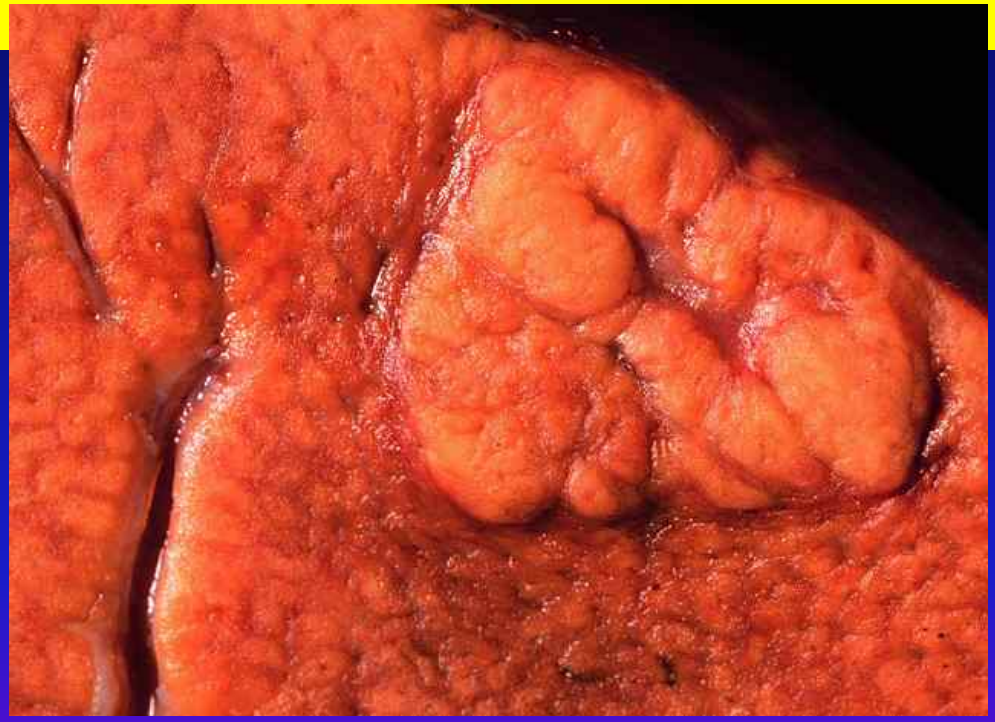
bloed, ademhaling & spijsvertering

Universitair Ziekenhuis Gent

Benigne levertumoren
Rol van moleculaire classificatie



Dutch liver week 2017

Anja Geerts, MD, PhD
Dienst Gastroenterologie & Hepatologie

Benigne levertumoren
Rol van moleculaire classificatie

No disclosures

Benign liver tumors (BLT)

- Extremely frequent (20 to 52% of population)
- Highly sensitive imaging > increasing incidence of focal liver masses, solitary or multiple
- Mostly asymptomatic
- Clinical relevance mostly for four lesions: hemangioma, focal nodular hyperplasia (FNH), hepatocellular adenoma (HCA) and hepatic cysts
- Clinical management: symptoms/ history/ hormonal status/ nature of tumor

EASL Clinical Practice Guidelines on the management of benign liver tumours

Journal of Hepatology 2016

vol 65 : 386-398

Benigne levertumoren
Rol van moleculaire classificatie

Casus

Vrouw 56 jaar

2004: rechter hepatectomie omwille van adenomen

APD: multiple adenomen (10tal)

diameter 2.5 tot 6cm.

wisselende graad van macrovesiculaire steatose

Benigne levertumoren
Rol van moleculaire classificatie

Casus

Vrouw 56 jaar

2016: Pijn abdominaal, met op beeldvorming 2 grote leverletsels linkerleverlob

03/2016: Resectie van twee grote leverletsels exofytisch uitgaande van segment II en III

APD: matig tot weinig gedifferentieerd HCC

Benigne levertumoren
Rol van moleculaire classificatie

Casus

Vrouw 56 jaar

03/2016: APD: matig tot weinig gedifferentieerd HCC

Immunohistochemie:

Beta catenine: pos

HSP 70: pos

Glypican 3: zwakke aankleuring

CRP: geen toename

Benigne levertumoren
Rol van moleculaire classificatie

Casus

Vrouw 56 jaar

03/2016: APD: matig tot weinig gedifferentieerd HCC

Uitwerking voor levertransplantatie

08/2016: 2 nieuwe letsels biopt APD, HNF1 gemuteerd hepatocellulair adenoom, transformatie naar goed gedifferentieerd HCC

08/2016: RFA 2 letsels

10/2016: RFA 1 letsel

01/2017: RFA 1 letsel

1/06/2017: Levertransplantatie

Hepatocellular adenoma (HCA) (1)

Epidemiology and etiology

- Incidence: 3 -4 per 100 000 women
- Mostly diagnosed in women age 35-40 years (female:male ratio of 10:1)
- Link between OCPs and increased risk of HCA in women
- Incidence increases also in males: link between use of anabolic substances in sport or use of anabolic androgenic steroids by body builders

- Incidence increases also with rising prevalence of obesity and metabolic syndrome
- Rare associations: MODY 3 associated HCA, glycogen storage disease I,III and IV

Hepatocellular adenoma (HCA) (2)

Pathophysiology and natural course

- Monoclonal proliferation of hepatocytes in normal liver
- Most often solitary lesion (<> liver adenomatosis more than 10 lesions)

- Two main complications: bleeding and malignant transformation into hepatocellular carcinoma

Introduction of a new subclassification for HCA Potential clinical impact: refinement of prognosis, evaluation and treatment

Four subtypes based on genetic and pathological criteria:

-HNF1-α (hepatocyte nuclear factor) inactivated HCA (30-40%)

- β-catenin mutated HCA (5-10%)

- Inflammatory HCA (> 50%) of which 10% have a β-catenin mutation

- Unclassified HCAs (< 10%)

