FACULTY OF MEDICINE AND HEALTH SCIENCES

BENIGNE LEVERTUMOREN

Prof Dr. Anja Geerts
Maag- darm en leverziekten

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UZ GENT

BACKGROUND

Heterogenous group of liver lesions

Frequently found incidentally – due to widespread imaging use

Often have a benign course

Some are of greater clinical relevance than others

Practical diagnosis and management of the more common benign tumours

- Hepatic haemangiomas
- Focal nodular hyperplasia (FNH)
- Hepatocellular adenoma (HCA)

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WELKE BENIGNE LEVERLETSELS MOETEN STRIKT OPGEVOLGD WORDEN?

1. Hemangiomen
2. Levercysten (ongecompliceerd)
3. Solitair FNH
4. Multiple FNH
5. Adenomen

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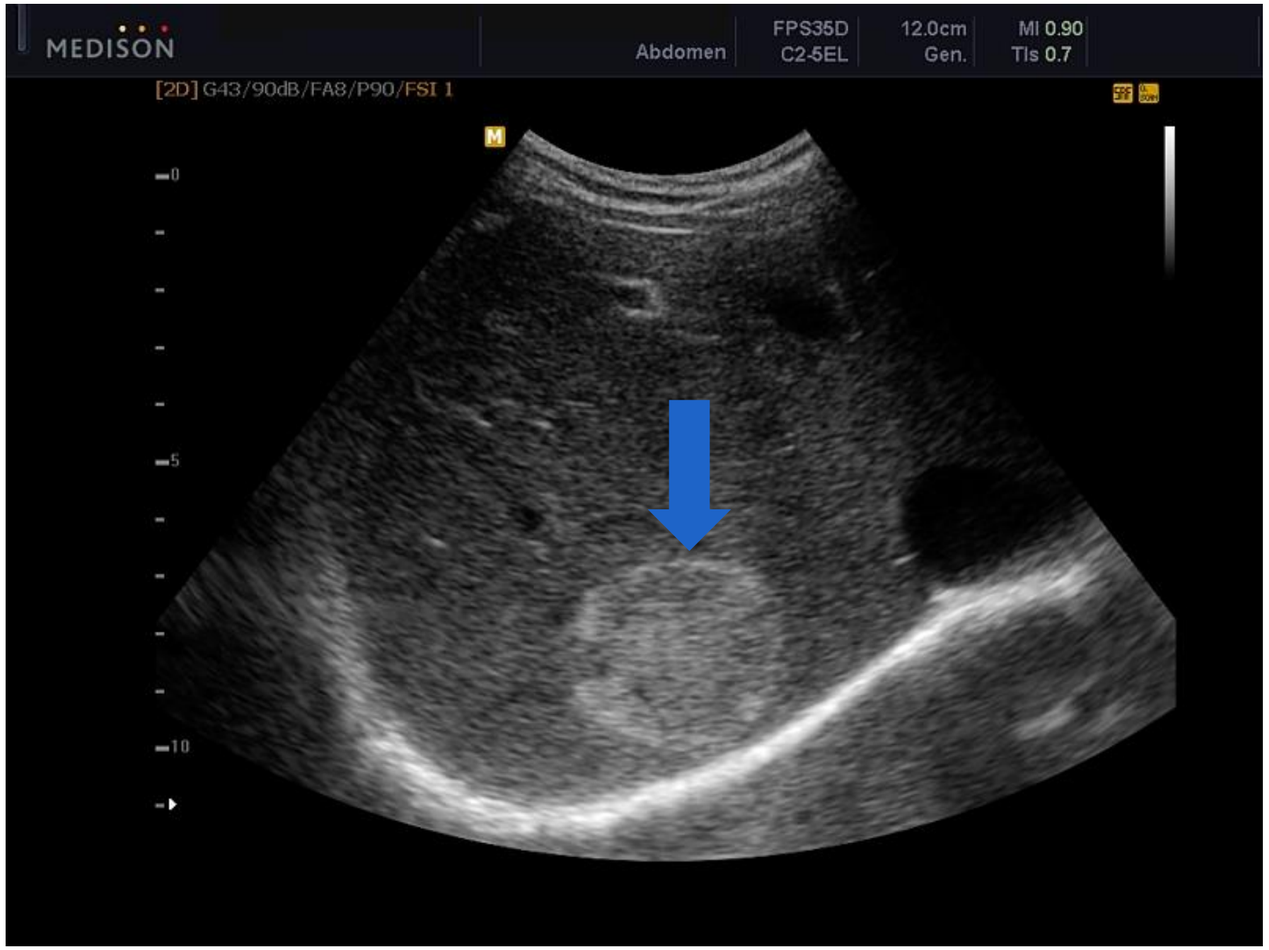
HELP! ER ZIT EEN VLEK OP MIJN LEVER



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BASIC MANAGEMENT OF A ‘LIVER NODULE’

