to say if the HCC occurs on a previous HCA (in the absence of a past history of HCA).					
[†] Taking or not oral contraceptives. [‡] Budd Chiari syndrome, portal vein agenesis and so on. [§] Steatosis may be lacking and some architectural abnormalities may be observed in atypical H-HCA. [¶] One or several criteria may be lacking. [#] Some minor cytological/architectural abnormalities and areas with many vessels may be observed. ^{††} The significance of other GS abnormalities is still unknown. ^{‡‡} This staining may be focal and missing on the section. β-cat: β-catenin; CRP: C reactive protein; DR: Ductular reaction; FAP: Familial adenomatous polyposis coli; GPC: Glypican; GSD: Glycogen storage disease; HSP: Heat shock protein; IHC: Immunohistochemistry; LFABP: Liver fatty acid binding protein; MODY: Maturity onset diabetes of the young; POCS: Polycystic ovary syndrome.					

were identified as a major event involved in the malignant transformation of HCA in association with β-catenin activation. *TERT* promoter mutations were not found in classical HCA, but they were found later in the malignant progression in borderline lesions (17%) and in transformed HCA to HCC (56%) with a frequency similar to that identified in classical HCC (54%). In HCC, *TERT* promoter mutations were significantly associated with *CTNNB1* mutations ($p < 0.0001$) [19]. These results suggest a step-by-step model where *CTNNB1* mutations are early mutational events in benign liver tumorigenesis, although not sufficient to induce hepatocellular carcinoma (HCC) in normal liver alone; telomerase reactivation through *TERT* promoter mutations is consequently required to promote full malignant transformation. Identification of *CTNNB1* and

TERT promoter mutation as key genetic determinants of malignant transformation in HCA will be useful to propose tailored treatment in these subtypes of patients.

Three pathways recurrently altered in HCA (*HNF1A* inactivation, STAT3 and/or β-catenin activation alone) are associated with the benign phenotype of the tumors and specific histological features. In contrast, the malignant transformation is strongly associated with characteristic gene mutations (*CTNNB1* exon 3 and *TERT* promoter mutations), chromosome alterations and hypomethylation accumulated in time frame together with previously described specific clinical features.

Epidemiology

The causes of HCA are still poorly understood. Several factors may play a role (Table 1).

• Hormones & drugs

More than 80% of HCA developed in normal or occasionally steatotic liver occur in women taking oral contraceptives (OC). Oral contraception is strongly associated with occurrence of HCAs after 2 years of OC use [20]. Indeed, a dose-dependent association has been described for estrogen exposure [21]. However, only a small number of patients using OC develop HCA (about 3 per 100,000 in exposed patients) [20]. Spontaneous regression of HCAs after withdrawal of estrogen has also been described, thereby suggesting that development of HCAs could be in particular cases dependent on the hormonal context [22,23]. The risk of HCA remains, however, extremely low among women exposed to OC. A role for an additional unknown minor allele associated with environmental factors is of concern.

Androgen consumption is a well-known risk factor for HCAs, particularly β -HCAs [24–26]. HCAs have been reported in patients with Fanconi anemia treated with an androgen, in cases of anabolic androgen steroid abuse in athletes, or due to an endogenous high level of androgen such as in Klinefelter's syndrome or polycystic ovary syndrome [27–29]. Dramatic regression of HCAs after withdrawal of androgen has been recurrently described [22,23] even when malignant transformation has occurred.

Several associations between HCA and antiepileptic drugs have been reported, but a causative effect remains to be shown [30,31].

• Obesity

HCA are also related to other risk factors such as obesity and alcohol intake. Obesity has recently emerged as a causal factor particularly in IHCA [32,33].

