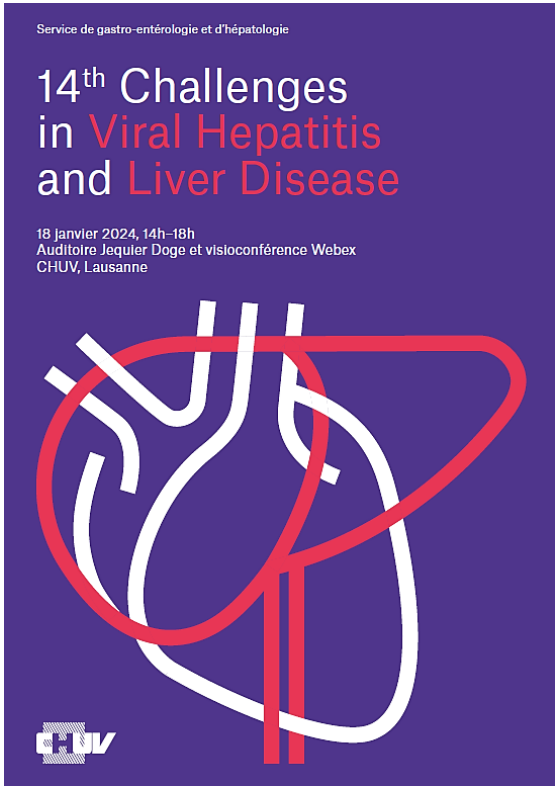


Hepatocellular Adenomas What's New?

Prof. Christine Sempoux, MD PhD

Institute of Pathology, CHUV,
University of Lausanne, Switzerland

NOWADAYS

Discussion in specialized MDT

Six subtypes

- based on histology, immunohistochemistry and molecular biology
- linked to clinical contexts

