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Hepatocellular Adenoma: What We Know, What We Do Not Know, and Why It Matters

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Abstract

In the last 2 decades there has been significant progress in research and diagnosis of hepatocellular adenoma (HCA), resulting in the establishment of a molecular and immunohistological HCA classification.

This review aims to fine-tune the current expertise in order to enhance the histopathological diagnostic possibilities, by refining issues that are already known, addressing diagnostic difficulties and identifying still unknown aspects of HCA.

We will discuss novel methods to identify HCA subtypes, in particular the sonic hedgehog HCAs and the interpretation of glutamine synthetase patterns for the recognition of beta-catenin mutated HCAs. The major complications of HCAs, bleeding and malignant transformation, will be considered, including the dilemmas of atypical and borderline lesions. Paragraphs on HCAs in different clinical and geographical settings, e.g. pregnancy, cirrhosis and non-western countries are included.

The natural history of the different HCA subtypes in relation with age, sex and risk factors is a feature still insufficiently investigated. This is also true for the risks of clinical bleeding and malignant transformation in association with HCA subtypes.

As HCA is a relatively rare tumor, a multicenter and multidisciplinary approach across geographical boundaries will be the appropriate method to establish prospective programs to identify, classify and manage HCAs, focusing on several aspects, e.g. etiology, underlying liver disease, complications, regression and growth.

Updating what we know, identifying and addressing features that we do not know matters to warrant optimal patient management.

Key words

Hepatocellular adenoma; genotype-phenotype classification; subtyping update

• Introduction

The last 2 decades saw an enrichment of knowledge in hepatocellular adenoma (HCA). Successive comprehensive molecular and immunohistological studies[1] resulted in the establishment and implementation of a genotype-phenotype HCA classification, also included in the 2019 edition of the WHO Classification of Digestive System Tumours.[2] The continuous evolution of scientific

studies and ever-increasing new insights from pathology practice necessitate updates to refine the diagnostic procedures for a state-of-the-art patient care.

This review aims to fine-tune the current expertise on the morpho-molecular HCA classification[3,4] ("what we know"), identify the gaps in our knowledge ("what we don't know") and discuss the means to address these limitations to provide optimal patient management ("why it matters"). Refinements of the classification will be focused on novel methods to identify HCA subtypes, in particular the sonic hedgehog HCAs (shHCAs) and the interpretation of glutamine synthetase (GS) patterns for the recognition of beta-catenin mutated HCAs. The major complications of HCAs, bleeding and malignant transformation, will be discussed including the dilemmas of atypical and borderline lesions. HCAs in unusual clinical settings and novel clinicopathological data from different parts of the world will finally be reviewed. The latter may alter our current epidemiological understanding of HCAs, which has been mainly based so far on studies from Europe and the USA. The new data may have consequences regarding the clinical context of HCAs, sex distribution, associated risk factors and subsequent clinical management.

- **Risk factors**

The most common risk factor for developing HCAs in Western countries is by far estrogen in oral contraceptives (OC), with the highest rate of use in European countries.[5,6] Following discontinuation of OC, which is now part of the recommended management of HCAs[7], HCAs may remain stable, regress, grow or recur.[8-13] HCAs are rare in or after the menopause.[14]

Anabolic steroid use is another hormonal risk factor for development of HCAs. Obesity, metabolic syndrome, vascular liver diseases (VLD), genetic diseases and alcohol consumption have also been identified as predisposing factors. Table 1 summarized the main risk factors including several liver diseases associated with HCAs. In addition, HCAs have been described in other situations, but, so far, without demonstration of a direct link, i.e. antiepileptic drugs [51-52], hemochromatosis.[53]

- **Basic histology**

The first mandatory step in the histological diagnosis of HCA preceding its classification is the evaluation of hematoxylin-eosin (H&E) stained samples to confirm its primary characteristics. HCA predominantly develops in a non-diseased liver and consists of a benign hepatocellular

proliferation arranged in regular 1-2 cell-layers but lacking the normal lobular architecture and devoid of portal tracts.[2-4,54-56] Apart from these common basic features each HCA subtype has its morphological hallmarks and surrogate immunohistological (IHC) markers. Additionally, regardless of their subtypes, HCAs may contain hemorrhage, necrosis, severe inflammation and fibrosis linked to bleeding and remodeling. Ductular reaction, iron deposits in macrophages or hepatocytes, pigments (mainly lipofuscins or cholestasis) and granulomas may complicate the histological diagnosis. FNH is usually easily differentiated from HCA by imaging. In non-conclusive cases, EASL guidelines recommend to perform a biopsy.[7] The differential diagnosis with HCA could sometimes be challenging because of the presence of steatosis, or sinusoidal dilatation (mimicking H-HCA or IHCA, respectively, see below) or when remodeling in an HCA leads to the presence of misleading fibrotic bands mimicking a FNH. In such cases, GS staining is very useful showing the characteristic "map-like" pattern of FNH [57-58]. However, additional HCA immunomarkers are mandatory for a definitive diagnosis (see below).

- **HCA classification**

The classification of HCAs is based on the molecular diversity, currently involving four major pathways [59]: inactivation of *HNF1A* gene [60], or activation of either IL6/JAK/STAT [61], or Wnt-beta-catenin signaling [62] or sonic hedgehog.[1] Subsequently, an immunophenotypic classification was established, which is more accessible in pathology practice than the molecular techniques.[1-4,15-17,54-56,63-66] A comprehensive description of the HCA phenotype classification is presented in 2 recent reviews.[3-4] Table 2 summarizes the current state of knowledge including the main clinicopathological characteristics. The following paragraphs will succinctly address particular and recent developments for each HCA subtype.

HNF1A mutated HCA (H-HCA)

Classical H-HCAs are steatotic but cases with little or no fat can be seen.[55-56] The tumor hepatocytes show clear or eosinophilic cytoplasm and an increase of lipofuscin. In a minority of

cases, H-HCA shows a few pseudo-glands which can be misleading in the differential diagnosis with HCC. Myxoid changes can be present in variable extent and many of these cases showed variants of *HNF1A* abnormalities (e.g. heterozygous, monoallelic) and concurrent variable abnormalities of other genes.[67-68]

Loss of LFABP is the hallmark of H-HCA, but lack of LFABP in a hepatic focal lesion does not automatically lead to the diagnosis of H-HCA. Loss or diminished expression of LFABP can be seen in HCC without any association with HCA.[69] Additionally, shHCA often exhibits a decreased expression of LFABP which can be misleading (see below).

Rarely, H-HCA may progress to HCC and the latter should especially be suspected in non-steatotic H-HCA, in myxoid H-HCA[67,70] and in VLD associated H-HCA.[37,71]

The pathogenesis of malignant transformation is unknown but as yet there is no evidence of the involvement of the b-catenin pathway. GS expression can be moderately increased in H-HCA but the significance of this finding is currently uncertain. The immuno-histological features of H-HCA are illustrated in Figure 1.

Inflammatory HCA (IHCA)

IHCA shows inflammation, ductular reaction and congestion but these characteristics can be missing and instead steatosis can be seen.[55-56]

The strong and diffuse expression of the CRP and SAA in the tumour is diagnostic for IHCA [2,31] whilst in the non-tumoral liver (NTL) the expression may vary from totally negative to a patchy and weak expression. If CRP positivity in NTL is more pronounced due to severe inflammation or a preceding vascular embolization, the interpretation of the tumoral positive immunostaining can be challenging. GS expression is variable from negative to some perivascular expression, sometimes predominant at the tumoral periphery leading to a misleading "pseudo-rim" (see below).

Figure 2 summarizes the major immuno-histological patterns of IHCA.

A subset of IHCA contains an additional *CTNNB1* mutation and represents another HCA subtype, b-IHCA (see below), that may progress to HCC. A recent study of malignancy in HCA reported a surprisingly high frequency of malignant transformation of IHCA without beta-catenin mutation [72]. However, these findings could not be replicated by the results of another recent study [73]

Beta catenin mutated HCA (b-HCA), b-catenin mutated inflammatory HCA (b-IHCA) and interpretation of GS

This group includes HCAs containing *CTNNB1* mutations in exons 3, 7 and 8: b-HCA and b-IHCA, representing 10 and 10-15% of all HCA subtypes, respectively.