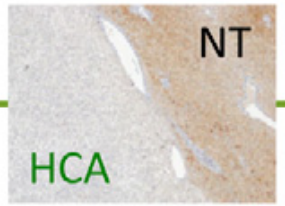
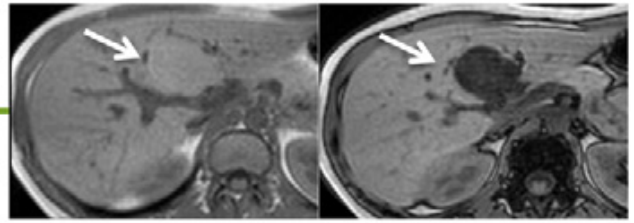
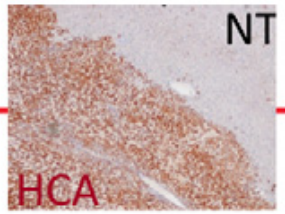
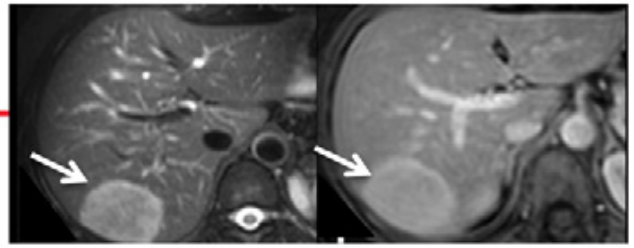
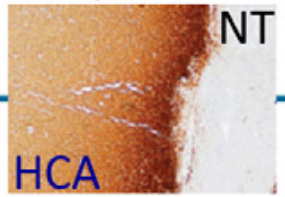
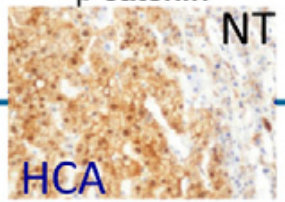
(Nault JC , Gastroenterology 2013;144:888-902)

Subclassification adenomas

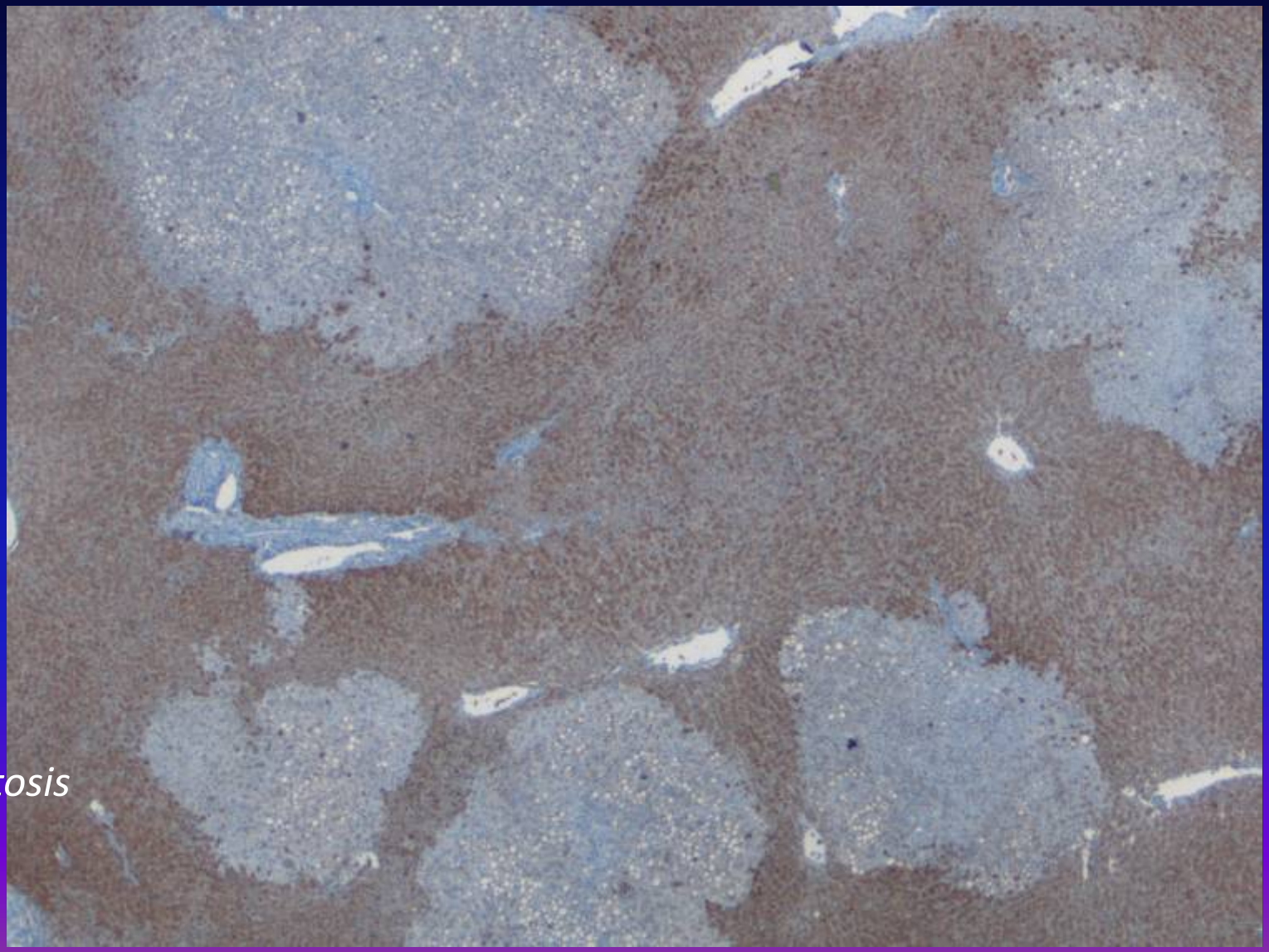
1. Adenomas with mutations in HNF1α (hepatocyte nuclear factor1α) *30-40%* ***(19%)***
2. Adenomas with activating β-catenin mutation *10%* ***(7%)***
3. Inflammatory type adenomas *40-50%* ***(63%)***
4. Unclassified *<10%* ***(11%)***

Validation of a liver adenoma classification system in a tertiary referral centre: Implications for clinical practice

Susanna M. van Aalten[1], Joanne Verheij[2], Turkan Terkivatan[1], Roy S. Dwarkasing[3], Robert A. de Man[4], Jan N.M. IJzermans[1,*]

Molecular classification	Main pathological and clinical features	Immuno histochemical markers	Radiological features
HNF1A mutations 30%–40%	Familial adenomatosis MODY3 diabetes Marked steatosis	Loss of LFABP expression 	Diffuse signal dropout on T1-weighted chemical shift sequence 
Inflammation 40%–50% *Gp130* 65% *GNAS* 5% *STAT3* 5% *NM* 25%	Obesitas/Metabolic syndrome Inflammatory syndrome Inflammatory infiltrates Dystrophic vessels Sinusoidal dilatation	Overexpression of SAA/CRP 	Hypersignal on T2W sequences Persistent enhancement in portal venous phase 
Inflammation + β-catenin mutations 5%–10%		Overexpression of glutamine synthase 	
β-catenin mutations 5%–10%	Males High risk of HCC Cytological abnormalities Pseudo-glandular formations	Nuclear expression of β-catenin 	Absence of typical radiological features Hyperintense T2/ hypointense T1
Unclassified 10%			