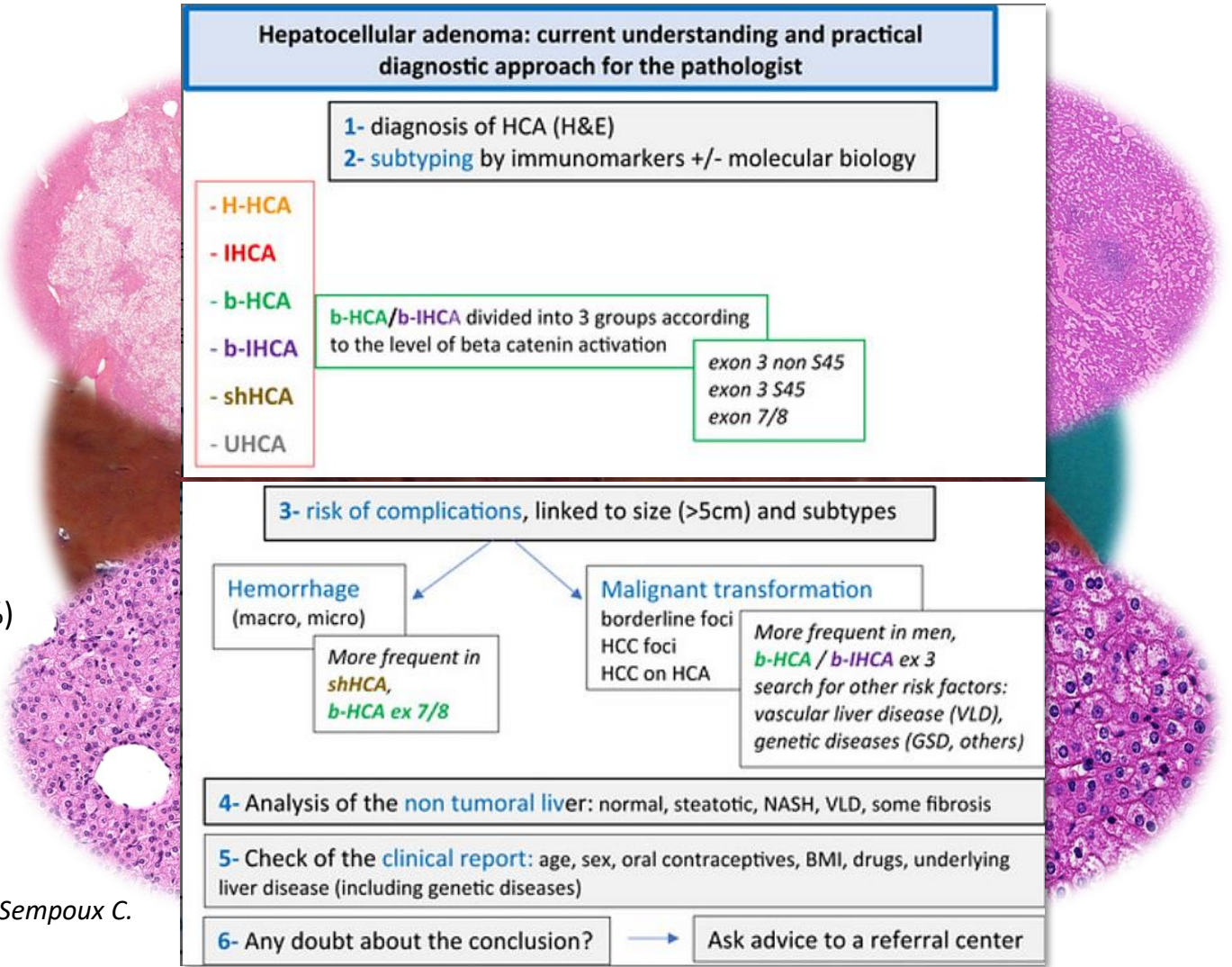
Two main risks

- bleeding (20-25%)
- malignant transformation (4-8%)

Linked to subtype

Consider

- the non tumoral liver
- the clinical context



Bioulac-Sage P, Gouw ASH, Balabaud C, Sempoux C. Histopathology 2022;80:878-897.

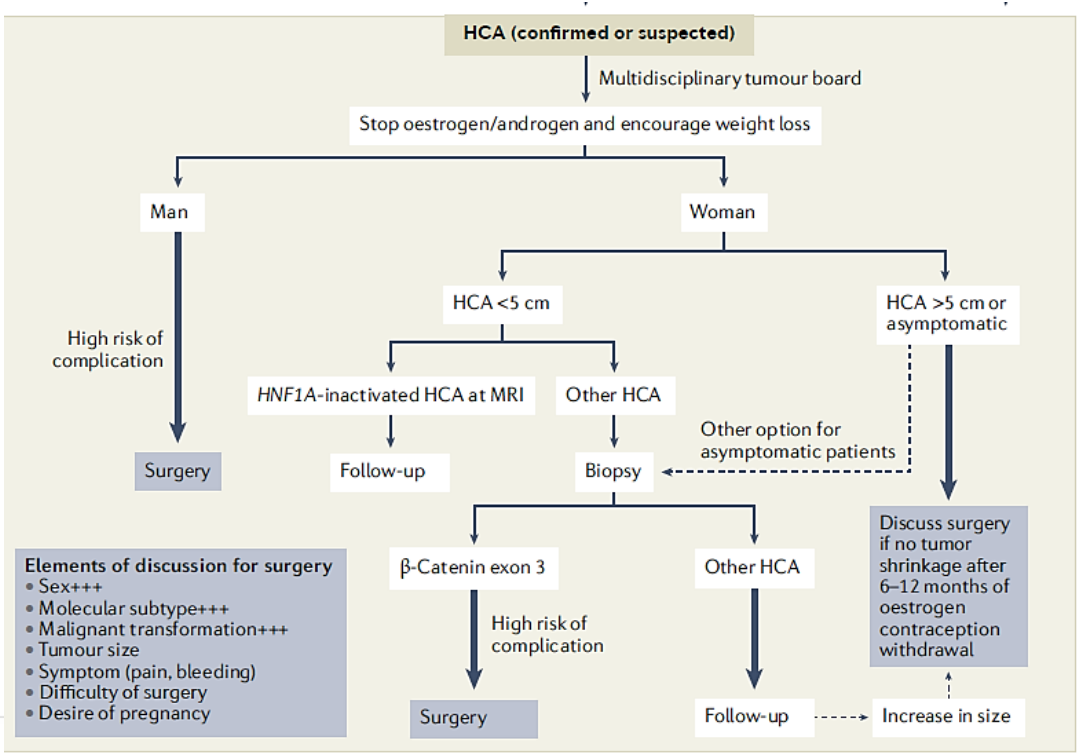
Benign liver tumours: understanding molecular physiology to adapt clinical management