Examination and baseline investigations

- Associated symptoms:
  - Abdominal pain
  - Weight loss
  - Hepatomegaly
  - Abnormal liver function tests
- Medical history
  - Conditions associated with liver lesions (e.g. cancer, anorexia, asthenia)
  - History of foreign travel or dysentery
  - Medication history, particularly OCPs
- Exclude primary tumour distant to liver
- Risk factors
  - History of/current viral hepatitis/cirrhosis
  - History of transfusion, tattoos, IV drug abuse
  - Family history of liver disease/tumours
  - Alcohol excess, smoking
  - Features of metabolic syndrome (obesity, T2DM, HTN, CV disease)
  - Drug history (methotrexate, tamoxifen, androgens)

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WELK TYPE BEELDVORMING HEEFT DE VOORKEUR?

- Echografie is voldoende om voor alle benigne leverletsels de diagnose te stellen
- Een CT met contrast als 1ste keuze onderzoek
- Een MRI met contrast als 1ste keuze onderzoek
- Een CT + MRI als 1ste keuze onderzoek

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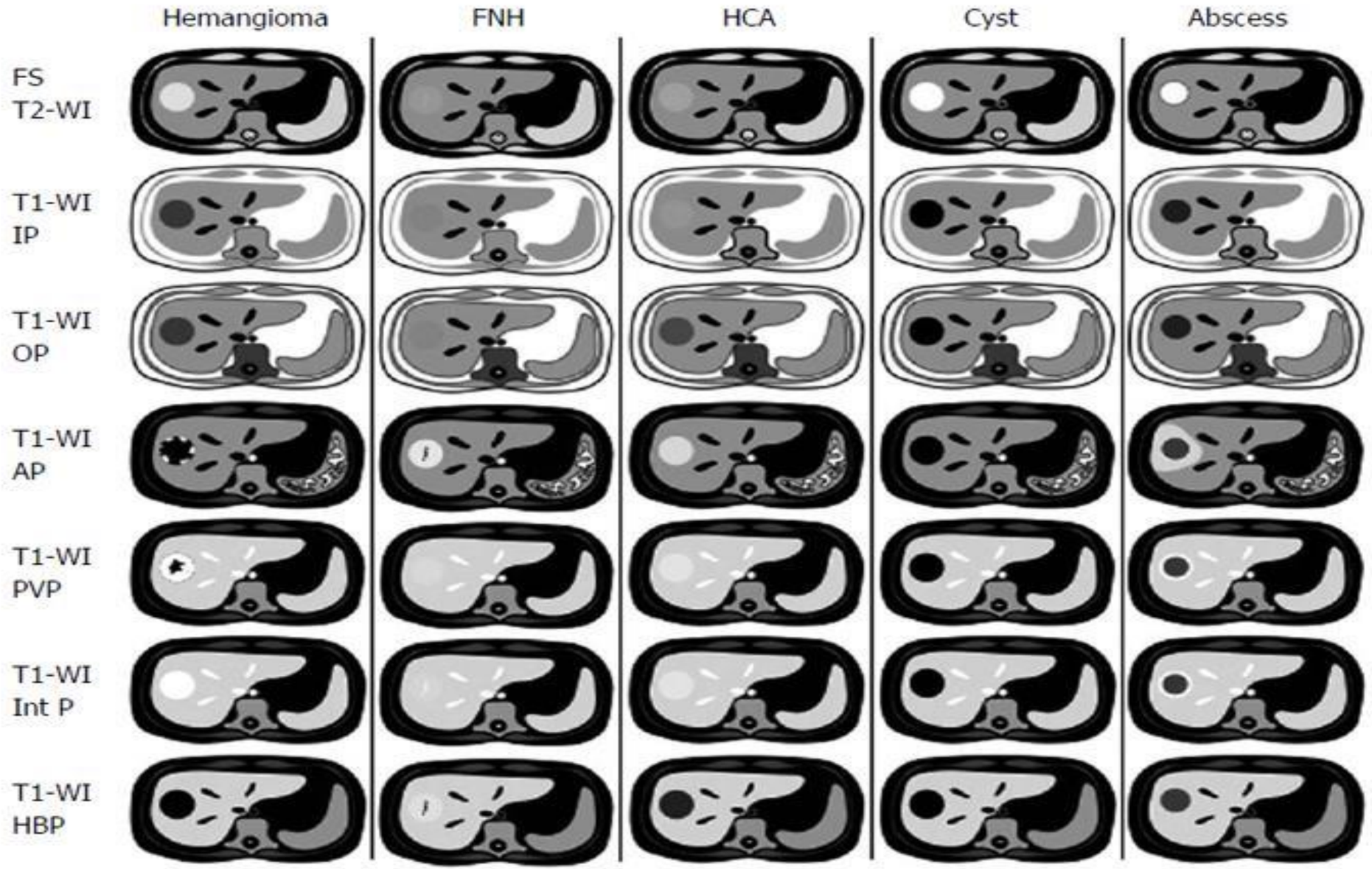