B-HCA does not show specific histological features apart from an increased frequency of cytomorphological atypia. The *CTNNB1* mutation is the genetic event that determines the b-HCA as a specific subtype, and it should not lead to the designation of "UHCA with b-catenin mutation" as recently reported.[74]

B-IHCA is primarily an IHCA, as determined by the mutations in the IL6/JAK/STAT pathway and shows the histological features of IHCA. The *CTNNB1* mutation in b-IHCA is an additional genetic event that makes this IHCA a b-IHCA. The diffuse and strong SAA/CRP expression is not influenced by the concomitant *CTNNB1* mutation. It is therefore mandatory to perform GS staining in all IHCA to detect the presence of an additional *CTNNB1* mutation.

As IHC detection of nuclear beta-catenin is not sensitive enough, the IHC hallmark of b-HCA/b-IHCA is an increased GS expression. Importantly, the patterns of GS expression are variable depending on the type of *CTNNB1* mutations.[62] A comprehensive description of the predictive patterns of GS in b-HCA and b-IHCA has been presented in a recent study along with a diagnostic algorithm of subtyping HCA.[75] In short, *CTNNB1* exon 3 non-S45 mutations show a diffuse homogenous GS expression, whereas exon 3 mutations in codon S45 show a diffuse heterogenous expression and exons 7/8 mutations show a focal patchy pattern of, often faint, staining. Exons 3 S45 and exons 7/8 mutations are also recognizable by the characteristic presence of a GS positive/CD34 negative rim in the periphery of the tumor at the junction with NTL. Hence, CD34 should also be included in the IHC panel of HCAs. This rim belongs to the HCA, as demonstrated by its CRP/SAA positive staining in b-IHCA. In addition, in b-HCAs, abnormal vessels are present usually not far from the rim. In b-IHCAs, the GS+/CD34- rim and the abnormal vessels are less obvious; and CD34 positivity is usually not as diffuse in the HCA center. Inconclusive cases, especially biopsy specimens, may require molecular analysis. Rarely, no mutation/deletion is found by molecular analysis, even in frozen tissue; after elimination of an abnormal GS expression due to necrosis, hemorrhage, or remodeling, it might be concluded that the abnormal GS expression could be due to technical issues or activation of other pathways.

These GS patterns and additional features of CD34 are detailed in Table 3 and in Figure 3.

Sonic hedgehog HCA (shHCA) ShHCA

occurs in women on long term OC, mostly overweight and older than 35 years, often in the context of metabolic syndrome and NASH features. Acute hemorrhage is the presenting symptom in the majority of cases, requiring emergency intervention.[1,76-77] Histologically shHCA is a non-encapsulated, monotonous, "bland," well-differentiated hepatocellular proliferation made of packed, clear and eosinophilic cells, often intermingled with areas of retracted hepatocytes with condensed nuclei, possibly related to ischemia. The tumors are well vascularized by numerous isolated arteries and veins, often with the presence of hemorrhagic areas, congestion, some fibrotic bands, without noticeable inflammation, ductular reaction, or steatosis. Adjacent to arteries and veins, peliotic changes and solitary or grouped cavities of various sizes are often present, with or without blood at different stages of degradation (red blood cells ghosts, loose fibrosis).[76-77] Even when smaller than 5 cm, shHCAs may contain hemorrhage. ShHCA identification is based on the diffuse or heterogenous overexpression of ASS1 in the tumor compared to the honey-comb staining in the NTL.[76] ASS1, a protein involved in the urea cycle, is physiologically expressed in the periportal and septal hepatocytes.[78] When expressed in other HCA subtypes, ASS1 level is always lower in the tumor compared to NTL.[74] PTGDS, a specific marker of shHCA[1] is not sensitive enough[74] in daily practice. CRP and GS are not expressed or show only some non-specific heterogeneous staining in shHCAs, whereas LFABP expression can be decreased, possibly misleading for the differential diagnosis with H-HCA. Performing ASS1 staining is therefore mandatory for the diagnosis of shHCA. Figure 4 summarizes these typical immuno-histochemical patterns.

Unclassified HCA

By definition, the term UHCA is reserved for those HCAs that cannot be designated to any known subtype described above, following immunohistochemical, molecular and proteomic analysis. This group is estimated to represent 7% of HCA after molecular analysis [1] and less than 2% by proteomic studies.[76-77]

• HCA complications

The 2 major complications of HCAs are bleeding in 20-25% [79-81] and progression to HCC in 4-10%.[82-84]

Hemorrhage

Clinical bleeding is defined as severe when it requires intensive care and moderate when there are clinical or radiological bleeding symptoms; [66] histological bleeding is defined as hemorrhage incidentally found at microscopic examination.[1] All HCAs carry a risk of clinical bleeding, and the main risk factor is traditionally reported to be the size (>5cm) [1,7], but bleeding has been reported for HCA even as small as 3.5 cm. [79,85] Exophytic growth and visualization of intratumoral arteries by magnetic resonance imaging (MRI) are other risk factors.[79] Recent studies showed shHCA[1,66], b-HCA exon 7/8 subtypes, both even if smaller than 5 cm, and chronic alcohol consumption as independent risk factors.[66] HCA can disappear after bleeding or arterial embolization.[81] To improve prevention of a hemorrhagic rupture in HCA, identification of risk factors is necessary; of which subtyping is an important one.

Malignant transformation

Malignant transformation of HCA has been reported with a frequency ranging from 4.2 to 10.6% in surgical series.[81] However, the evaluation is biased due to the sole inclusion of surgical samples. In addition, the presence of an HCA in an HCC, or a history of incomplete resection of an HCA is a prerequisite for the diagnosis of HCA-derived HCC; therefore, the precise frequency of pre-existing HCA behind a fully developed HCC in a non-cirrhotic liver is unknown.[86, 73]
The reported risk factors for malignant transformation of HCA are male gender, size (>5cm), *CTNNB1* mutation, in particular exon 3, and concurrent liver diseases, particularly glycogen storage disorders (GSD) and VLD.[84] The higher risk of malignant transformation in male patients is well-recognized since the work by Dokmak who showed a tenfold higher risk in men than in women [5], leading to the recommendation in clinical guidelines to remove or ablate any HCA in men.[7] The higher risk for malignancy in *CTNNB1* mutated HCA subtypes has been shown in several studies, reaching 40%.[1,87] More recently, it has been linked to the level of the beta-catenin pathway activation; higher in exon 3 non-S45, moderate in exon 3 S45 and almost negligible in exons 7/8 mutations [1,62], despite a report of an HCC developing in a b-IHCA exon 7/8.[88] In case of b-HCA and b-IHCA, the second molecular event leading to HCC has been shown to be a *TERT* promoter mutation [89] whereas in the other HCA subtypes the pathway leading to malignant transformation is still unknown. Another unsolved issue is the prognosis of HCA-derived HCC that are mostly well-differentiated[73]. A recent study showed a better long-term survival for these

patients than for those with non-HCA derived HCC in non-cirrhotic livers.[72] According to the few studies that have been able to follow patients with an exon 3 *CTNNB1* mutated HCAs that was incompletely resected, malignant transformation seems to take at least 10 years.[90]
Specific clinical contexts and/or liver diseases, such as GSD [91] and VLD [36-37] seem to be associated with a higher risk of malignant transformation of HCA, not only in the case of b-HCA/b-IHCA[92] but also for H-HCA in VLD.[70-71] Even if 5 cm is commonly considered as the threshold, a few cases of malignant transformation have been reported in lesions smaller than 5cm[82,93], both in men and in women.

- **Atypical HCA and borderline HCA**

In a large study of 533 HCAs, Nault [1] reported that 7% of HCAs share intermediate histological features with HCC. For such cases, it is difficult to establish firm criteria to definitely distinguish between HCA and HCC. As such, a conclusive diagnosis will remain challenging in some cases for which the term *borderline HCA-HCC* seems to be appropriate. [2,94] The application of terminologies such as "atypical HCA" for non-histological criteria but also for clinical or other criteria such as male gender, for HCA occurring in older women, or for all *CTNNB1* mutated HCAs will be confusing.
In the current state of our knowledge, some principles could help the pathologists in their routine practice. The terminology "atypical" or "borderline" should be reserved for the histological description. Prior to use it, the lesion should be diagnosed as an HCA and be subtyped precisely. Then, according to the WHO 2019 [2], borderline HCA denotes HCA with atypical morphological features but insufficient for a definitive diagnosis of HCC. The best accepted atypical morphological features are loss of reticulin, presence of pseudoglands or pseudoacini and cytological atypia (small cell changes, higher nucleo-cytoplasmic ratio, large nucleoli…) which will be deemed insufficient for the diagnosis of HCC [95] when present focally and moderately, instead of multifocally and extensively. Importantly, pseudoglands can be present in androgen-associated HCAs and pigmented HCAs[96], while cytological atypia may be seen in these HCAs as well as in H-HCAs and HCAs associated with VLD or in case of remodeling after bleeding. While these morphological features rely on its extent to tip the balance from HCA to HCC, the threshold for sufficient/insufficient is still arbitrary, despite proposals for quantification.[97] Furthermore, their specificity to predict malignant transformation remains to be demonstrated. [98]

The "classical" tools used by pathologists to distinguish HCC from dysplastic nodules in cirrhosis, including immunohistochemistry, can sometimes be useful in discriminating HCA-HCC but cannot be fully and straightforwardly translated in this context [99] because different pathogenetic mechanisms may probably be involved. *TERT* promoter mutation that could prove the malignant transformation [89] is not always present, in HCA derived HCC, even in b-HCA and b-IHCA[100]. Of note, Jones et al reported the potential usefulness of Ki67 hot-spot digital analysis in distinguishing HCA and well-differentiated HCC.[101]

In a second step, implementation of clinical context will also be helpful for further patient management. The impact of finding borderline features in a biopsy is obviously different than in a fully resected HCA and should prompt closer surveillance or resection/ablation.