Jean-Charles Nault[1,2,3,4]✉, Valérie Paradis[5,6], Maxime Ronot[6,7] and Jessica Zucman-Rossi[3,4,8]✉

Nature Reviews, Gastroenterology & Hepatology
November 2022

"The management of benign liver tumours requires a **comprehensive assessment** by radiologists, hepatologists, surgeons and pathologists that **considers the molecular diversity** of these tumours in a **minimally invasive step-by-step diagnostic process and management** based on an evaluation of the risk of complications."

"…the molecular classification of these tumours has helped redefine this disease and provide critical tools for **personalized management**."



OUTLINE

1. Precise morpho-molecular subtyping

   reflects the underlying molecular alterations resulting in specific deregulated mRNAs
   4 different pathways, 5 subtypes + 1 unclassified (<2%)

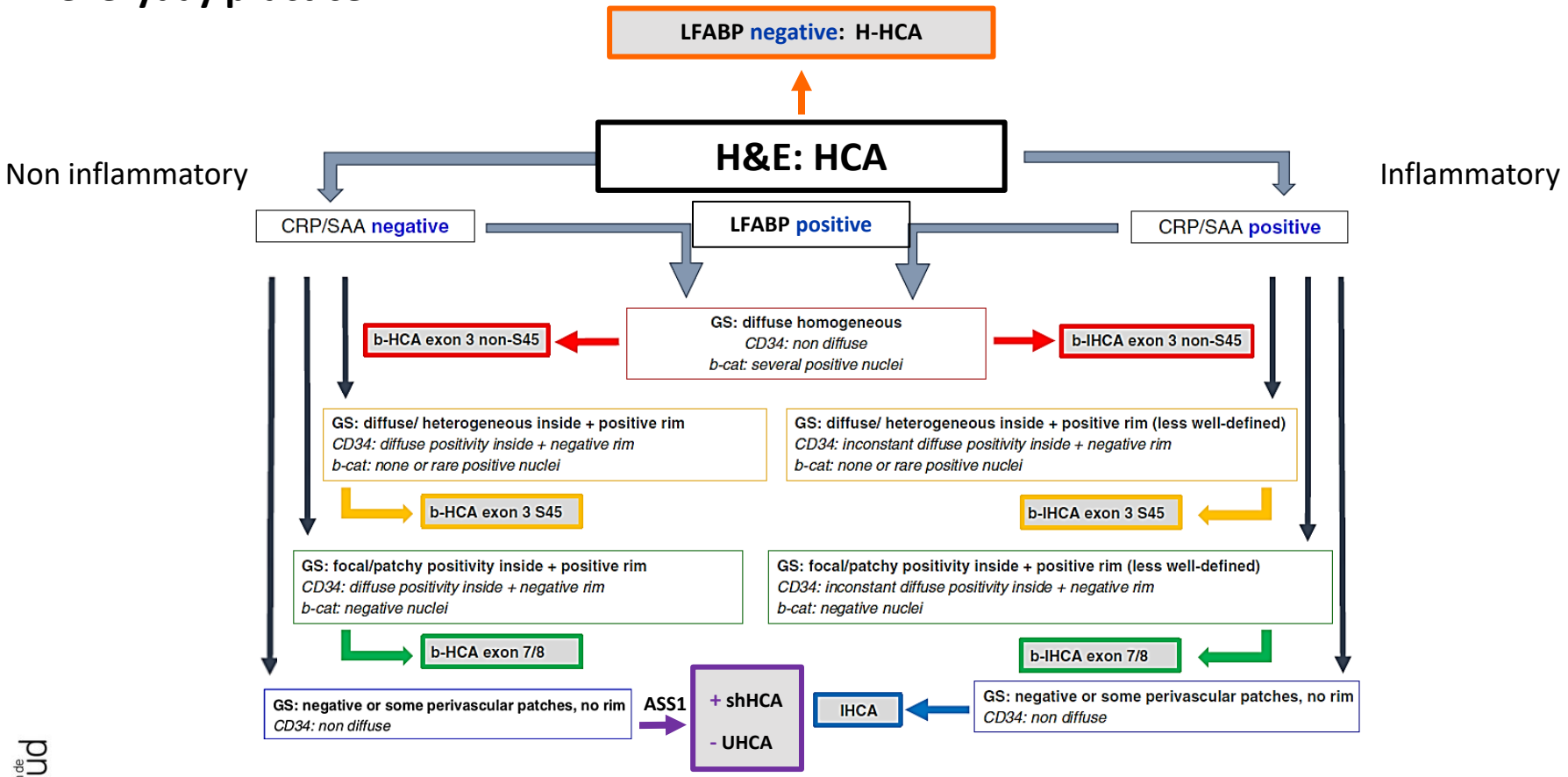
2. Clinical diversity

   importance of the clinical context (patient and his/her liver)