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Following examination and baseline investigations

Contrast-enhanced imaging for tumour characterization

- Imaging and baseline investigations should be sufficient to diagnose benign liver tumours
- In cases of significant doubt, a biopsy or resection may be appropriate
- Invasive procedures should only be pursued after consideration by an experienced MDT

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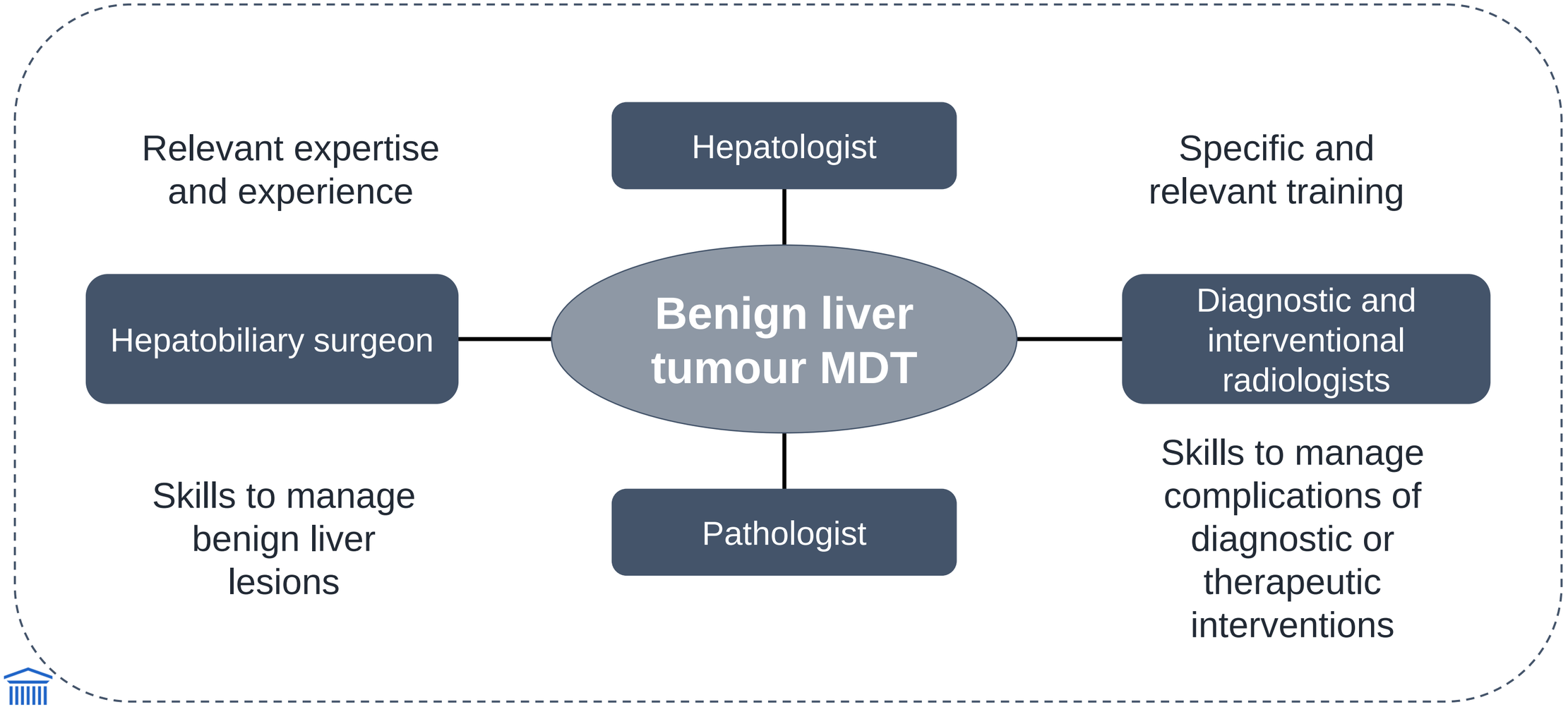
THE BENIGN LIVER TUMOUR MDT



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Hepatic haemangiomas

Epidemiology/clinical characteristics

Diagnostic recommendations

Management recommendations

HEPATIC HAEMANGIOMAS: EPIDEMIOLOGY/CLINICAL CHARACTERISTICS

Most common benign liver tumours

- Prevalence on imaging series: ~5%[1]
- Prevalence on autopsy series: up to 20%[2,]
- Female to male ratio ranges 6:1
- Can occur in all age groups
- Congenital hamartomatous proliferation of vascular endothelial cells

Rarely of clinical significance : spontaneous or posttraumatic rupture: very rare

- Often solitary and small (<4 cm), although can reach 20 cm in diameter[2]
- Most patients are asymptomatic even with large haemangiomas[2]
- Larger tumours (>10 cm) may be symptomatic – associated with pain and features of KMS (inflammatory reaction syndrome and coagulopathy [3]