Joanne Verheij, MD, PhD
Department of Pathology
Academic Medical Center
Amsterdam



adenomatosis

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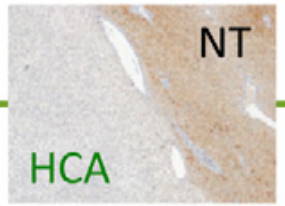
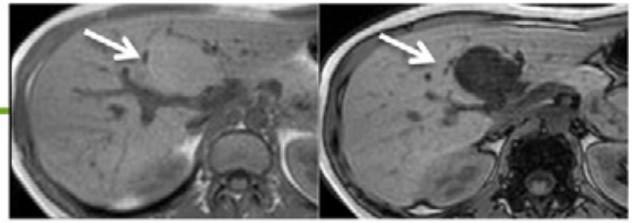
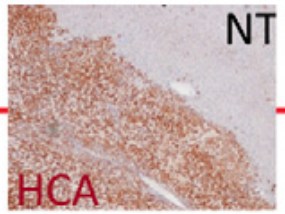
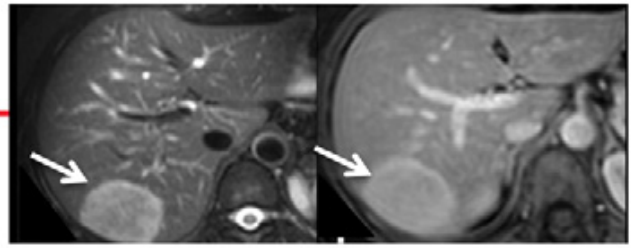
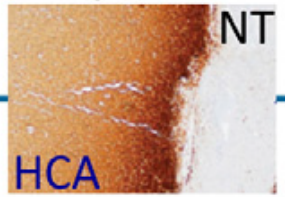
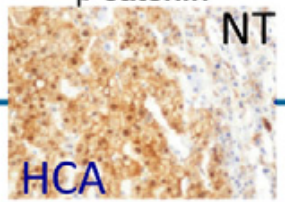
HNF1A mutations 30%–40%	Familial adenomatosis MODY3 diabetes Marked steatosis	Loss of LFABP expression 	Diffuse signal dropout on T1-weighted chemical shift sequence 