   type and risk of complications

3. Modern clinical management

   indications for biopsy
   specialized MDT and registries

In everyday practice



Adapted from Sempoux et al. AJSP 2021

Clinical diversity and complications

- Women, OC and healthy liver (85% of cases): **all HCA subtypes, mainly H-HCA**
- Women, high BMI, metabolic syndrome: **IHCA, b-IHCA§, shHCA often adenomatosis**
- Men, high BMI, metabolic syndrome : **IHCA**, **b-IHCA§**
- Women and men >60 : **H-HCA***
- Men, androgens: **b-HCA§, b-IHCA§**
- Women, men, MODY 3: **H-HCA, often adenomatosis**
- Women, men, vascular liver diseases: **all HCA subtypes, H-HCA**
- Children, metabolic (GSD), vascular liver (CPSS) diseases: **all HCA subtypes, mainly b-HCA§**
- Cirrhotic livers (alcohol): **« IHCA »****

Bleeding
Malignant transformation

5 cm

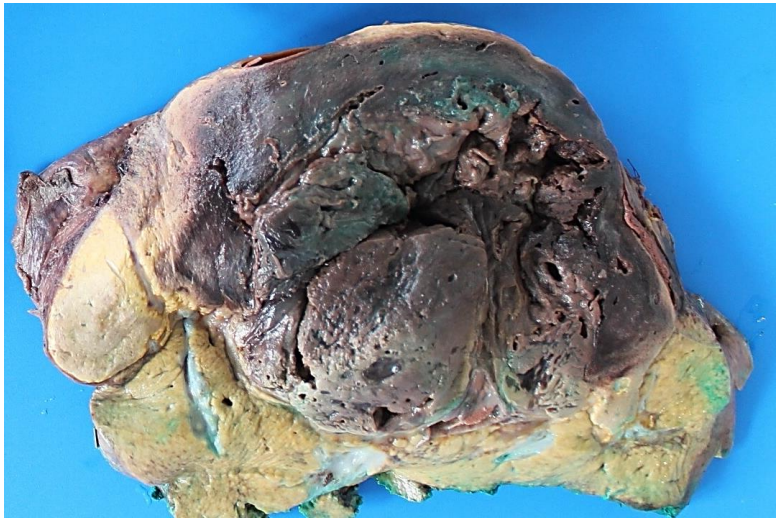
b-HCA and b-IHCA with exon 7/8 mutations