• Vascular diseases

Hepatocellular nodules including large regenerative nodules (often called FNH-like lesions), HCA, HCC are frequently observed in liver vascular diseases and more particularly in Budd Chiari syndrome and congenital portosystemic shunts [34–39]. Hepatocellular nodules with characteristics of IHCA have been reported in alcoholic cirrhosis by Japanese authors [40]. These recent preliminary data broaden considerably the scope of HCA field limited so far to the normal liver. However, a word of caution is necessary because in both situations gene mutations have not yet been reported.

• Genetic diseases

Genetic diseases also play an important role:

- Maturity-onset diabetes Type 3 (MODY3), monogenic noninsulin-dependent diabetes patients carry a germline inherited *HNF1A* mutation in one allele [5]. HCA that develop in patients with MODY3 present another somatic mutation inactivating the second allele of *HNF1A* in the tumor hepatocytes. Patients with germline mutations of *HNF1A* are predisposed to develop liver adenomatosis [5,41];
- Glycogenosis 1a is a rare recessive metabolic disease characterized by germline mutations inactivating glucose-6-phosphatase [42,43]. More than 50% of these patients develop HCAs during follow-up [43,44]. Two studies have recently shown that all HCAs observed in patients with glycogenosis were β -HCAs, IHCAs or unclassified [45,46];
- Familial adenomatosis polyposis (FAP) patients may rarely develop HCA. H-HCA has been observed as well as a biallelic inactivation of the *APC* gene [47,48];
- McCune–Albright syndrome, an orphan disease characterized by mosaic somatic *GNAS*-activating mutations, predisposes patients to the development of IHCA [49].

Strikingly, these genetic diseases predispose to the development of specific molecular subtypes: H-HCA in patients with MODY3, IHCA in patients with McCune–Albright syndrome and absence of H-HCA in glycogenosis [2]. However, whereas genetic diseases constitute strong risk factors, penetrance of the HCA phenotype is incomplete and particularly rare in patients with MODY3. Thus, additional modifier genes or environmental factors remain to be identified to fully understand which patients will develop HCA. In summary, HCA could be caused by a 'benign tumorigenic field effect.' This predisposition could be the result of a conjunction between genetic and genotoxic factors leading to proliferation of benign hepatocytes [2].

Diagnosis

• Clinics

HCA lesions are mainly discovered following abdominal pain and incidentally using imaging-based exploration. Liver enzyme levels are often normal, apart from anicteric cholestasis (Table 2). An inflammatory syndrome (elevated CRP) is a

Table 2. Hepatocellular adenoma and its subtypes: diagnosis and management.

	H-HCA	IHCA	β-IHCA	β-HCA	UHCA
Diagnosis (imaging and if necessary biopsy)					
Imaging : MRI and CEUS	Specific criteria [†]	Specific criteria [†]	Specific criteria (see IHCA) biopsy is necessary	No specific criteria, biopsy is necessary	No specific criteria, biopsy is necessary
Number: from single to multiple in all subtypes					
specificity	Adenomatosis	Adenomatosis [§]			
Laboratory tests	Raised GGT, AP	Raised CRP [¶] , ACD	Raised CRP [¶] , ACD		
Biopsy to identify subtypes			Needed	Needed	Needed
Arguments for malignancy (requires liver biopsy)			<i>TERT</i> promoter mutation	<i>TERT</i> promoter mutation	
Management					
Biopsy requirement for management ^{††}					
Destruction of the nodule ^{††}	Tendency to go over 5 cm ^{§§}	Tendency to go over 5 cm ^{§§}	Tendency to eradicate smaller nodules if risk of malignancy	Tendency to eradicate smaller nodules if risk of malignancy [#]	
<ul style="list-style-type: none"> • Stop oral contraceptives: the classical rules to eradicate HCA greater than 5 cm in women and of any size in men may not be true in all circumstances. • Follow-up: US every year and more if indication of regression. HCA could regress spontaneously with aging (it is rare to observe HCA in aging). • No absolute contra-indication of pregnancy. 					
[†] MRI: diffuse decrease in signal intensity on opposed-phase MR images (intratumoral fat deposition). CEUS: homogeneous hyperechogenicity at baseline sonography. Centripetal or mixed arterial filling and isoechogenicity in portal and late venous phases. ^{††} MRI: atoll sign (hyperintense signal band in the periphery of the lesion and isointensity of the center of the lesion) or high signal intensity on T2-weighted images. CEUS: strong hypervascularity in arterial phase with persistent enhancement on MR images in late portal venous phase; strong hypervascularity in the arterial phase with centripetal enhancement filling and peripheral linear vascularities in the early phase of filling. In the late portal venous phase, peripheral rim of sustained enhancement with a hypoechoic central area (washout). [§] Less frequent than in H-HCA. [¶] In the absence of hemorrhage or necrosis. [#] Withdrawal of male hormones may lead to complete regression even HCC. ^{†††} Yes for clinical research; no for routine except when the typing may influence the management (HCA diagnosis uncertain by imaging, failure of imaging criteria in favor of borderline lesion). ^{††††} Resection, radio frequency, embolization. ^{§§} Multiple nodules ACD: Anemia of chronic disease; AP: Alkaline phosphatase; CRP: C-reactive protein; GGT: γ-glutamyl transferase.					