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1. Horta G, et al. Rev Med Chil 2015;143:197–202; 2. Bahirwani R, Reddy KR. Aliment Pharmacol Ther 2008;28:953–65;
3. O'Rafferty C, et al. Br J Haematol 2015;171:38–51;
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HEPATIC HAEMANGIOMAS: DIAGNOSTIC RECOMMENDATIONS

Classic appearance on US is a homogenous hyperechoic mass

Recommendations	Grade of evidence	Grade of recommendation
In patients with a normal/healthy liver, a hyperechoic lesion is very likely to be a liver haemangioma US is sufficient for diagnosis in cases of typical radiology (homogeneous hyperechoic, sharp margin, posterior enhancement, absence of halo sign) in lesions <3 cm	II-2	1
Contrast enhanced imaging is required in oncology patients and patients with underlying liver disease	II-2	1
Diagnosis by contrast-enhanced imaging is based on a typical vascular profile, characterized by peripheral and globular enhancement on arterial phase followed by a central enhancement on delayed phases MRI provides additional findings: e.g lesion signal on T1-, T2-weighted sequences; diffusion imaging	II-2	1

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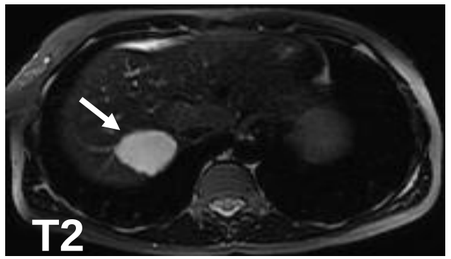
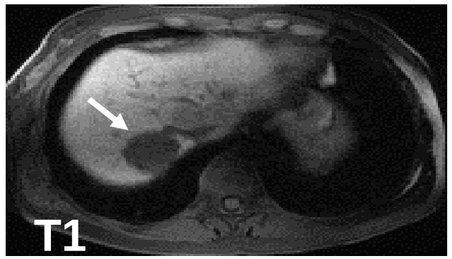
HEPATIC HAEMANGIOMAS: IMAGING

Typical haemangioma

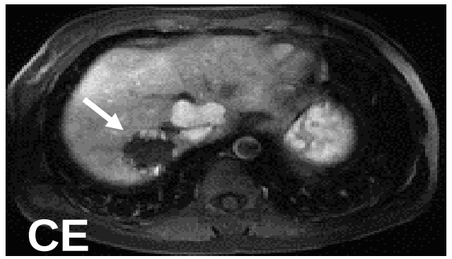
MRI

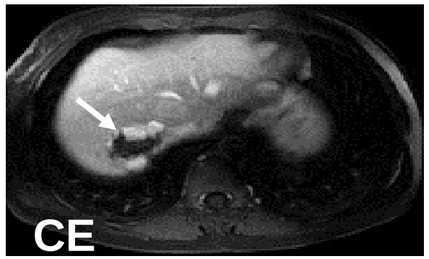


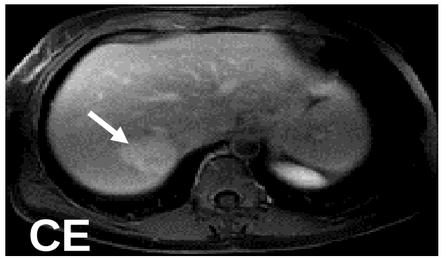
Strongly hyperintense



Hypointense







Lesion shows peripheral and discontinuous enhancement followed by complete fill-in on delayed-phase imaging

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HEPATIC HAEMANGIOMAS: MANAGEMENT RECOMMENDATIONS

- Haemangiomas are mostly asymptomatic incidental discoveries
  - May change in size during long-term follow-up
  - No relationship between size and complications
  - Little relationship between symptoms and characteristics

Biochemistry: often normal
Biopsy: obsoleet
Therapy:
-Surgery only for complicated or severely symptomatic lesions
Alternative treatment: transarterial embolisation

Grade of evidence Grade of recommendation

Recommendations		
Due to its benign course, imaging follow-up is not required for typical haemangioma	II-2	1
Pregnancy and OCPs are not contraindicated	III	2
Conservative management is appropriate for typical cases	II-2	1
Refer to benign liver tumour MDT in the presence of KMS, growing lesions or lesions that are symptomatic by compression	III	1