**Yasir et al. Am J Surg Pathol 2022*

***Sasaki et al. Histopathology 2015; Calderaro et al. Modern Pathology 2016, Gordic et al. Eur J Radiol Open 2017*

Bleeding

All HCAs, clinically significant in 20-25%



- **HCA risk factors:**
  - exophytic growth
  - size > 5cm
  - adenomatosis
  - sonic hedgehog activation: shHCA (even if <5cm)
  - wnt/b-catenin activation: b-HCA/b-IHCA exon 7/8

- **Clinical risk factors:**
  - alcohol consumption

Hepatocellular Adenoma Risk Factors of Hemorrhage: Size Is Not the Only Concern!

Single-center Retrospective Experience of 261 Patients

Céline Julien, MD,✉ Brigitte Le-Bail, PhD,† Kevin Ouazzani Touhami, MD,‡ Nora Frulio, MD,§ Jean-Frédéric Blanc, PhD,¶ Jean-Philippe Adam, MD,* Christophe Laurent, PhD,* Charles Balabaud, MD,|| Paulette Bioulac-Sage, MD,|| and Laurence Chiche, MD*||✉*

NEW !!

Klompenhouwer et al. Liver Int 2020, Julien et al. Ann Surg 2021

Malignant transformation

Monoclonal lesions → potential for malignant transformation (4-8%)

- **HCA risk factors:**

  b-HCA / b-IHCA exon 3

  size > 5cm

- **Clinical risk factors:**

  male gender (10 x)

  glycogen storage disease

  androgens

  vascular liver diseases (H-HCA !)

- **HCC on HCA: we are sure only if**

  both components present on the slide or if there is a past history of incompletely resected HCA

Long-term outcomes following resection of hepatocellular adenomas with small foci of malignant transformation or malignant adenomas

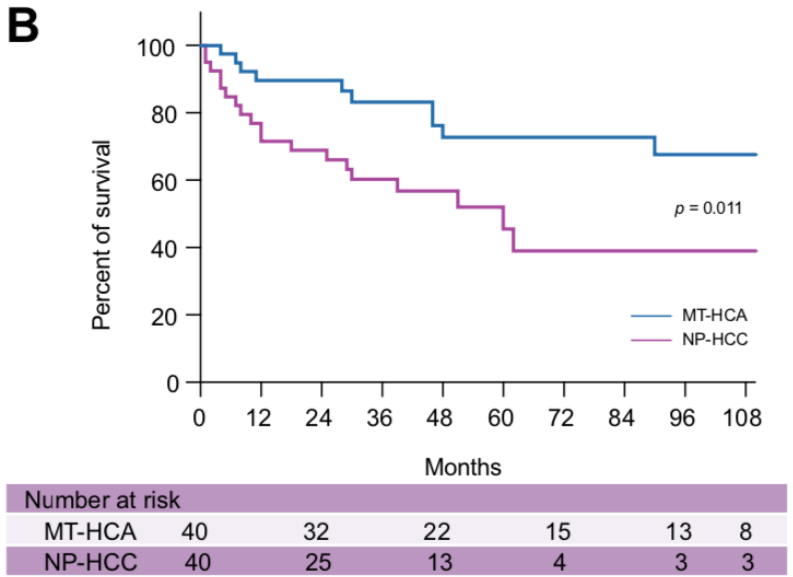
Sophie Chopinet,[1] François Cauchy,[1] Christian Hobeika,[1] Aurélie Beaufrère,[2] Nicolas Poté,[2] Olivier Farges,[1] Safi Dokmak,[1] Mohamed Bouattour,[3] Maxime Ronot,[4] Valérie Vilgrain,[4] Valérie Paradis,[2] Olivier Soubrane[1,*]

[1]*Department of HPB and Liver Transplantation, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris and Université de Paris, Clichy, France;* [2]*Department of Pathology, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris and Université de Paris, Clichy, France;* [3]*Department of Oncology, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris and Université de Paris, Clichy, France;* [4]*Department of Radiology, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris and Université de Paris, Clichy, France*

JHEP Reports **2021.** https://doi.org/10.1016/j.jhepr.2021.100326

NEW !!