characteristic of IHCA (Table 2) in the absence of hemorrhage or necrosis [50]. All tumor markers routinely used are normal. Bleeding and malignant transformation to HCC can occur as severe complications, respectively, in 30–50% and 5% of the cases [51–53]; they can reveal HCAs. β-HCA (with or without additional inflammatory phenotype) are known to be at higher risk of malignant transformation, particularly in man [12].

• Imaging

Imaging-based diagnosis of HCA is made preferentially using MRI and liver-specific contrast agents such as gadobenate dimeglumine or

gadoxetate to distinguish HCA from FNH and to identify the two major adenoma subtypes (H-HCA and IHCA) (Table 2). Typical H-HCA are characterized by hyper- or iso- intensity on T1-weighted (T1W) images, with diffuse signal dropout on phase opposed T1-weighted chemical shift sequence due to intratumoral fat; iso- or slightly hyperintensity on T2-weighted images, and moderate arterial enhancement not persisting in the portal venous and delayed phases on Gadolinium-enhanced T1W. Typical IHCA are characterized by isointensity on T1W images, generally without signal dropout on phase opposed T1-weighted chemical shift sequence,

marked hyperintensity on T2-weighted images, with stronger signal intensity in the outer part of the lesion and intense arterial enhancement persisting in the portal venous and delayed phases on Gadolinium-enhanced T1W [54–57].

MRI liver specific contrast agents can help to differentiate FNH from HCA: FNHs are iso- or hyper-intense whereas most HCAs appear hypo-intense at the biliary phase [57].

Ultrasound and contrast-enhanced sonography can help in differentiation of 1-FNH and HCA and 2- of HCA subtypes [58].

• Pathology

Histological analyses of biopsied or resected hepatocellular tumors developed in an otherwise normal liver is refined by the use of a panel of markers qualified through the HCA molecular classification (glutamine synthase, β -catenin, LFABP, CRP/SAA) [13–17,59] (Table 2). H-HCAs are easily identified using hemalun and eosin staining (H&E) when in its classical presentation (fat homogeneously distributed). Unfortunately, it is not always the case. Therefore to avoid any errors it is recommended to use LFABP to confirm or not the diagnosis. The same applies to the identification of IHCA. Classical IHCAs (sinusoidal dilatation, inflammation, ductular reaction and thick arteries in pseudoportal tracts) are easily identified on H&E. CRP staining not only confirms the diagnosis of typical IHCA but allows the recognition of atypical IHCA (with fat, absence of sinusoidal dilatation, few inflammatory cells and so on). The diagnosis of β -HCA is often made by default, since β -HCA have sometimes no specific characteristics. Occasionally, these β -HCAs exhibit cholestasis, glandular formations and cell dysplasia. The diagnosis is made by strong and diffuse or patchy expression of GS and confirmed by aberrant β -catenin nuclear staining. However this last staining is not obvious because the number of stained nuclei can be very low and therefore easily missed. β -IHCA combines the criteria of IHCA and β -HCA. HCA without markers are said unclassified.