Inflammation 40%–50% *Gp130* 65% *GNAS* 5% *STAT3* 5% *NM* 25%	Obesitas/Metabolic syndrome Inflammatory syndrome Inflammatory infiltrates Dystrophic vessels Sinusoidal dilatation	Overexpression of SAA/CRP 	Hypersignal on T2W sequences Persistent enhancement in portal venous phase 
Inflammation + β-catenin mutations 5%–10%		Overexpression of glutamine synthase 	
β-catenin mutations 5%–10%	Males High risk of HCC Cytological abnormalities Pseudo-glandular formations	Nuclear expression of β-catenin 	Absence of typical radiological features Hyperintense T2/ hypointense T1
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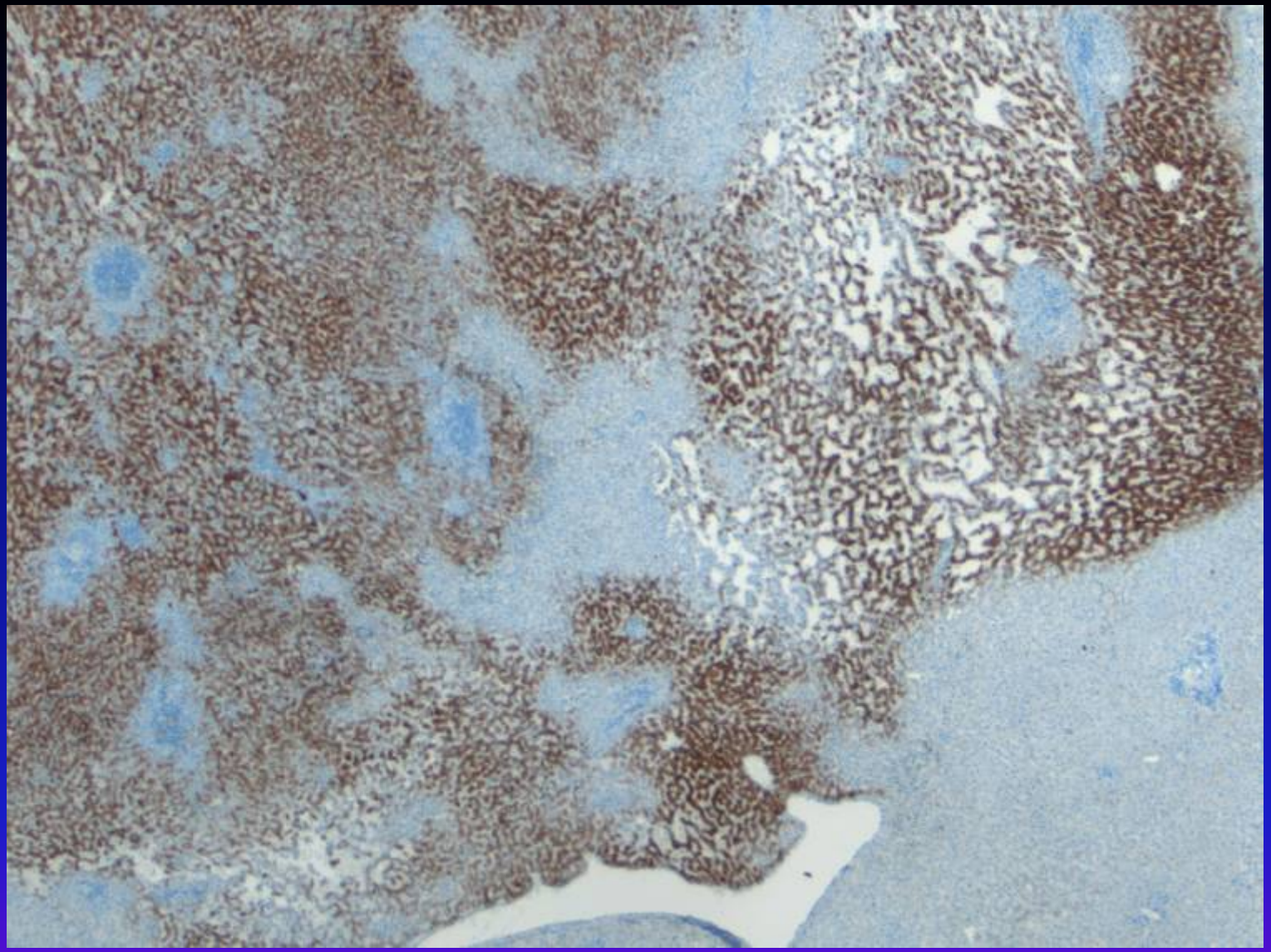
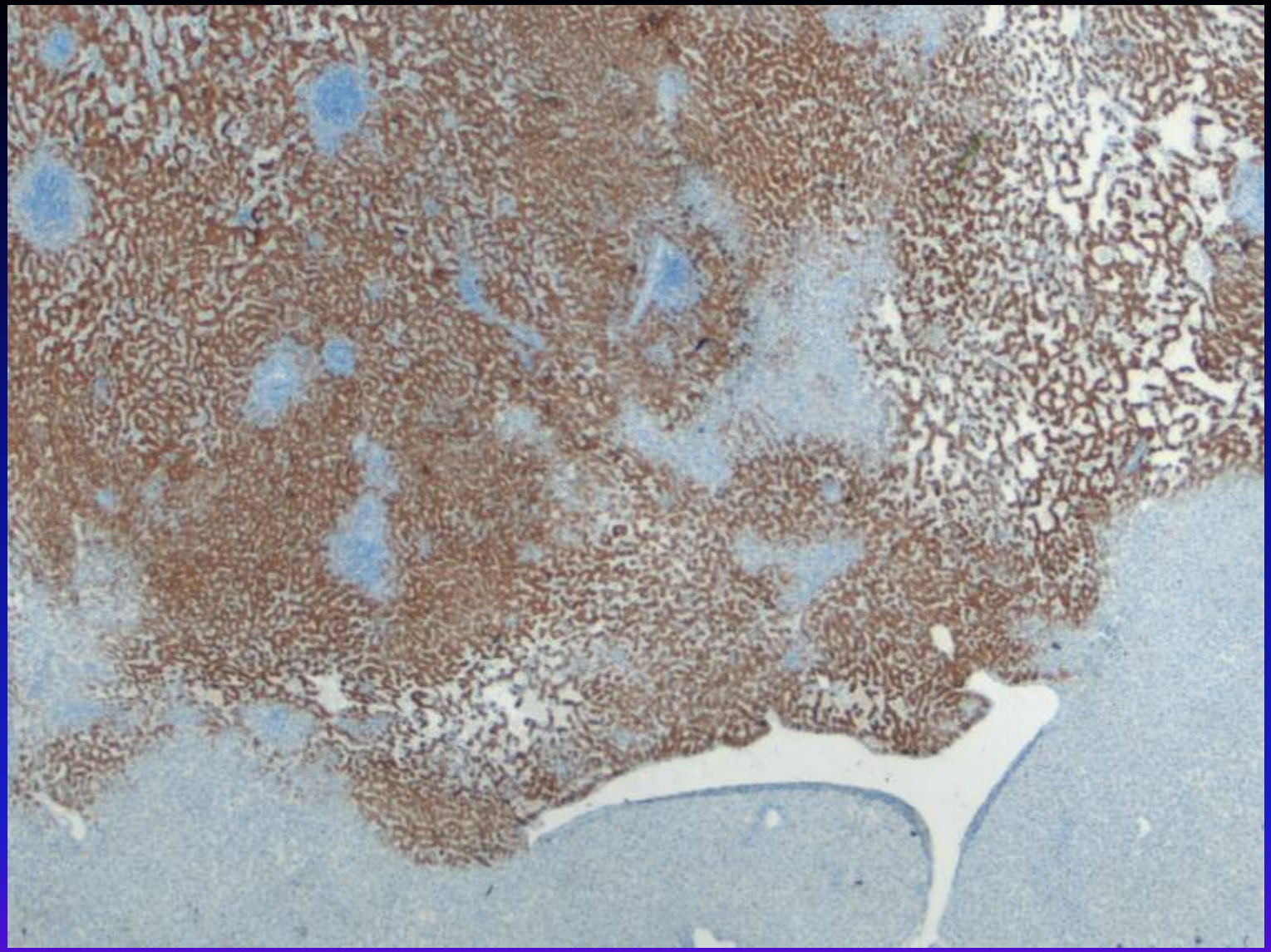
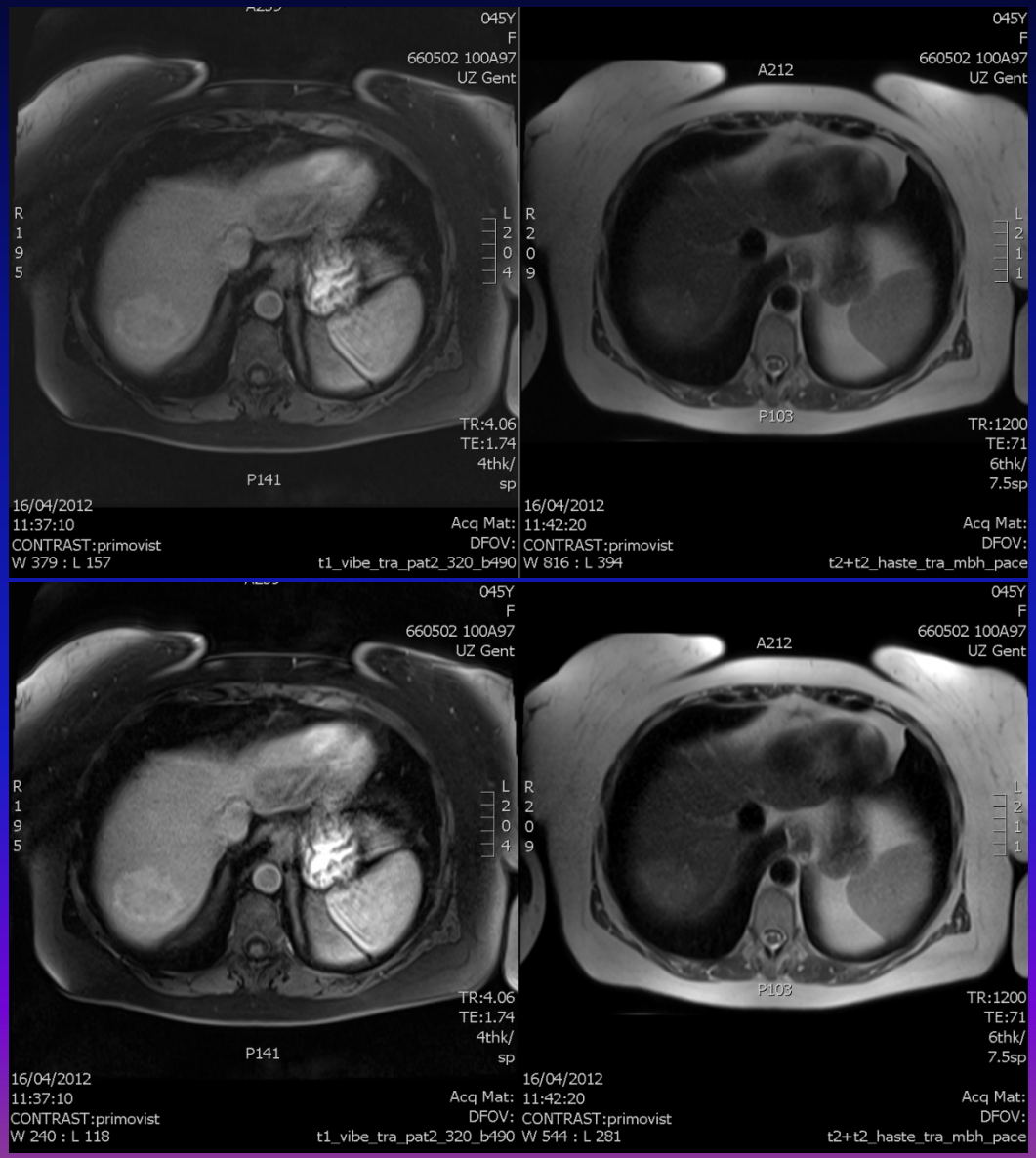