For an adequate diagnostic process and clinical management of these cases, future studies will be needed to stratify the significance of the individual morphological criteria to identify malignant features. Similarly, molecular studies are indispensable to establish a profile of relevant abnormalities with regard to malignant transformation. Proteomic studies seem to be promising in finding specific signatures.[102]

- **HCA in particular clinico-pathological contexts**

Metabolic disorders

Overweight/obesity, often associated with diabetes type 2 and NASH, particularly in US and Europe, favor the emergence of HCA namely IHCA, b-IHCA and shHCA (Table 1) [25-31]. Of note, obesity per se may increase the risk of HCC on non-cirrhotic liver.[103]

GSD is well known to be associated with various kinds of benign nodules (FNH, FNH-like, macroregenerative nodules, different HCA subtypes except H-HCA, as well as a high risk of malignant nodules.[43-44,104-105]

Liver adenomatosis (LA)

LA does not present a clinical risk when the majority of nodules are small (< 5 cm) and do not grow during follow-up.[106.] However, close monitoring and specific management are necessary due to the diversity in subtypes, mainly H-HCA and IHCA, more rarely shHCA and subsequent variation in risks for hemorrhage and malignant transformation.[107] In patients with germline *HNF1A* mutation, familial LA occurred equally frequently in males and females, with a higher

rate of bleeding in male patients.[107] OLT is rarely justified.[108-109] Microadenomas (<5mm) are frequently seen in LA, usually H-HCA or IHCA but can be also incidentally discovered in liver specimens resected for other types of tumors or concurrent other HCA subtypes.[110]
In H-HCA, growth can be due to collision of adjacent nodules.[111] Collision of tumors between H-HCA or IHCA and FNH has been observed.[112-113]

Inter and intra tumoral heterogeneity

Most of the molecular alterations in HCA are mutually exclusive, except b-catenin and the inflammatory pathways, which define the b-IHCA subgroup. In rare cases, the *CTNNB1* mutation within an IHCA can be present focally [114], supporting that it corresponds to a secondary event in IHCA and representing intratumor heterogeneity.
Intra-tumor heterogeneity has also been observed by molecular analysis but without IHC or clinical observable consequences in H-HCA and IHCA.[1]
Inter-tumor genetic heterogeneity of the main driver genes can be observed in patients with multiple HCAs belonging to the same molecular subtype (b-HCA and b-IHCA with different *CTNNB1* exons mutations) or with different driver genes, such as IHCA and b-IHCA, H-HCA and IHCA, IHCA and shHCA.[1] Inter-tumoral heterogeneity may raise serious clinical difficulties, i.e.in case of multiple IHCA where some lesions are b-IHCA exon 3 non-S45 carrying a risk of malignant transformation, or multiple b-HCAs of which some contain *CTNNB1* exon 3 mutation with increased risk of developing HCC and some contain exon 7/8 mutation with lower risk for HCC but more risk of substantial bleeding. In the absence of subtype identification possibilities by imaging modalities, size alterations remain a valuable indicator for surveillance and therapeutic decisions.

HCA and pregnancy

Pregnancy is no longer considered to be contraindicated in patients with HCA[115] but close clinical follow-up is recommended during the entire duration of the pregnancy regardless the size of the HCA by frequent ultrasound monitoring,[7] as growth of the lesion and hemorrhage are potential complications. However, HCA < 5cm seems to present minimal risk of growth [116]whilst hemorrhage was reported to be rare and associated with HCA > 6.5 cm although it can be fatal.[117] Bleeding can be a major complication close to term and in the postpartum period in b-HCA ex 3 S45 and ex 7/8.[66] As yet, association of these complications with specific HCA subtypes during

pregnancy is not established because of limited data, partly due to the fact that the diagnosis of HCA during pregnancy is not tissue based.

Necessity and treatment options of HCA during pregnancy varies from ”wait-and-see” to ablative intervention and surgery, depending on the individual context. Due to the increased risk of hemorrhage, resection is recommended for larger nodules (> 5 cm), if possible before pregnancy. If discovered during pregnancy, the 2nd trimester was reported to be the optimal moment; alternatively, ablative treatment can be considered if surgery is not possible.[118]

HCA in males

In western countries, only roughly 10% of HCAs are observed in males. A slight male preponderance or practically equal distribution of male and female patients are reported in studies from Eastern countries with very low OC use[16, 17, 27]. In these studies IHCA was the most frequent subtype observed both in the total study population as in the male patients. Overweight and obesity were associated with the IHCA subtype in 2 of the 3 studies [16,27] whilst the 3rd study [17] mentioned excessive alcohol intake in all IHCA patients but none in the other subtypes. Of note, a recent study from Turkey mentioned female preponderance of HCA despite low numbers of OC use in the study population [15].

Published series are too small to compare the percentage of the different subtypes between men and women; however, in our experience, the subtypes with the highest percentage of men are b-HCAs and b-IHCAs exon3 non S45.[66]

The rule to eradicate all HCA in males regardless the size is based on the risk of malignant transformation. It is likely that the risk of malignant transformation increased in specific contexts, e.g. anabolic steroid, VLD, NASH, alcohol abuse and b-HCA/b-IHCA exon 3. The 10-year cumulative risk of progression to HCC in men with biopsy-proven HCA was 60%.[119] Prospective studies for “à la carte management “are needed.[120] Data are not known in women.

Pediatric HCA

Pediatric age range is defined as ages 0-18. HCAs are rare in children [121] representing < 5% of pediatric hepatic tumours.[122] A recent study of 31 patients, of whom 10 were prepubescent and 21 between 15-21 years, reported frequent association of pediatric HCAs with syndromes.

The percentage of the different HCA subtypes was: 16% b-HCA, 10% b-IHCA, 29% H-HCA, 35% IHCA, and 10% UHCA by immunohistochemical staining.

The group with symptoms contained a greater percentage of b-catenin activated HCAs whilst the group without syndromes showed a similar subtype distribution as in adults.[123]
HCA have been reported in biliary diseases such as biliary atresia, obliterative cholangiopathy[124] and in Alagille syndrome associated with decreased bile ducts, cardiac abnormalities, vertebral body fusion defects, and a typical facies caused by a mutation in *NOTCH2*. [125]

HCA in Vascular liver diseases (VLD)
VLD can give rise to different hepatocellular nodules, ranging from focal nodular hyperplasia (FNH), a reactive polyclonal lesion resulting from hyper-arterialization, to HCA and also to HCC found mostly in Budd-Chiari syndrome and porto-congenital shunts. In the context of VLD, all subtypes of HCA have been described.[36-37,126] Of note, two cases of H-HCA adenomatosis, have been reported in congenital hepatic fibrosis (CHF), another example of VLD. [127-128]

HCA in cirrhosis
HCA is only rarely observed in a cirrhotic liver and the diagnosis may be challenging as it includes a differential diagnosis with nodular lesions characteristically present in cirrhotic livers, such as regenerative nodules, dysplastic nodules and (early) HCC. Another impediment is the interpretation of the IHC markers. Because cirrhotic nodules result from chronically diseased livers with longstanding inflammation and damage, these markers have different expression patterns and significance than in normal livers. GS can be enhanced in regenerative and dysplastic nodules. Diffuse CRP overexpression has been reported in a few high-grade dysplastic nodules whilst focal expression of CRP or SAA is not infrequently found in cirrhotic nodules.[129] Hence, in the cirrhotic setting, IHC for subtyping HCA may often be inconclusive, necessitating molecular analysis to confirm the diagnosis of HCA. The IHCA-like nodules in alcoholic cirrhosis described by Sasaki showed similar morphological and IHC features as IHCA.[130] Molecular analysis was applied in another study of 10 nodules of 3 alcoholic cirrhotic livers allowing a definitive diagnosis of IHCA in these few cases.[129] To date, no other subtypes of HCA have been reported in cirrhosis in the literature.
Using the terminology “adenoma” in the context of cirrhosis remains controversial [131-132] and can certainly not be done without a precise complete molecular analysis. In this particular setting,

making a diagnosis of a IHCA in a needle biopsy of a nodule in a cirrhotic liver has been strongly discouraged.[133]

- **HCA around the world (epidemiology)**

An overview of the global prevalence of HCA is difficult if not impossible to establish. There is an uneven distribution of the origins of HCA series and case reports. The majority of studies are mainly derived from Europe and the USA, more rarely from other countries, such as Australia, Japan, South Korea, Taiwan. The majority of these studies are retrospective, covering large periods of time, with incomplete data with regard to histological details, morpho-molecular subtyping, complications and/or imaging features. In addition, there are many case reports from over the world with limited clinical interest.