HCA management

Large HCA (>5cm) developed on normal liver are resected to avoid the two major risks: bleeding and malignant transformation. This rule needs to be adapted to the clinical context (age, sex, etiology, number and location of HCA, risk of malignancy) (Table 2).

• Agreements

There are agreements among surgeons to stop oral contraceptives (OC) (decrease size is rare, disappearance exceptional), to stop if possible male hormone administration (very effective), to remove nodule(s) in men (to avoid malignant transformation), to perform embolization to stop bleeding in case of hemodynamic instability, to remove large tumors (size being a major criteria for complications, bleeding and HCC transformation [60–62]. The risk of hemorrhage is directly correlated with the size of the tumor, and HCAs greater than 5 cm have a higher risk of hemorrhage [63–65]. The magnitude of the risk of malignant transformation varies between 4 and 8% in the largest series in the literature [52]. However, most of the series that report malignant transformation focused on HCA treated by resection [2]. This could lead to an overestimation of the risk of malignant transformation [2].

There are also agreements:

- To say that (rare events for nodules smaller than 5 cm) surgery is safe (no mortality, little morbidity), that the prognosis after complete resection of HCA with malignant transformation is generally good [61,62];
- To favor coelioscopy whenever possible [66];
- To accept that pregnancy is not an absolute contra-indication [67];
- To assert that MRI with the hepato-biliary phase combined eventually to CEUS and biopsy usually allowed to make the differential diagnosis with FNH [57,58];
- To remove a nodule when there is a doubt after a careful workup including biopsy when the differential diagnosis between HCA and HCC cannot be made [61,62].

• Absence of consensus

There is currently no consensus concerning: the minimum size to remove nodule(s) to prevent complications (hemorrhage, HCC transformation: 5 cm generally accepted); the removal of any nodule easily accessible to avoid follow-up; the surveillance (mode and rhythm) of non-resected nodules and/or after resection; when a biopsy is mandatory; the use of radiofrequency versus surgery [68]; and the greater risk of bleeding of IHCA compared with other subtypes independently of the size [62].

• Recent proposals awaiting approval

Proposals concerning the management depending on subtypes have been made [2,61,62] with some discrepancies and controversies [2,61,62,69–71]. H-HCAs have a low risk of malignant transformation; some authors propose to perform a biopsy to be sure of the diagnosis, others relying on imaging whenever possible.

Conclusion & future perspective

The molecular classification of HCA has had a major impact on the pathophysiology of the disease. Great progress has been made for the diagnosis of HCA using MRI, and tissue analyses (biopsies and surgical specimens) using immunohistochemical markers. However, as a future perspective we need to focus our effort on some key areas.

Lack of data

It is important to stress that there are areas where data are lacking [2].

- HCA developed on normal liver (absence of genetic and liver disease). In both sexes, epidemiologic data are warranted to understand the worldwide difference in the incidence of HCAs through the scope of the genotype/phenotype classification. Also in both sexes, the surveillance of HCA (methods and rhythm) according to subtypes would be particularly important data to obtain. In women, first, are there differences among the various OC generations and composition to induce HCA? Second, only a few patients exposed to estrogen developed HCAs, which suggests that additional genetic and/or environmental factors remain to be discovered. Third, driver genetic alterations in the small groups of non-mutated inflammatory and unclassified HCAs are still unknown. Fourth, the natural history of HCA subtypes in terms of growth and regression after stopping OC (HCA are rare in menopause women) is poorly understood. And, finally, the safety or not of re-administration of oral contraceptives, intra-uterine devices with progesterone, menopausal hormone therapy once the HCA has been removed (and none left) or in patients with micro-HCA, is unknown.
- HCA in genetic diseases (MODY3, GSD, FAP, etc): immunopathological data are still scarce.