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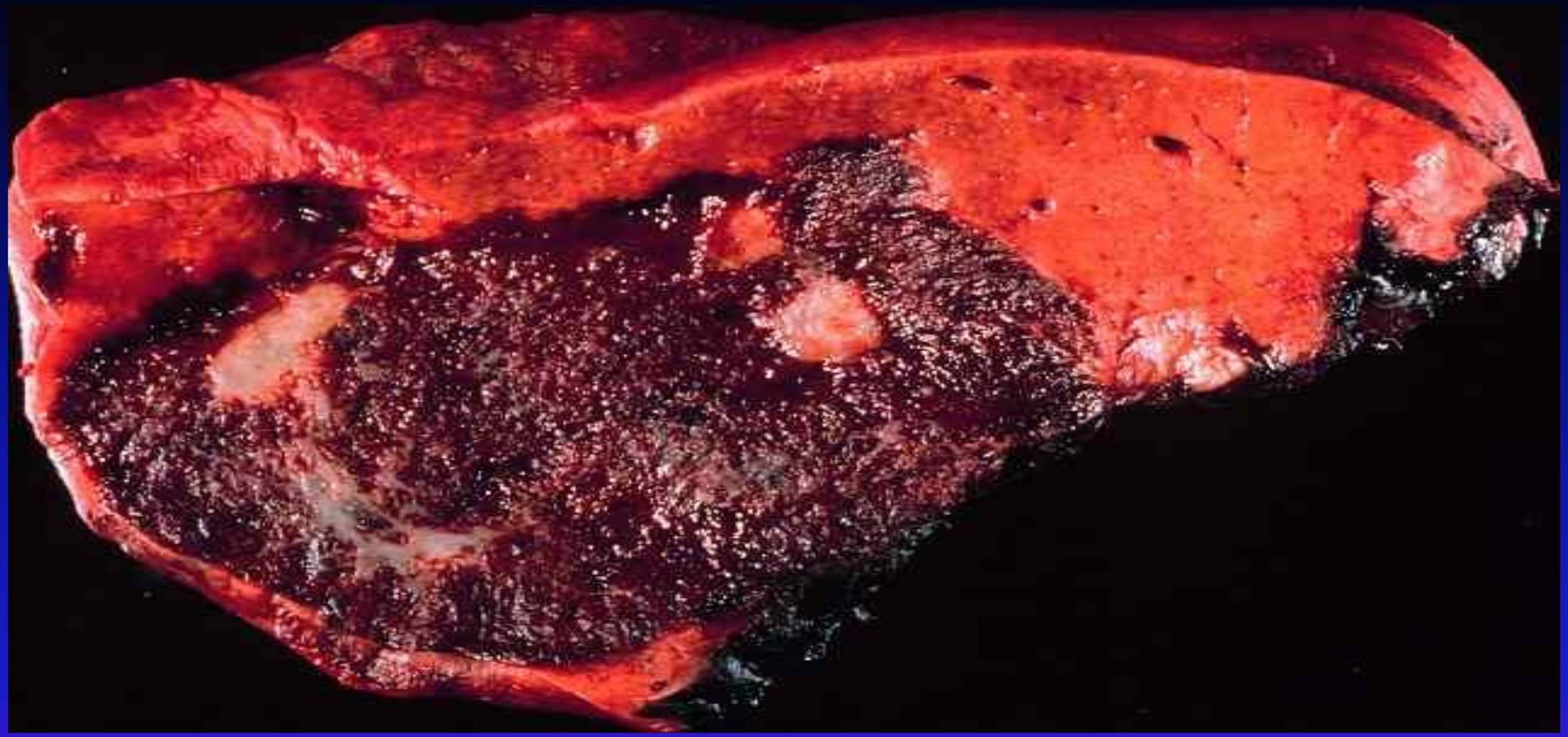

Macroscopic evaluation: well-delineated lesion, flat lesion with red-blue color

Focal nodular hyperplasia

Epidemiology/clinical characteristics
Diagnosis and imaging
Recommendations
Management algorithm

FNH: EPIDEMIOLOGY/CLINICAL CHARACTERISTICS

Epidemiology: Second most common solid BLT

- Clinically relevant prevalence: 0.03% (autopsy series: 0.4–3%)[1,2]
- Up to 90% of patients are female

Clinical characteristics

- Most cases are solitary and <5 cm; multiple FNH in 20–30% of cases[3,4]
- Nonneoplastic lesion that is caused by a hyperplastic response of hepatocytes to a congenital vascular malformation or a disruption in blood supply
- No malignant potential
- Coexist with hemangiomas in up to 20%
- Size is stable over time in most cases[5]
- Most cases are asymptomatic and complications are extremely rare