In Western countries, OC is the major risk factor for HCA. In countries where contraceptive methods differ, without significant use of OC, the incidence of HCA is lower and there is also a higher male/female ratio [27,134] Anabolic androgenic steroids, initially created for therapeutic purposes, are now also consumed by bodybuilders for years, or applied by non-athletes for aesthetic goals.[135] Whether this might explain the prevalence of HCA in men in certain countries remains to be explored. Distribution of subtypes has also been shown to be different in a recent study from Turkey, with a high number of H-HCAs and b-HCAs and a very small number of IHCAs despite obesity in this population. In addition, b-HCAs were more frequently found in women than in men and showed borderline features in half of the cases.[15]

Obesity, once considered a high-income country problem, is now on the rise in low- and middle-income countries, particularly in urban settings. Globally there are more people who are obese than underweight – this occurs in every region except parts of sub-Saharan Africa and Asia.[136] However, data on HCA are not available.

- **Perspectives**

Since the beginning of this century, we have made great progress in the understanding of HCA due to the molecular classification, its practical application using immuno-histochemistry, and consequently in the identification of patients at risk of significant bleeding and malignant transformation.

However, several raised questions remain unresolved.

1. *Epidemiology and risk factors:*

As alluded before, the exact prevalence of HCAs is not known which is also true for the risk factors and the influence of the latter on HCA prevalence. For instance, it is not known whether the modification of the hormonal content of OC alters the incidence of HCAs.

There is also no data regarding the interrelationship between the currently known risk factors such as drugs containing estrogen/androgen, obesity, alcohol and genetic factors such as MODY 3 and genetic polymorphisms. The latter may explain the individual differences in having a single nodule or myriads of nodules in which the so-called "molecular subtype field effect" may play a role.[1]

2. *Subtypes*

Despite progress in subtyping HCA, the natural history of the different HCA subtypes in relation with age, sex and etiology is not known, especially when OC is not the predominant risk factor. The main challenge, to determine the HCA subtype prior to take the therapeutic decisions, either by imaging or a biopsy, remain poorly studied. MRI is the first technique to discriminate between HCA, FNH or HCC. MRI can subclassify H-HCA (sensitivity 87%-91%, specificity 89% -100%) and IHCA (sensitivity 85%- 88% and specificity 88%-100%,).[125-128] Hepatospecific contrast uptake on hepatobiliary phase is strongly associated with marked activation of the β-catenin pathway in HCA, and its use might improve HCA subtyping on MRI.[141]

Subtyping on biopsy, which should contain both tumor and NTL, has been shown to be reliable for main subtypes [57-58], but not studied in detail for b-HCA/b-IHCA or for shHCA. When HCA subtyping by IHC and/or imaging modalities is inconclusive, molecular techniques, preferably on frozen tissue remain the gold standard.[1] Proteomic analysis is a promising technique for subtyping HCA and has the great advantage of its applicability on tiny and fixed tissue.[102] It might change the game and our understanding.

3. *Clinical bleeding and malignant transformation*

The exact incidence of bleeding and malignant transformation according to subtypes is not established.

The identification of subtypes containing higher risks of bleeding (b-HCA /b-IHCA exon 7/8 and shHCA) and malignant transformation (b-HCA /b-IHCA exon 3) by imaging modalities is still under construction.

The identification but also the significance of a histological "borderline" lesion is still an enigma, partly due to the absence of clear-cut criteria and helpful markers. TERT is thought to represent an irreversible step towards malignancy in *CTNNB1* mutated HCA[89]. But, the evolution and exact prognosis of the malignant transformation of HCA at different stages up to a well-differentiated HCC are still issues that need further studies that may lead to abandon the term "hepatocellular neoplasm of uncertain malignant potential" (HUMP).[104-142]

4-Novel techniques

The results of the proteomic studies [102] remain to be validated on larger studies to establish the role of this technique in HCA diagnosis.

Progress in imaging and application of artificial intelligence in liver pathology interpretation will probably help in improving recognition of subtypes with higher risks for hemorrhage or malignant transformation with subsequent treatment adjustment.

A large number of cases will be required, necessitating a multicentric collaboration.

Next-generation sequencing allows a broad range of applications (gene expression profiling, chromosome counting, detection of epigenetic changes, and molecular analysis).

Finally, a specific molecular oriented treatment for HCA subtypes would be a major breakthrough particularly to avoid OLT in liver adenomatosis [109] or difficult resection of large lesions.

- ## Conclusion

In the last 20 years, knowledge of HCA has changed drastically. The classification in several subtypes and identification of specific complications for the b-HCA/b-IHCA and shHCA can initiate treatment modification in the coming years. Because HCA are rare benign tumors at risk of complications with a different sex ratio and lower incidence in countries not using OC, the only way to make progress is to gather as many multicentric and multidisciplinary liver centers as possible (radiologists, pathologists, hepatologists, surgeons, geneticists, pediatricians, molecular biologists, obstetricians). Today we have the tools to start a pragmatic and realistic global program to document HCA cases. In close collaboration, the centers will be the right place to establish prospective programs to identify, classify and manage HCA focusing on etiology, underlying liver disease, complications, growth, involution and disseminate the knowledge in joint papers (Figure 6). The latter may form the base for liver societies (EASL, AASLD, APASL, ALEH, ALPA, IASL) to adjust the relevant guidelines.

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Legends

- **Tables**

Table 1: Risk factors and related HCA subtypes

Table 2: Different subtypes of HCA: genotypic-phenotypic classification and main clinico-pathological features

Table 3: Immunohistochemical stainings in b-HCA with different levels of *CTNNB1* pathway activation: high (1), moderate (2), low (3)

- **Figures**

Figure 1: *HNF1 A* mutated hepatocellular adenoma (H-HCA)

A: classical and very typical aspect on H&E: the hepatocytic proliferation is highly steatotic, with lobulated contours (arrows), easy to differentiate from the surrounding normal non-tumoral liver (NT)

B: steatotic areas are separated by thin strands of atrophic, non steatotic hepatocytes (asterisk)

C-F: high magnification of different cytological aspects (often intermingled): macrovesicular steatosis (C), macro- and microvesicular steatosis (D), microvesicular steatotic and clear cells (E), glycogenated nuclei (F)

G: typical microadenoma discovered distant from a large H-HCA in the resected specimen

H-I: rarer features: fluffy, « myxoid » area (asterisk, H), a few pseudo-glands (arrows, I) in otherwise typical LFABP negative H-HCA

J: lack of LFABP immunostaining highlights microadenomas (asterisks) in the surrounding of a large H-HCA

K-L: this non-steatotic tumor without obvious limits (arrows) from the NT (K) is easily identified as a H-HCA by lack of LFABP (asterisk) contrasting with normal expression in NT (L)

M: LFABP staining is lacking in both steatotic and non-steatotic hepatocytes of the HC

Figure 2: Inflammatory hepatocellular adenoma (IHCA)

A-F: classical features of IHCA: hepatocellular proliferation, non-encapsulated, with poorly defined limits from NT (arrows) on HE, marked sinusoidal dilatation (A) filled with red blood cells, nearby thick arteries and inflammatory cells (thick arrow, B); pseudoportal tracts (dotted arrows) with a few fibrotic bands stained by Masson's trichrome inside this focally steatotic IHCA (C) ; pseudoportal tracts may exhibit several arteries (D) and variable amount of ductular reaction highlighted by CK7 immunostaining (arrows, E); strong and diffuse CRP expression with sharp demarcation from NT (F); a microadenoma in the surrounding liver is also identified (arrowhead)