HCA with malignant transformation have a better long-term prognosis than HCC on non cirrhotic liver

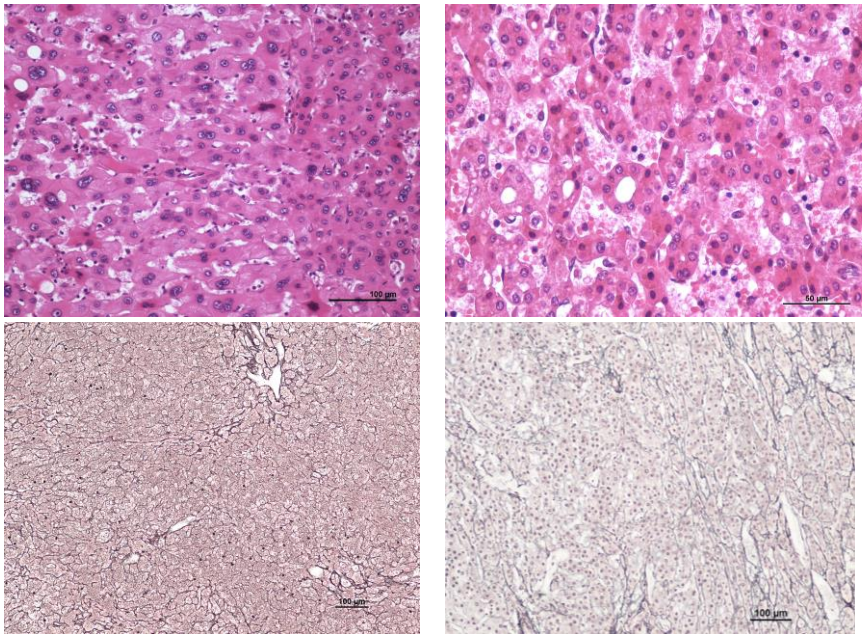


Number at risk						
MT-HCA	40	32	22	15	13	8
NP-HCC	40	25	13	4	3	3

Atypical hepatocellular adenomas/borderline HCAs (WHO 2019)

A subtyped HCA presenting atypical **morphological** features, worrisome but **insufficient** (focal and/or incomplete, threshold?) to make a definite diagnosis of HCC (7% of cases*)

Cellular and nuclear atypia
Architectural atypia (pseudoglands)
Reticulin framework loss
No definite tool (IHC, MB, …)



Confusing terms in the literature, some definitions of atypical HCAs including clinical features (male or older women) or the subtype (*CTNNB1* mutated neoplams)

⇢ **should be reserved for the histological description**
⇢ **more impact on biopsy (2nd opinion, referal center)**
⇢ **WD hepatocellular neoplasm**

NEW !!

*Nault et al. Gastroenterology 2017

Torbenson M. Surgical Pathology 2018, WHO 2019, Dourthe C et al. Hepatology 2021, Bioulac-Sage et al. Histopathology 2022

Management should be adapted to the subtype more than to the size (> 5 cm)

NEW !!

-> Subtyping of HCA with imaging: >90% specificity for IHCA and H-HCA

-> Subtyping of HCA with biopsy:

→ not needed if

- resection is planned (men, >5cm, bleeding, growing lesion…)
- imaging is certain

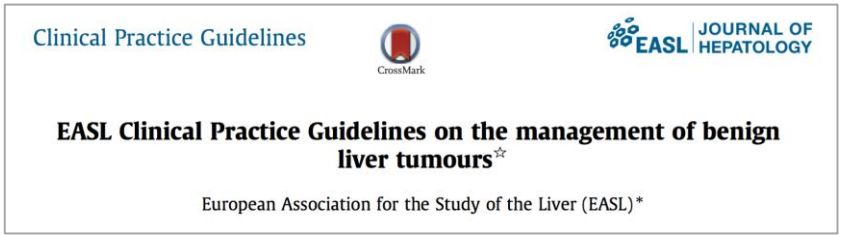
→ needed if

- ablation is planned (can be done at the same time)
- < 5cm in a woman:
  b-HCA, b-IHCA: risk of malignancy, of bleeding if exon 7/8
  shHCA: risk of bleeding
- uncertain diagnosis on imaging: *HCA vs FNH, HCA vs HCC*