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1. Rubin RA, Mitchell DG. Med Clin North Am 1996;80:907–28; 2. Marrero JA, et al. Am J Gastroenterol 2014;109:1328-47;
3. Nguyen BN, et al. Am J Surg Pathol 1999;23:1441–54; 4. Vilgrain V, et al. Radiology 2003;229:75–9;
5. D'Halluin V, et al. Gastroenterol Clin Biol 200&
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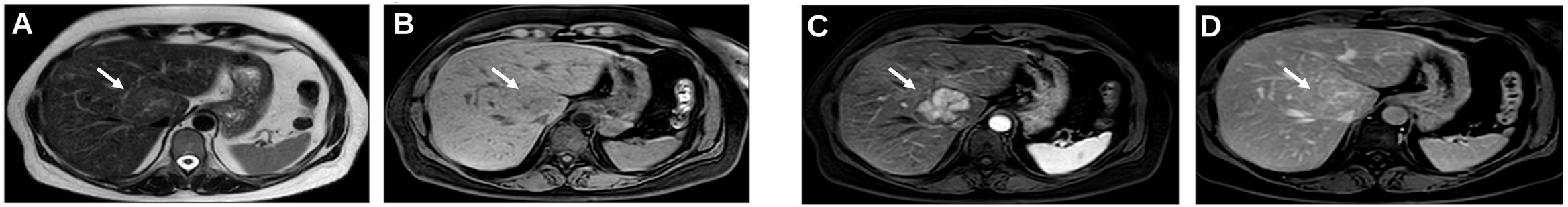
FNH: IMAGING

Diagnosis is based on a combination of five imaging features:

1. Lesion homogeneity, excluding the central scar
2. Slight difference from adjacent liver tissue on pre-contrast US, CT and MRI (**A & B**)
3. Strong, homogeneous enhancement on arterial phase CEUS, CT or MRI with a central vascular supply (**C**); becomes isointense to liver tissue on portal venous and delayed phases (**D**)
4. Central scar best seen on MRI
5. Lack of capsule with often lobulated contours

T2- and T1-weighted images

Contrast-enhanced images



Lesion barely visible

Lesion easily visible

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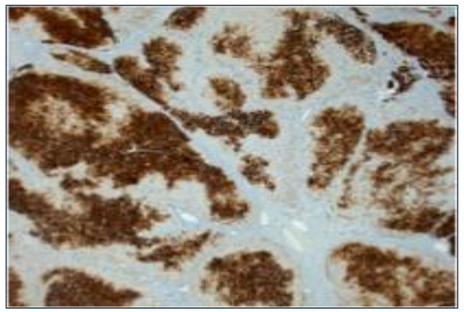
FNH: DIAGNOSTIC RECOMMENDATIONS



Biochemistry: often normal
Biopsy: only in doubt

MRI sensitivity

- Lesion >3 cm – very good
- Lesion <3 cm – second imaging modality advised, such as CEUS

Refer to a specialist centre if in doubt

Recommendations		
CEUS, CT, MRI: nearly 100% specificity with a combination of typical imaging features	II-2	1
MRI has the highest diagnostic performance overall Highest diagnostic accuracy by CEUS is achieved in FNH <3 cm	II-2	1

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FNH: MANAGEMENT RECOMMENDATIONS

In the absence of symptoms : a conservative management

No indication for discontinuing OCPs

Follow-up during pregnancy is not necessary

Recommendations	Grade of evidence	Grade of recommendation
For a typical FNH lesion, follow-up is not necessary unless there is underlying vascular liver disease	III	2
Treatment is not recommended	II-3	2
If imaging is atypical, or the patient is symptomatic, refer to a benign liver tumour MDT	III	1

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FNH: MANAGEMENT ALGORITHM

Suspected FNH

Contrast-enhanced imaging (preferably MRI)*

Diagnosis FNH certain

CEUS

<3 cm

Diagnosis FNH doubtful

Diagnosis uncertain

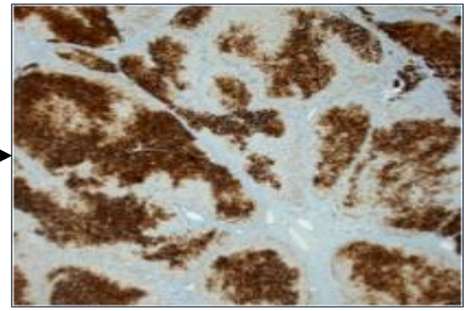
>3 cm

Biopsy

Discharge, no follow-up needed

Confirmed FNH

Map-like pattern of GS is specific to FNH



GS immunohistochemical staining is useful in difficult cases

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*Imaging modalities may include US, CEUS, CE-CT and CE-MRI