G-H: this tumor does not exhibit classical features of IHCA on H&E (G), but is easily diagnosed as such by the diffuse CRP expression with sharp limits from NT (H)

I: CRP is expressed only in tumoral hepatocytes of IHCA, steatotic or not, but not in sinusoidal and inflammatory cells

J: GS is expressed in some patches, often perivascular, mainly at the periphery of this subcapsular IHCA; but it is not a true rim, hence this is not a b-IHCA

K-M: this microadenoma exhibited classical immuno/histological features of IHCA (K, L), without argument for additional b-catenin mutation (M): GS staining is negative, contrasting with normal staining around veins in NT (arrows, M)

Figure 3: b-HCA and b-IHCA

A-C: one example of b-HCA exon 3 S45

A: Glutamine synthetase (GS) expression is heterogeneous and moderate in the tumor (T), except in the rim (asterisk) where it is strong, contrasting with non-tumoral liver (NT) where GS is restricted to hepatocytes around central veins (arrow)

B: CD34 is diffusely expressed in T, except in the rim (asterisk)

C: numerous abnormal vessels are visible in T (H&E)

D: another example of rim immunostained by GS in b-HCA ex 3 S45

E-I: different aspects of rim (asterisk) immunostained by GS (E-H) in b-HCA ex 7/8, already visible on H&E (I: same case as H)

J: b-IHCA ex 3 S45; GS is heterogeneous, moderately expressed in T, associated with thick patches around veins (arrows), as strong as in the rim (asterisk)

K-L: 2 examples of b-IHCA ex 7/8; in T, GS patches are prominent around veins (arrows) and irregularly organized in the rim; CRP immunostaining (inset in K) shows the limit between T and NT

Fig. 4: Different examples of shHCA

A: this tumor (T) is separated from the steatotic non-tumoral liver (NT) by an hemorrhagic area (arrow); numerous cavities filled or not by erythrocytes (asterisks) are dispersed in the tumor

B: in this shHCA, clear cells (°) are intermingled with retracted hepatocytes with condensed nuclei (+)

C: this shHCA exhibits large hemorrhagic cavities

D-E: this shHCA with a bland aspect, nearby a severely steatotic NT (D), overexpressed ASS1 contrasting with the typical « honey-comb » aspect of NT (E)

F-G: this shHCA overexpressed ASS1 compared with NT (F); LFABP is decreased in T whereas it is normally expressed in NT (G)

Figure 5: two examples of HCA with malignant foci

A-E: b-HCA. The 9 cm tumor (H&E, A; arrow indicates the tumoral limit) resected in a 40 years old woman, exhibited several atypical foci (circle) with thickened hepatocytic plates, numerous pseudoglands structures (D) and cholestasis (E); GS staining is diffusely and strongly expressed (B) and there is abnormal b-catenin nuclear staining focally and irregularly expressed (C), in favor of high level of b-catenin pathway activation. Seven years after the complete resection, the patient is in good health.

F-I: H-HCA. *HNF1A* adenomatosis (somatic mutation) in a 27 years old man with a Fallot tetralogy; atypical features on a biopsy of a 8.5cm tumor (not shown); liver transplantation. Classical aspect of H-HCA on H&E (F), with lack of LFABP in T contrasting with normal expression in NT (G). The main tumor exhibited atypical foci with pseudo-glandular structures (H) and decreased reticulin network (I) diagnosed as malignant foci. Seven years after the transplantation, the patient is in good health.

Figure 6 - Hepatocellular adenoma from daily practice to a scientific network

Table 1- Risk factors and related HCA subtypes

Sex/Age	**Women, reproductive age** (88 % of cases in Europe), 20% not taking oral contraceptives [5-6] *N.B:* *Low OC use: still female predominance in Turkey* [15] *but male preponderance in Eastern countries* [16-17]	**All subtypes**
Sex hormones	Oral contraceptives [18]	**All subtypes**
	Androgens/Danatrol: given for anemia, hereditary angioderma, endometriosis [19-21]	**b-HCA / b-IHCA**
	Anabolic androgenic steroids: body builder, transgender individuals [22]	**b-HCA / b-IHCA**
Sex hormones dysregulation	Polycystic ovary syndrome [23-24] *Rare: Klinefelter syndrome, sex hormones producing tumors (Sertoli-Leydig cell tumors)*	**IHCA** **IHCA**
Metabolic syndrome	**BMI > 25-30** **Morbid obesity** **Diabetes type 2** A major risk today [25-31]	**IHCA, shHCA**
Alcohol	Excessive alcohol consumption is often reported	**IHCA**

	in patients with HCA [6]	
Liver diseases	NASH [32-33], alcoholic cirrhosis [34-35] Vascular liver diseases: congenital porto-systemic shunts, Budd Chiari syndrome, cardiac hepatopathy, congenital hepatic fibrosis, Turner syndrome…[36-38]	**IHCA, shHCA** **b-HCA / b-IHCA** **H-HCA**
Genetic diseases	MODY 3 (can be seen in adolescent)[39-42] GSD [43-44] Familial adenomatous polyposis coli [45-48] *Rare: McCune-Albright syndrome [49],* *Alagille [50], Hurler syndromes, Galactosemia….*	**H-HCA** **IHCA, b-HCA** **b-HCA** **IHCA**

HCA: hepatocellular adenoma; H-HCA: *HNF1A* mutated HCA; IHCA: inflammatory HCA; b-HCA: b-catenin activated HCA; b-IHCA: b-catenin activated and inflammatory HCA; shHCA: sonic hedgehog HCA; BMI: body mass index; NASH: non alcoholic steatohepatitis; MODY: maturity onset diabetes of the young; GSD: glycogen storage disease

Table 2: Different subtypes of HCA: genotypic-phenotypic classification and main clinico-pathological features

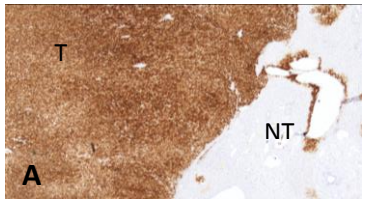
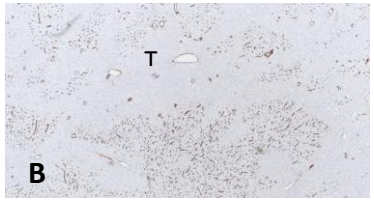
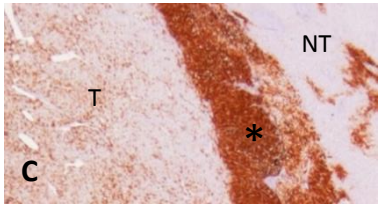
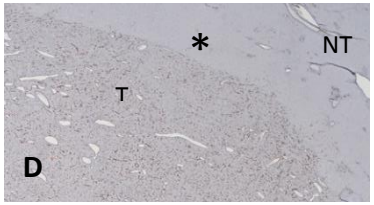
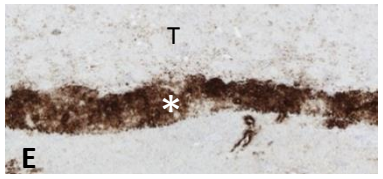
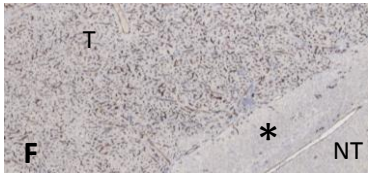
HCA subtype (F/M)*	Molecular biology	IHC markers	Main pathological features	Main clinical features
H-HCA 31% (68/9)	Biallelic inactivating mutation of ***HNF1A*** Somatic: 90% Germline: 10% (MODY3)	Loss of **LFABP**	macro-micro steatosis; clear ballooned cells; few pseudoglands; rarely myxoid changes	Solitary, multiple, LA, frequent micro-adenomas in background liver. MODY3: familial form, equal sex distribution.
IHCA 33% (72/10)	**IL6/JAK/STAT** pathway activation (different mutations)	Diffuse positivity of **SAA/CRP**	Sinusoidal dilatation; pseudo-portal tracts; inflammation, ductular reaction; steatosis	Obesity, metabolic syndrome, alcohol, solitary, multiple, LA
b-HCA 11.2% (24/4)	***CTNNB1 exons 3, 7, 8*** mutations/deletions leading to different levels of b-catenin	**GS patterns in b-HCA and b-IHCA** **Exon 3 non S45:** diffuse homogeneous **GS** (in b-IHCA also diffuse SAA/CRP positivity)	Some cytoarchitectural atypia	**High risk of HCC**, linked to TERT promoter mutation, more males, androgens, metabolic diseases, mainly solitary tumors.
b-IHCA		**Exon 3 S45:** diffuse heterogeneous **GS** (in b-IHCA also diffuse SAA/CRP positivity)	Numerous abnormal vessels in	Younger females, **risk of HCC** (level unknown)