SAA



CRP

Inflammatoir adenoma



"Atoll sign "

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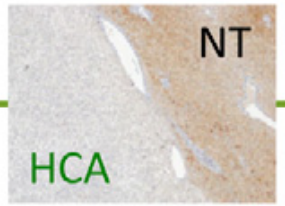
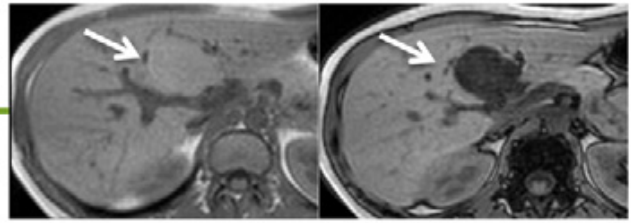
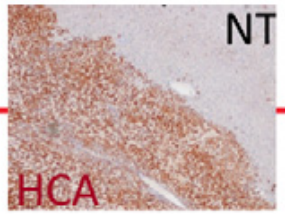
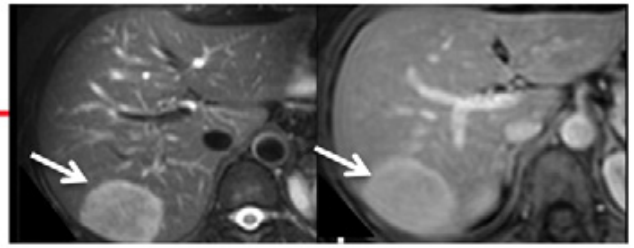
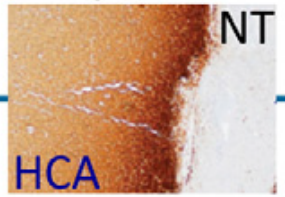
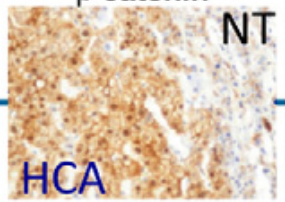
HNF1A mutations 30%–40%	Familial adenomatosis MODY3 diabetes Marked steatosis	Loss of LFABP expression 	Diffuse signal dropout on T1-weighted chemical shift sequence 
Inflammation 40%–50% *Gp130* 65% *GNAS* 5% *STAT3* 5% *NM* 25%	Obesitas/Metabolic syndrome Inflammatory syndrome Inflammatory infiltrates Dystrophic vessels Sinusoidal dilatation	Overexpression of SAA/CRP 	Hypersignal on T2W sequences Persistent enhancement in portal venous phase 
Inflammation + β-catenin mutations 5%–10%		Overexpression of glutamine synthase 	
β-catenin mutations 5%–10%	Males High risk of HCC Cytological abnormalities Pseudo-glandular formations	Nuclear expression of β-catenin 	Absence of typical radiological features
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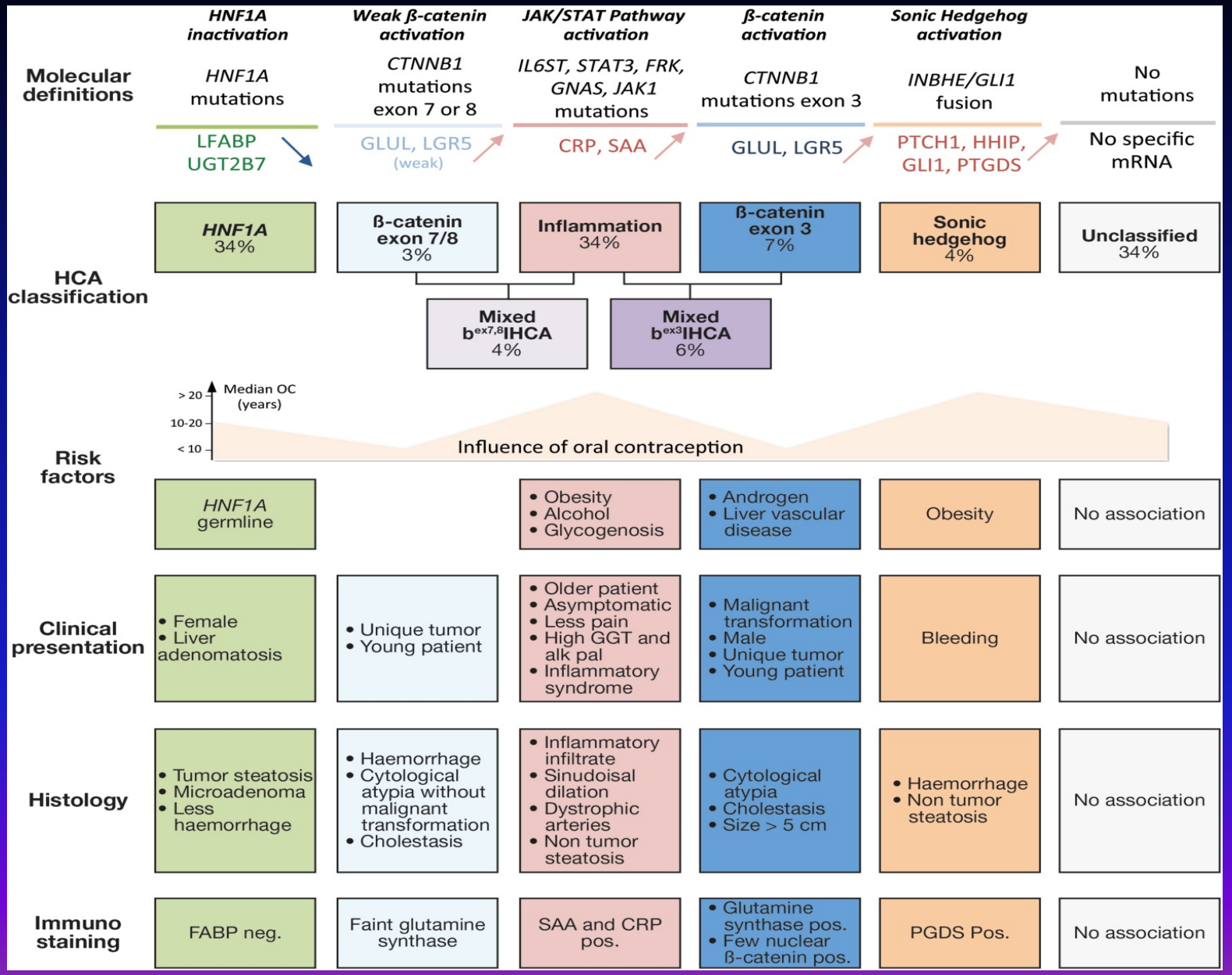
GS