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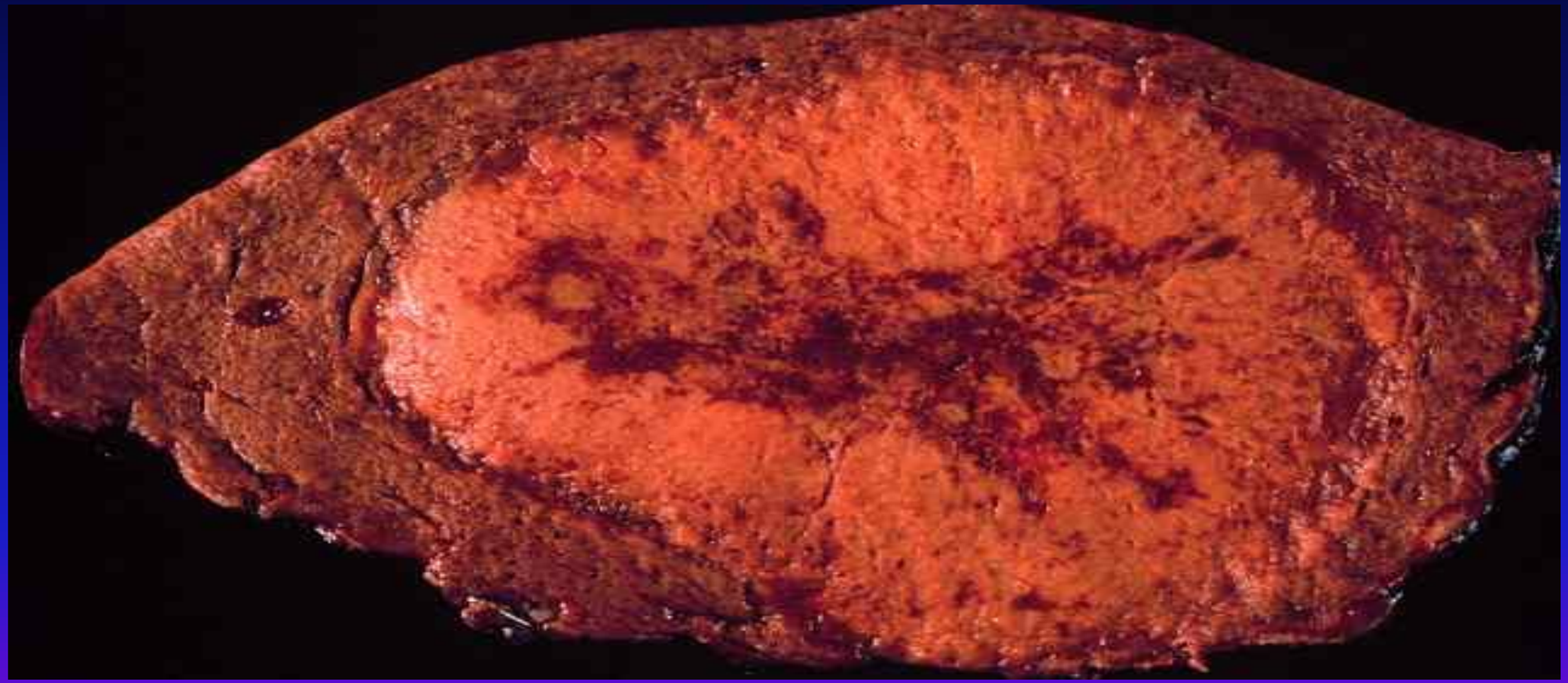

Hepatocellular adenoma

Epidemiology/clinical characteristics
Molecular classification
Key recommendations
Management algorithm

HCA: EPIDEMIOLOGY/CLINICAL CHARACTERISTICS

Epidemiology[1–3]

- Reported prevalence: 3-4/ 100000
- ~10x less common than FNH
- Most common in women (10:1 female to male), especially aged 35–40 years

Potential role of sex hormones

- 30–40-fold increase in incidence with long-term OCP use[4]
- Incidence among males is associated with androgenic steroids[5,6]
- Recent increase in prevalence associated with rising obesity and metabolic syndrome[7–9]
- Rare associations: MODY 3 associated HCA, glycogen storage disease I,III and IV

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

Significant risk of haemorrhage and malignant transformation

- Especially with lesions ≥5 cm

HCAs need to be followed more closely than other benign tumour

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1. Bonder A, Afdhal N. Clin Liver Dis 2012;16:271–83; 2. Karhunen PJ. J Clin Pathol 1986;39:183–8;
3. Cherqui D, et al. Gastroenterol Clin Biol 1997;21:929–35; 4. Giannitrapani L, et al. Ann NY Acad Sci 2006;1089:228–36;
5. Socas L, et al. Br J Sports Med 2005;39:e27; 6. Nakao A, et al. J Gastroenterol 2000;35:557–62;
7. Bunchorntavakul C, et al. Aliment Pharmacol Ther 2011;34:664–74; 8. Bioulac-Sage P, et al. Liver Int 2012;32:1217–21;
9. Chang CY, et al. Int J Hepatol 2013;2013:604860; EASL CPG benign liver tumours. J Hepatol 2016;65:386–98

INTRODUCTION OF A NEW SUBCLASSIFICATION FOR HCA

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%)

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Nault JC , Gastroenterology 2013;144:888-902

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)