- HCA in diseased liver: the nature of nodules and particularly the occurrence of HCA in diseased livers (NASH, vascular diseases, alcoholic cirrhosis) is a new field of investigation.
- HCA with borderline lesion, HCA with HCC: the identification of pathological criteria for malignant transformation and their significance in terms of progression, degree of malignancy according to the subtypes are warranted to accurately evaluate the risk of malignant transformation and understand the underlying molecular events. It is likely that classical criteria of malignancy (cytological and architectural abnormalities) may not apply if we accept the fact that so-called HCC derived from HCA do not give rise to metastasis; it is also likely that the process of malignant transformation for the same subtype differs according to the etiology and the underlying liver disease.
- HCC expressing immune-pathological markers of HCA (lack of LFABP, expression of CRP, expression of β -cat nuclear staining): tools will be useful to identify the malignant transformation of an HCA.

The applicability of the findings in clinical practice

MRI and IHC cannot be performed everywhere in the world and technical skills and expertise are not and will not be available everywhere; a problem that can be solved at least partly by referring images to expert reference centres. Even in developed countries there is a slow spreading of knowledge particularly in the surgical field. Many surgeons are still not yet convinced that HCA subtypes are important for the management of patients. Indeed many surgical papers are still published without IHC data.

Of minor importance is:

- A misuse of terms prejudicial to a correct identification of HCA subtypes: steatotic HCA instead of H-HCA (not all H-HCA are steatotic, IHCA can be steatotic); telangiectatic HCA instead of IHCA (not all IHCA are telangiectatic and sinusoidal dilatation is a frequent feature in H-HCA and possible in FNH);
- The term adenomatosis means different things to pathologists/hepatologists and surgeons [72–74], and should be used cautiously;

- The acronym HUMP for hepatocellular neoplasm of unknown malignant potential has been proposed in 2013 [75] to characterize ‘atypical nodules, borderline nodules.’ Because the acronym ignores the HCA classification its use should be strictly limited.
- The term mixed tumor has been coined to characterize nodules combining pathological criteria of HCA and focal nodular hyperplasia. In fact it may represent a collision of two separate lesions occasionally present in the same liver.

Management guidelines

Because HCA is a rare multifaceted disease, with still ignored entire components, it is not surprising that proposed guidelines are not well followed or adapted to specific conditions. It is believed however that management according to HCA subtypes is probably the right track. In addition to HCA subtypes in various clinical conditions (age, sex, etiology, background liver), it is reasonable to think that HCA number and location in the liver will play a great role [76,77]. To solve issues mentioned above, we need to collect data from different parts of the world, we need expert centers where there is a multidisciplinary approach including surgeons, radiologists, pathologists, hepatologists working in close relationship with molecular biologists before establishing guidelines. Facilities and expertise in terms of imaging and diagnosis on tissues will remain however a limit. Furthermore, the opposition between surgeons in favor of “take it or leave it” and those prone for a surveillance is not ready to be

settled for the same size and subtype [78]; it is understandable that surgeons have also to take into account where the patient lives, its degree of anxiety, the risk of complications (although it is a benign disease) and perhaps the cost of the surveillance [79]. Medical treatment probably may solve the dilemma in the near future. Administration of the SRC inhibitor dasatinib significantly reduced the oncogenic activity of FRK mutants. JAK1-mutated hepatoma cells significantly responded to *in vitro* exposure to the JAK1/2 inhibitor ruxolitinib [9].

One other major argument to keep on working on the natural history and management of HCA is that the malignant transformation of HCA, in spite of its rarity, represents one, among several, HCC etiology developed in normal liver [80].

In conclusion, thanks to molecular biology and translational research, dark ages in the understanding of HCA pathogenesis are behind us; however, before we can propose reasonable management guidelines adapted to all clinical and pathological conditions, we still have a long way to go.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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