Nault JC, Gastroenterology 2017;152: 880-894

Diagnosis HCA

MRI

- Specific hepatobiliary contrast agents (gadoxetate disodium (Primovist), gadobenate dimeglumine (Multihance)
- Differential diagnosis with FNH
- Hepatobiliary phase: 91-100% sens, 87-100% specificity
- Discriminate different subtypes of HCA

Liver biopsy: panel of IHC (LFABP, SAA,CRP, GS, b-catenin)

Complications of HCA (1)

Bleeding

- 15% chance of hemorrhage for every HCA

(Van Aalten et al 2012)

- Mostly in larger lesions (> 5cm)
- Enhanced risk in lesions in left lateral liver and exophytic growth

Complications of HCA (2)

Bleeding

- Risk across the subtypes of HCA : IHCA (30%) > H-HCA (8%) / higher risk in new classification sonic-Hedgehog HCA
- All subtypes bear this intrinsic risk, which diminishes the utility of subtype classification in clinical management of prevent bleeding
- Size remains the most important marker to predict those at risk of bleeding

Complications of HCA (3)

Malignant transformation

- Rarely reported, but accepted risk particularly when diameter exceeds 5 cm
- Overall frequency of malignant transformation: 4.4% of all HCAs (Stoot et al 2002)
- HCA shows a higher risk of malignancy in men
- b-HCA is know to trigger mitogenic signaling. Malignant progression in up to 46%.
- B-catening can also be activated in IHCA

> Mainly b-HCA and IHCA are prone to malignant degeneration

Treatment options of HCA

1. Surgery

- Lesions > 5cm
- Rare: liver transplantation (liver adenomatosis)

2. Radiofrequency ablation

- Centrally located-lesions
- Multiple adenomas
- > 5cm : MWA (microwave ablation)

3. Arterial embolization

- First line treatment in case of acute bleeding

Question 1

- Man 45 jaar
- Echografie focaal leverletsel 3cm
- MRI (Multihance MR): leveradenoom

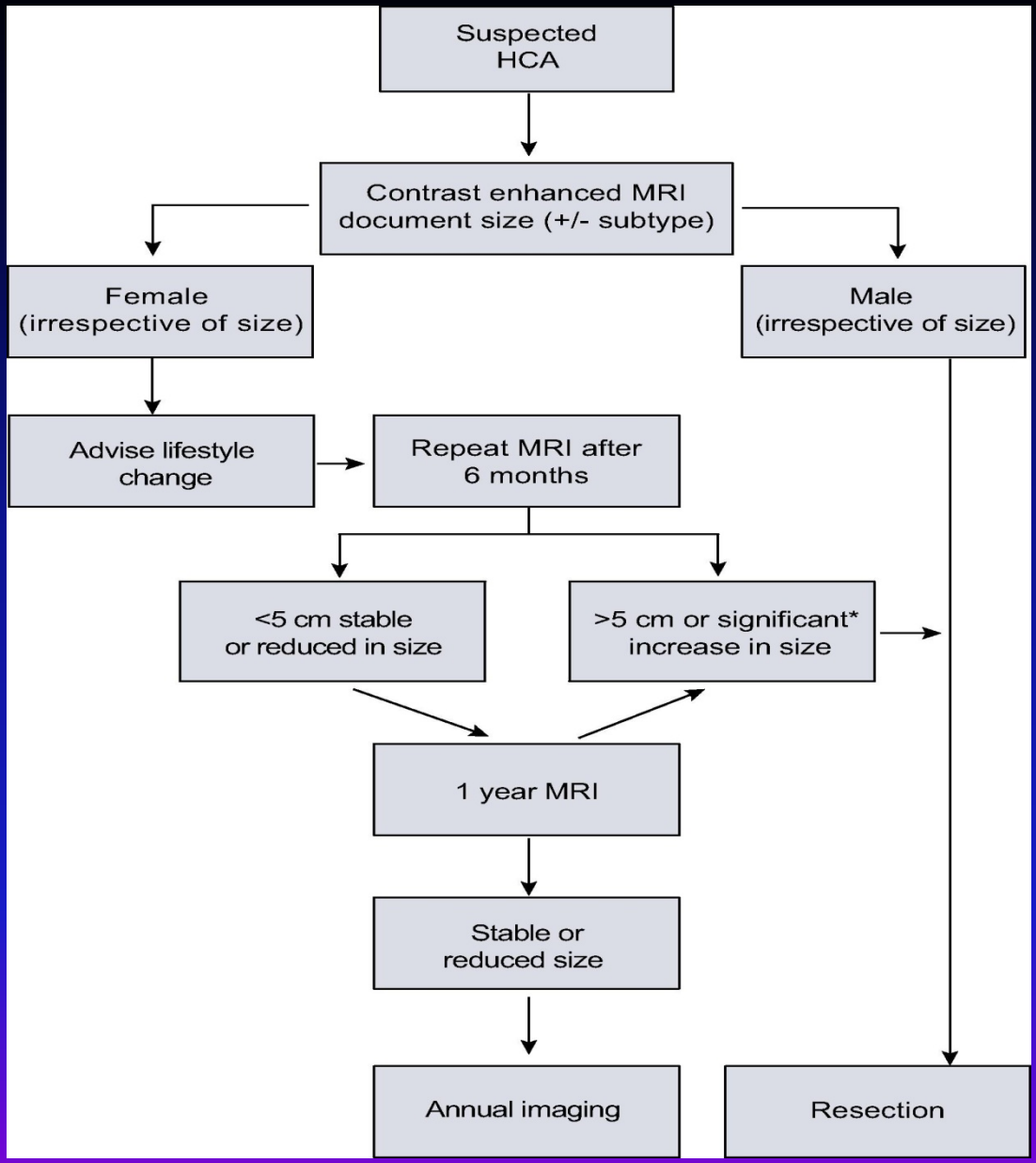
Wat te doen?