14.1% **(25/10)**	pathway activation	GS positive/CD34 negative rim (less obvious in b-IHCA)	the HCA center not far from the rim, (mostly in b-HCA)	
		Exon 7/8: focal patchy **GS** (in b-IHCA also diffuse SAA/CRP positivity) GS positive/CD34 negative rim (less obvious in b-IHCA)		Younger females, low risk of HCC. **risk of hemorrhage**
shHCA **10%** **(25/0)**	**Sonic-hedgehog** pathway activation due to fusion of *INHBE* with *GLI1*	Overexpression of **ASS1** T > NT **PTGDS** positivity (more specific but less sensitive than ASS1)	Bland pattern; various degree and stages of hemorrhagic foci; vessels abnormalities frequent severe steatosis in NT	Only females, often older than in other subtypes obesity **high risk of hemorrhage**
UHCA **<2%** **(1/0)**	No identified mutation	Normal positivity for LFABP, all other markers negative or non-specific	Non specific	Non specific

* Percentages of cases and F/M ratios are derived from reference 64; the percentage of shHCA is based
on ASS1 immunostaining, other teams are using PTGDS [1]

ASS1: argininosuccinate synthase 1; CRP: C-reactive protein; *CTNNB1*: cadherin-associated protein β1;

HCA: hepatocellular adenoma; b-HCA: b-catenin activated HCA; b-IHCA: b-catenin activated and inflammatory HCA; H-HCA: *HNF1A* mutated HCA; IHCA: inflammatory HCA; GS: glutamine synthetase; IHC: immunohistochemistry; LFABP: liver fatty acid binding protein; SAA: serum amyloid A; IL6: interleukin 6; JAK: Janus kinase; PTGDS: prostaglandin D2 synthase; shHCA: sonic hedgehog HCA; STAT: signal transducers and activator of transcription; TERT: telomerase reverse transcriptase; UHCA: unclassified HCA

Glutamine synthetase (GS) staining patterns	**b-catenin nuclei**	**CD34 positivity** (sinusoidal /endothelial cells)	**Underlying molecular abnormality** [72]	**GS illustration** b-HCA exon 3 non S45 (**A**), exon 3 S45 (**C**), ex 7 (**E**)	**CD34 illustration** b-HCA exon 3 non S45 (**B**), exon 3 S45 (**D**), ex 7 (**F**)
1- diffuse/homogeneous, moderate to strong in the entire HCA; *no visible rim* (**A**)	focal positivity; sometimes negative	expanding but not diffuse (**B**)	suggestive of **exon 3 non S45** specificity 100% sensitivity 80-83%		
2- diffuse/heterogeneous "starry sky", faint to moderate, in the HCA center; *+ a GS positive rim** (**C)**	rare positivity; usually negative	diffuse except in the GS positive rim* (**D**)	suggestive of **exon 3 S45** specificity 92-93% sensitivity 100%		
3- patchy, focal, faint, in the HCA center; *+ a GS positive rim** (**E**)	negative	diffuse except in the GS positive rim* (**F)**	suggestive of **exon 7/8** specificity 96-100% sensitivity 55%		

NT

Table 3 - Immunohistochemical stainings in b-HCA with different levels of *CTNNB1* pathway activation: high (1), moderate (2), low (3)