NB: H-HCA: lower risk of complication, follow-up can be proposed even if > 5cm if diagnosis is confirmed

Reliable histological diagnosis requires
1) immunohistochemistry (+/- MB)
2) non tumoral liver for comparison

Mutidisciplinary approach is essential in HCA


Clinical Practice Guidelines

CrossMark

EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on the management of benign liver tumours☆

European Association for the Study of the Liver (EASL)*

J Hepatol 2016

The benign liver tumour multidisciplinary team

The team should be one with expertise in the management of benign liver lesions and should include a hepatologist, a hepatobiliary surgeon, diagnostic and interventional radiologists and a pathologist. Each member of the team must hold specific and relevant training, expertise and experience relevant to the management of benign liver lesions. The team should be one with the skills required not only to appropriately manage these patients, but also manage the rare but known complications of diagnostic or therapeutic interventions.

With the aim of **building guidelines** in mind, it is important to collect **standardized** clinical, imaging and histopathological data that led to the clinical management decision in each case.

Blanc et al. Clinics and Research in Hepatol and Gastroenterol 2015, Haring et al. BMJ 2021

The Swiss Adenoma Registry
SASL study 45

NEW !!

Prospective and retrospective national data collection

Retrospective identification of any eligible patients with established HCA diagnosis at the referring Centers (BE, BS, GE, VD, SG, TI, ZH) since January 1, 2018.

Prospective inclusion of any new diagnosed case, starting in January 2022 fulfilling inclusion criteria. All prospectively included patients will have a regular follow-up at one of the above-mentioned referring Centers.

Epidemiological and clinical data, histopathological and radiological comprehensive description, including diagnosis procedures (morpho-molecular characterization and imaging), treatment and follow-up.

-> to characterize HCA in Switzerland and build a consensus for multidisciplinary standardized management

Points that we discuss during our MDT meetings

HPB Cancer Center Lausanne

Clinical context: hepatologist advice

Imaging findings

- DD with FNH feasible in 90% (MRI – Primovist)
- DD with HCC
- Identification of the HCA subtype

Biopsy: yes if

- Diagnosis unclear by imaging
- HCA between 2 and 5 cm to adjust management to subtype
- HCA > 5 cm that we do not plan to resect

Adenomatosis?

- Are the HCAs all the same? Imaging +/- biopsies

Surgery: yes or no, type, risk?

+ Surveillance: rhythm? Desire for pregnancy?

In summary

Hepatocellular adenomas: what is new?

For pathologists

When a biopsy is performed, precise and complete subtyping is mandatory

- **H-HCA**: steatosis not always present, malignant transformation exists (VLD)
- **IHCA**: check the possibility of an additional *CTNNB1* mutation-> b-IHCA
- **b-HCA and b-IHCA**: not a single subtype : different *CTNNB1* mutations with specific phenotypic features, exon 3: risk of malignancy, exons 7/8 : risk of bleeding, perform MB if needed
- **shHCA**: ASS1+, bleeding even if <5cm, women, high BMI, adenomatosis
- **UHCA**: only after excluding carefully one of the other subtypes, including with MB

In summary

Hepatocellular adenomas: what is new?

For hepatologists and surgeons

Be aware of the clinical diversity and relative risk of complications

- discussion in specialized MDT and tailored management
- size is not the only criteria
- men: not always *CTNNB1* -> not always at risk
- high BMI: not only IHCA, also shHCA with high risk of bleeding and frequent adenomatosis
- progress in MRI to subtype HCA
- importance of building registries to collect data on this rare entity