- Resectie van leveradenoom
- Opvolging, controle MR over 6 maand
- Resectie bij groei > 5 cm

Question 2

Wanneer een biopsie verrichten in een leveradenoom?

- Bij alle adenomen > 5 cm
- Bij alle adenomen, onafhankelijk van diameter
- Enkel indien twijfel over kenmerken op beeldvorming < 5 cm



EASL clinical practice guidelines on the management of benign liver tumours.
J Hepat 2016 vol 65; 386-398

Role of biopsy/subclassification (1)

Biopsy may be considered within a benign liver tumour MDT to exclude malignancy. In the case of tissue availability obtained for diagnostic purpose, curative intervention is advised for the activated b-catenin mutated HCA, irrespective of size.

-H-HCA < 5 cm or IHCA < 5 cm : managing conservatively. Follow-up after 6 months to establish growth pattern. For lesions stable for 12 months, annual follow up is acceptable.

-For lesions stable or reducing in size after 5 years, biannual imaging can be proposes

EASL clinical practice guidelines on the management of benign liver tumours.
J Hepat 2016 vol 65; 386-398

Role of biopsy/subclassification (2)

HCA subtyping has not yet an impact in general clinical practice, although may be used in specialists centers.

Methods for the molecular analysis of HCA are not presently sensitive enough for widespread application. However, these molecular data have paved the way to the routine pathological assessment of HCA now including immunostaining with a combination of antibodies (LFABP, GS, b-catenin, SAA/CRP) which can subtype the majority of HCA.

There is no justification therefore to recommend histopathology or molecular subtyping of HCA as routine clinical practice.

EASL clinical practice guidelines on the management of benign liver tumours.
J Hepat 2016 vol 65; 386-398

Role of biopsy/subclassification (3)

- No consensus regarding the diagnostic work-up subclassification

- Nault et al

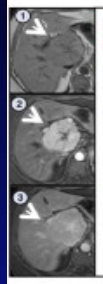
Histological analysis as backbone of HCA diagnosis with detection or exclusion of b-HCA as the main input

Biopsy offered in all cases <5cm with no typical sign of H-HCA

(Lesions of > 5 cm: resection)

Suspicion of benign hepatocellular tumors
Liver tumor, normal tumor markers, absence of cirrhosis, no past history of cancer, no typical features of angioma at MRI

Contrast-enhanced MRI,
CT scan or ultrasonography



Diagnosis of FNH at *MRI*
① Isosignal or faint hyposignal in T1
② Diffuse enhancement at the arterial phase
③ Central scar in hypersignal in T2 and enhancement during late phase

Suspicion of FNH
at imaging but absence of all typical criteria using at least two radiological exams

Tumor biopsy

Histological diagnosis and immunohistochemistry
- Normal like hepatocytes in 1 to 2 cell thick plates
- Fibrous central scar with dystrophic arterial vessels
- Map like pattern of glutamine synthase staining

Other liver tumors

Firm diagnosis of FNH

No treatment

Suspicion of HCA
(absence of FNA critera at imaging)

Female

Male

HNF1A mutated HCA *(MRI features)*

Inflammatory HCA *(MRI features)*

Undetermined HCA or doubt with HCC

Stop OC

Radiological diagnosis
No biopsy

< 5cm
Biopsy

> 5cm
Surgery

Histological diagnosis of HCA
IHC: LFABP1, CRP SAA, β-catenin, glutamine synthase
Search for β-*catenin* mutations

Other liver tumors

Loss of LFABP
HNF1A mutated HCA

50% of the β-catenin mutated HCA are also inflammatory

Overexpression of CRP/SAA
Inflammatory HCA

Overexpression of GS and β-catenin nuclear accumulation or β-catenin mutations
β-catenin mutated HCA

Size < 5cm

Size > 5cm

Stop OC
Clinical and contrast-enhanced MRI/ultrasonography or contrast enhanced ultrasonography
Follow up