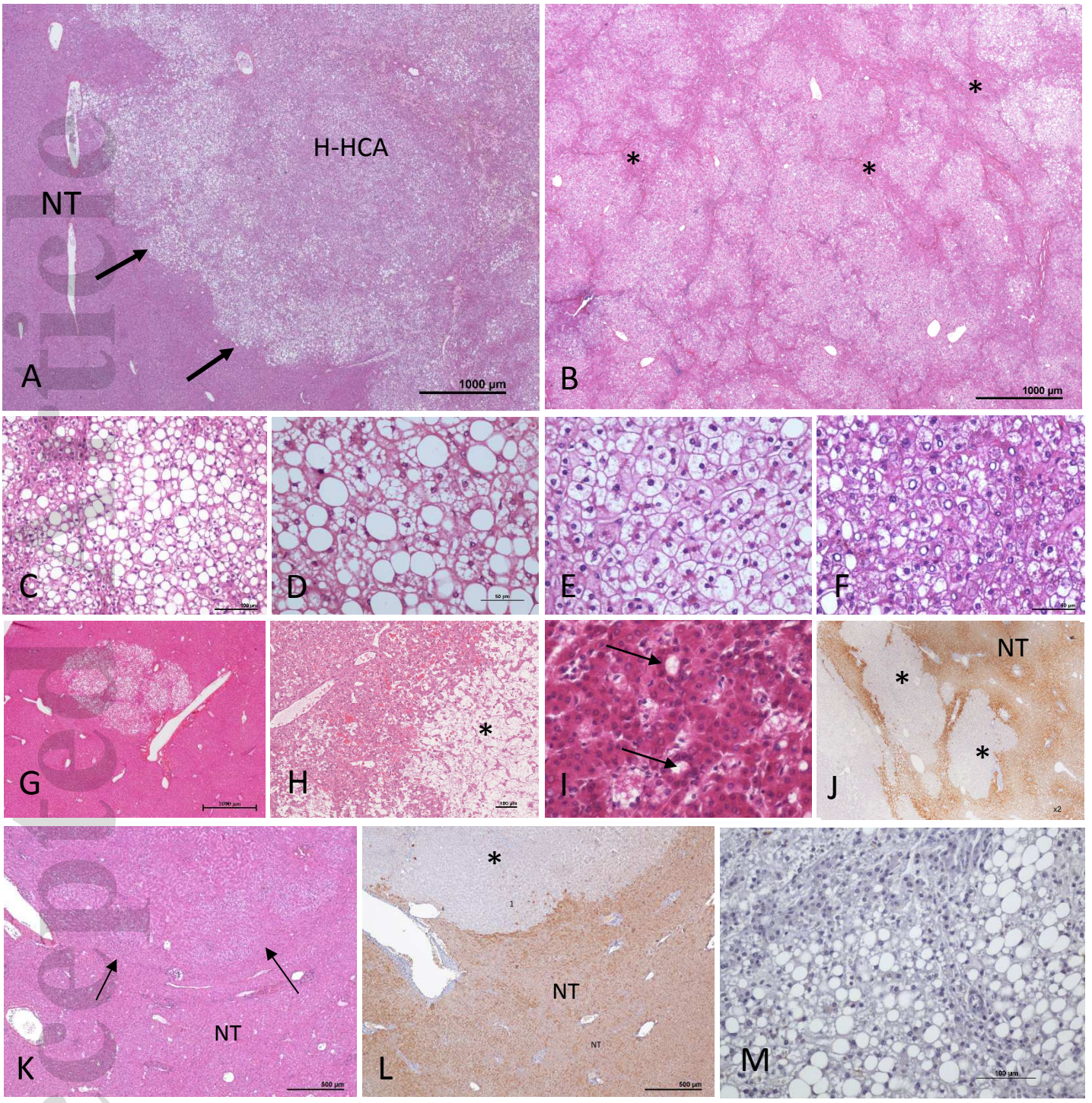


Figure 1: H-HCA

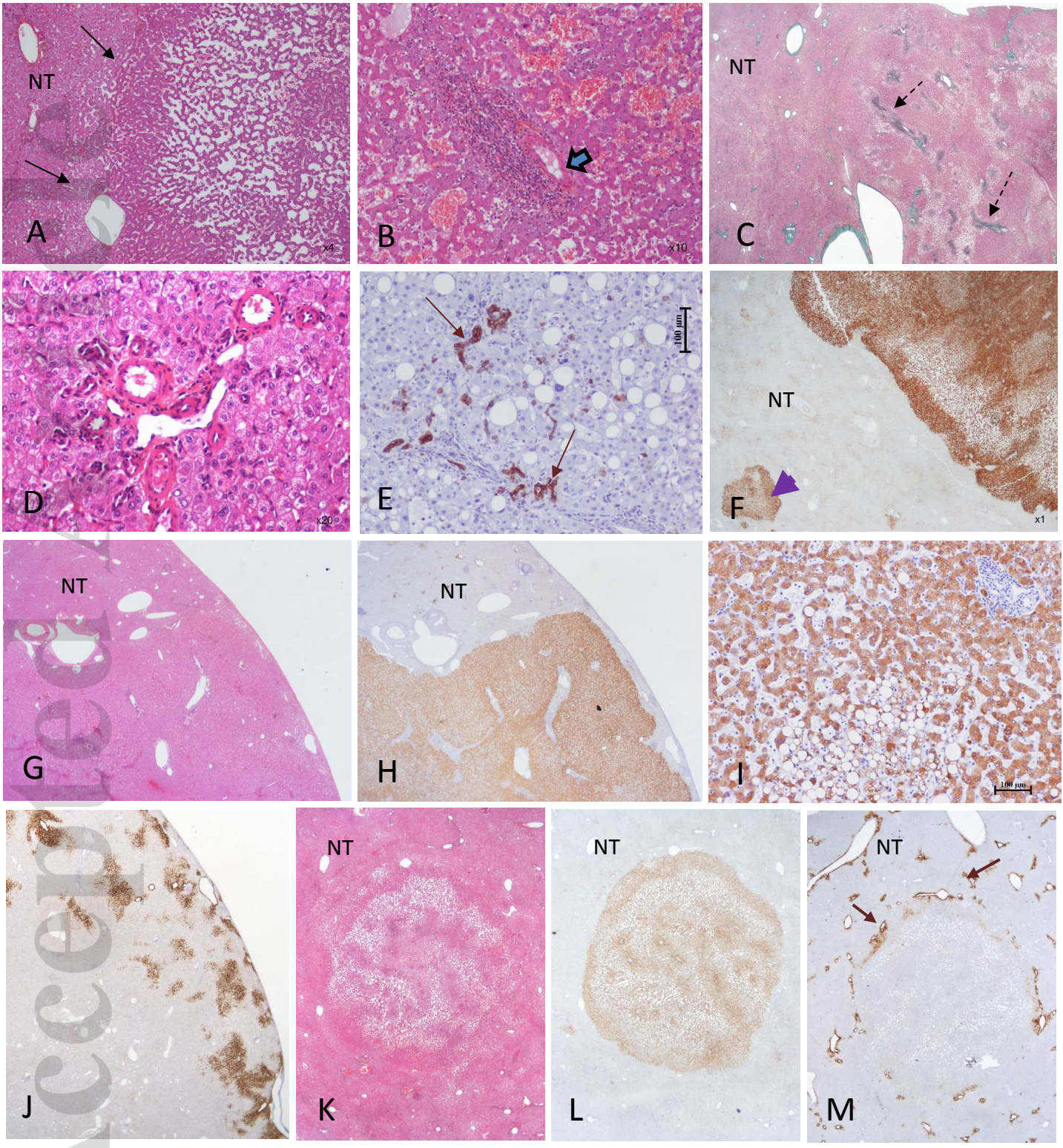


Figure 2: Inflammatory hepatocellular adenoma

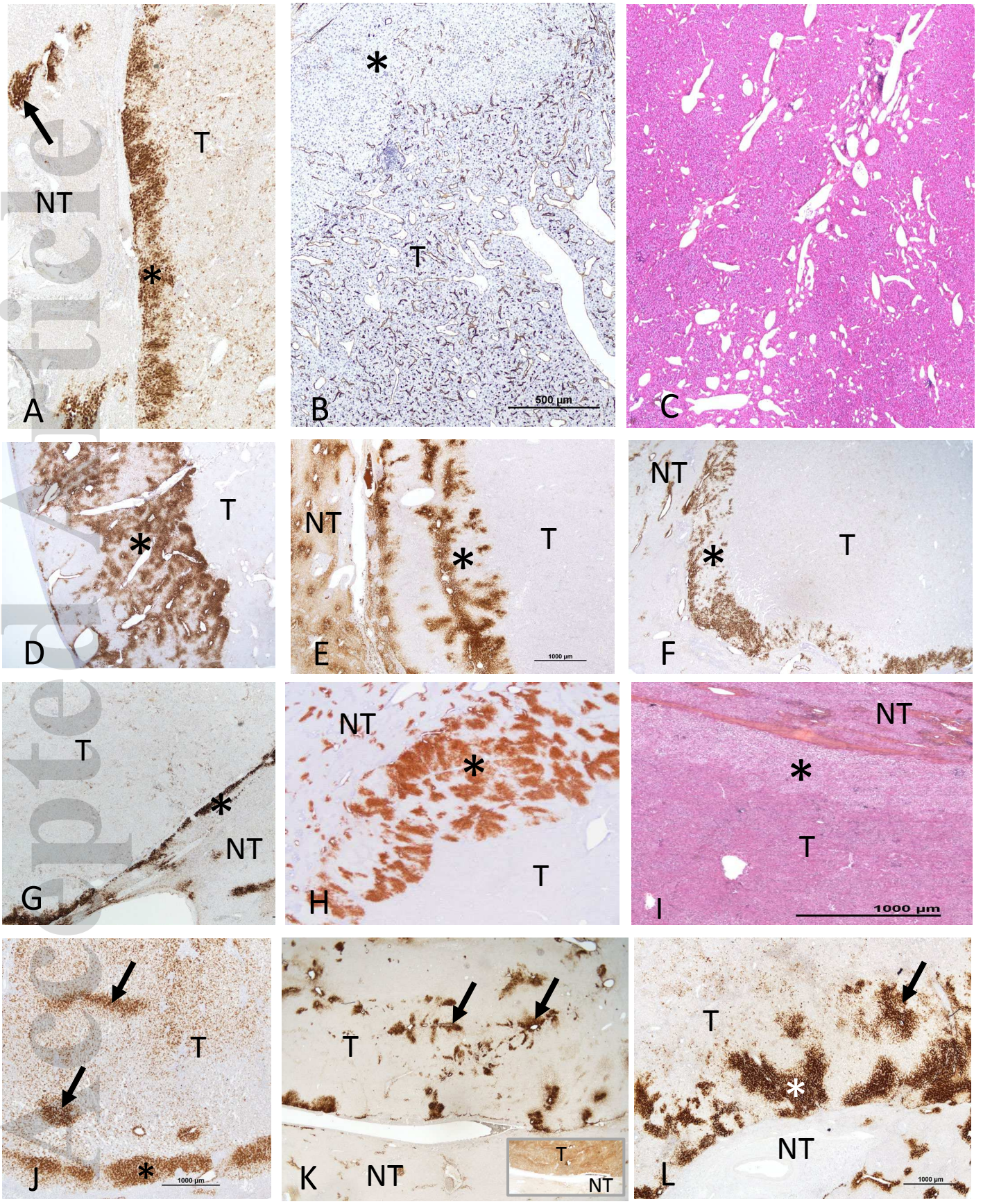


Figure 3: b-HCA and b-IHCA

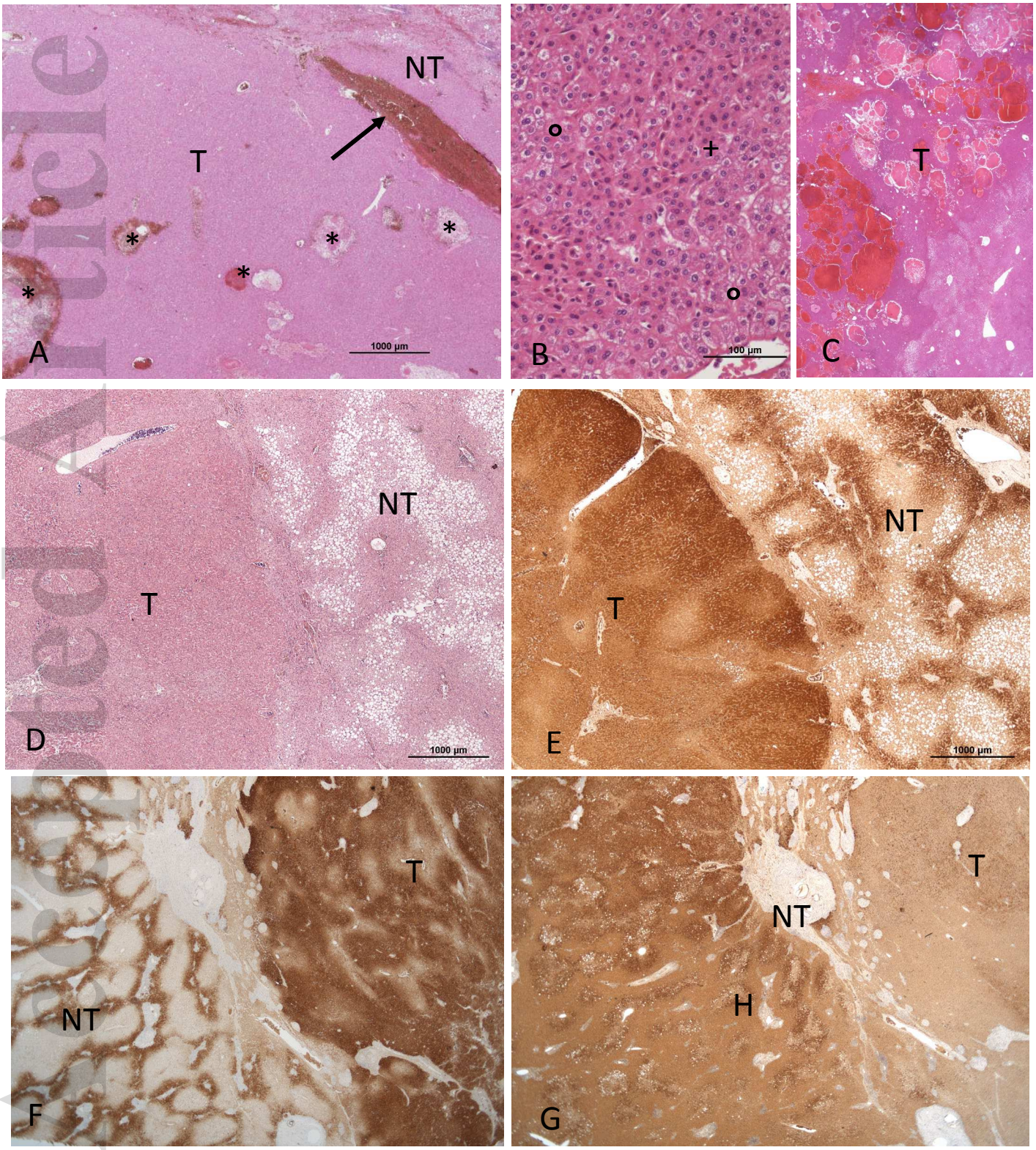


Figure 4: shHCA

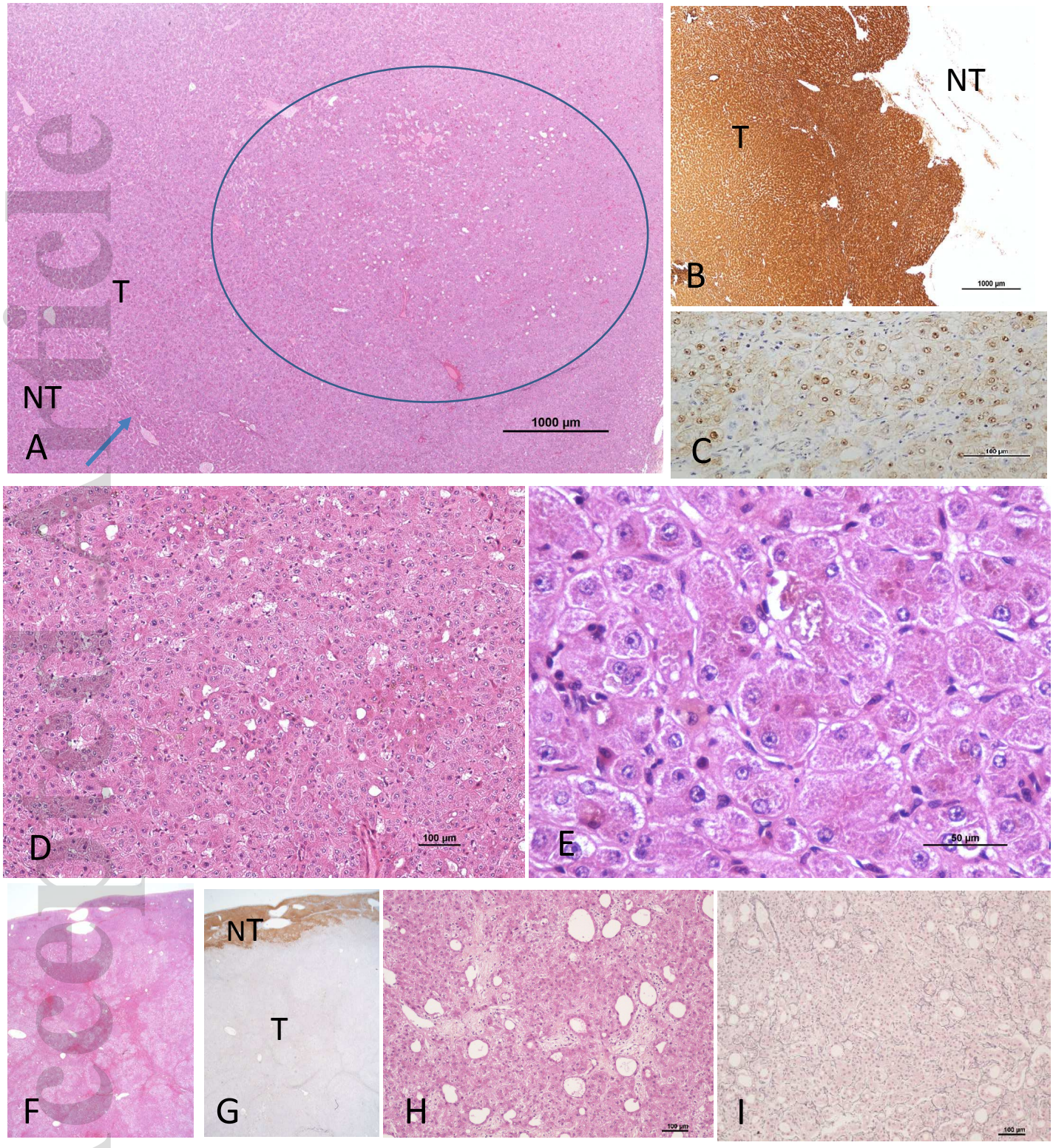
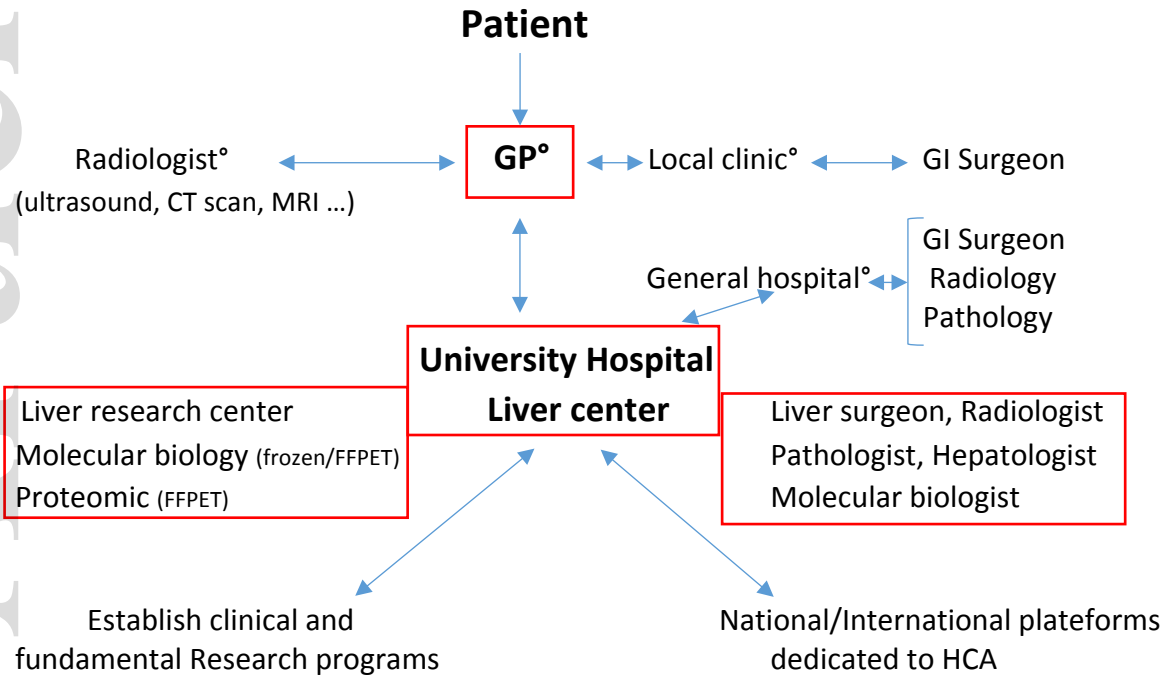


Figure 5: HCA with malignant foci

Figure 6: Hepatocellular adenoma from daily practice to a scientific network



*Coordination between University liver centers through a platform

°use all modern techniques to exchange documents

GP: general practitioner; GI: gastro intestinal; FFPET: formalin fixed paraffin embedded tissue