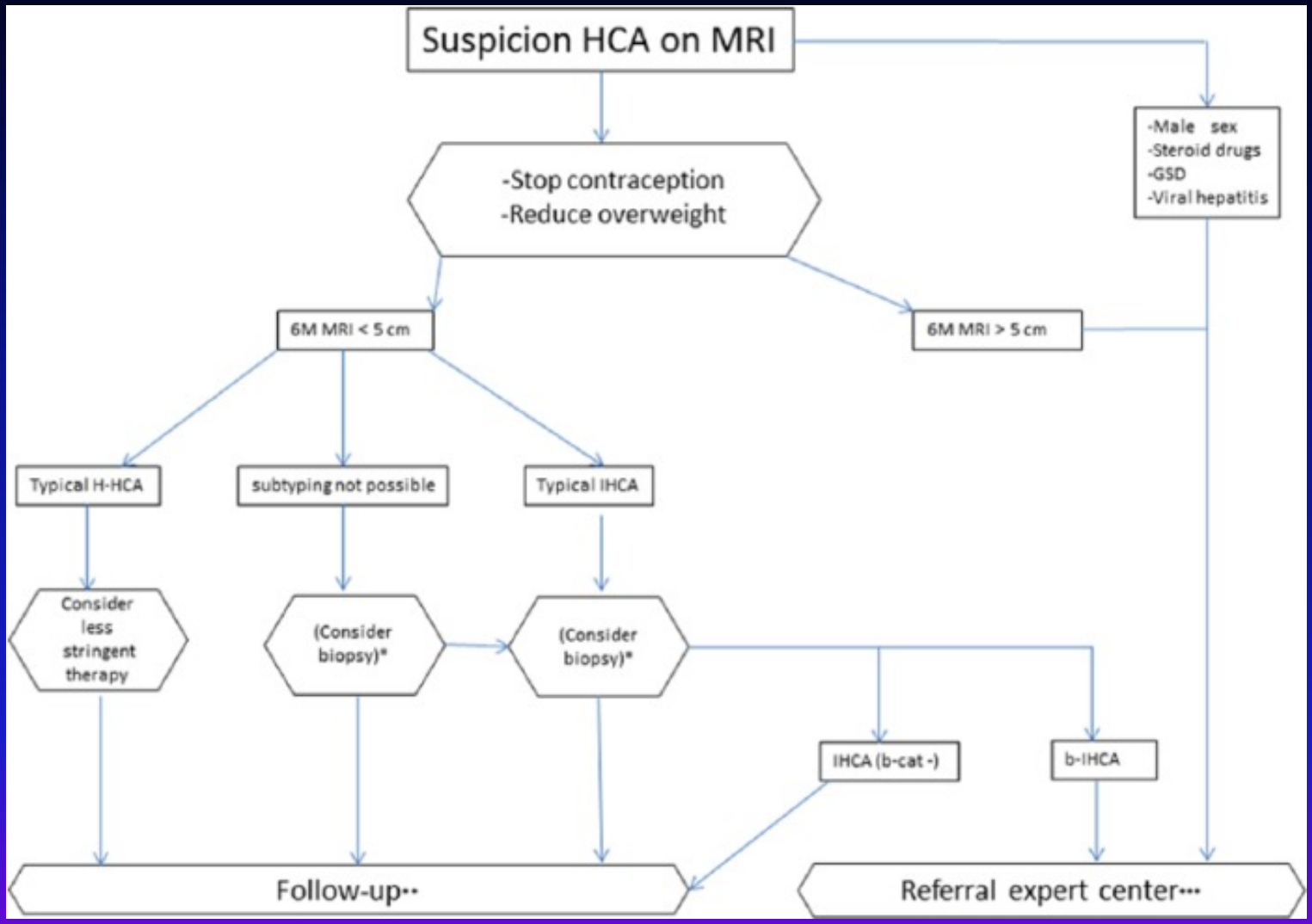
Stop OC*

Surgery

Role of biopsy/subclassification (3)

Biopsy only in cases of doubt in DD with FNH or atypical presentation on MRI (doubt of HCC in non-cirrotic liver)

For daily practice: liver biopsy only in selected cases of doubt on imaging



Thomeer et al Ther Adv Gastroenterol 2016;9:898-912

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.

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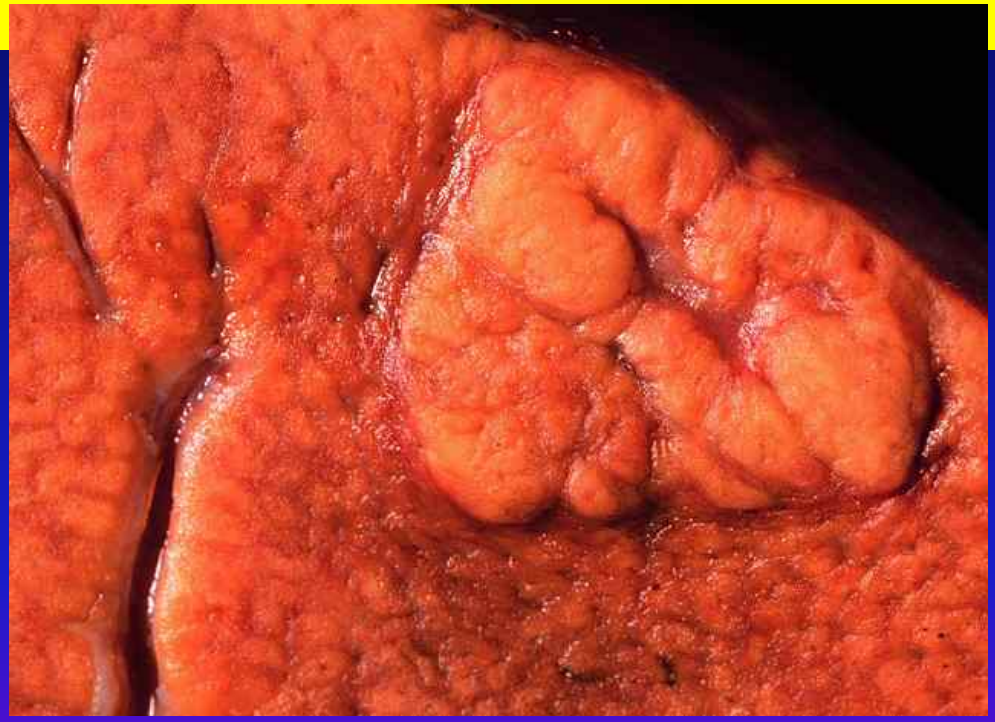
Benigne levertumoren
Rol van moleculaire classificatie



Dutch liver week 2017

Anja Geerts, MD, PhD
Dienst Gastroenterologie & Hepatologie

Referenties

Na te lezen artikels

- EASL clinical practice guidelines on the management of benign liver tumours. J Hepat 2016 vol 65; 386-398
- Hepatocellular benign tumors- from molecular classification to personalized clinical care (Nault JC , Gastroenterology 2013;144:888-902)
- Molecular Classification of Hepatocellular Adenoma Associates With Risk Factors, Bleeding, and Malignant Transformation (Nault JC, Gastroenterology 2017;152: 880-894)
- Hepatocellular adenoma: when and how to treat? Update of current evidence (Thomeer et al Ther Adv Gastroenterol 2016;9:898-912

- *Je*