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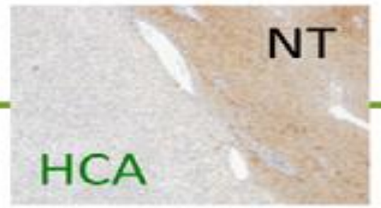
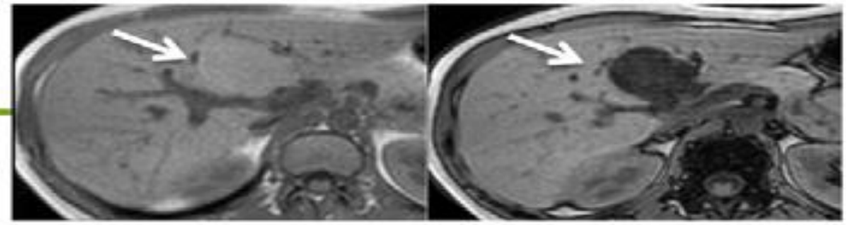
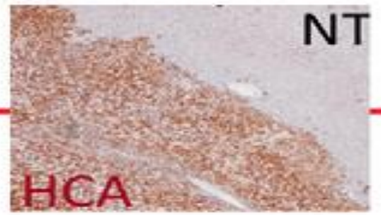
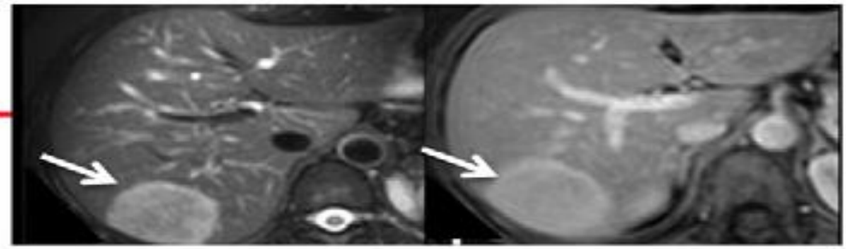
Molecular classification	Main pathological and clinical features	Immuno histochemical markers	Radiological features
HNF1A mutations 30%–40%	Familial adenomatosis MODY3 diabetes Marked steatosis	Loss of LFABP expression	Diffuse signal dropout on T1-weighted chemical shift sequence
Inflammation 40%–50% *Gp130* 65% *GNAS* 5% *STAT3* 5% *NM* 25%	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
Unclassified 10%			

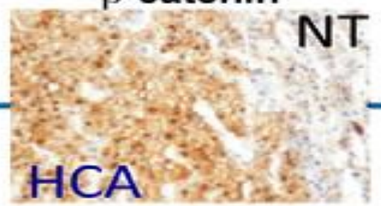
Obesitas/Metabolic syndrome











Hyperintense T2/ hypointense T1

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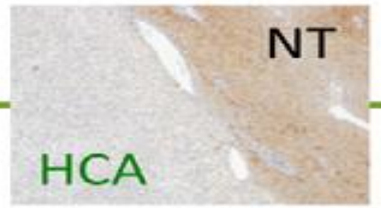
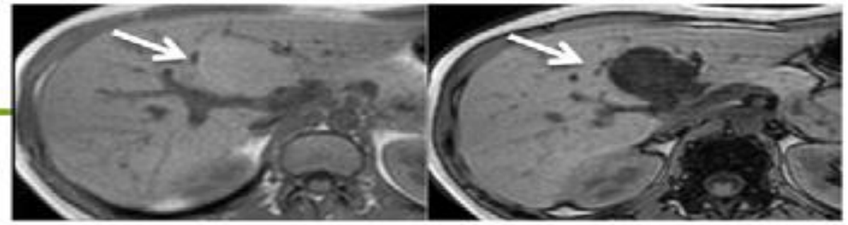
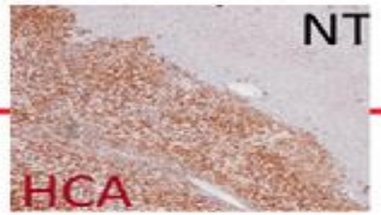
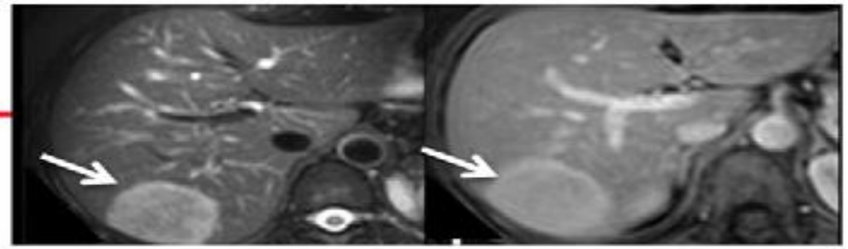
Unclassified 10%			

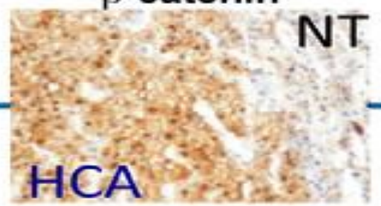
Obesitas/Metabolic syndrome











Hyperintense T2/ hypointense T1

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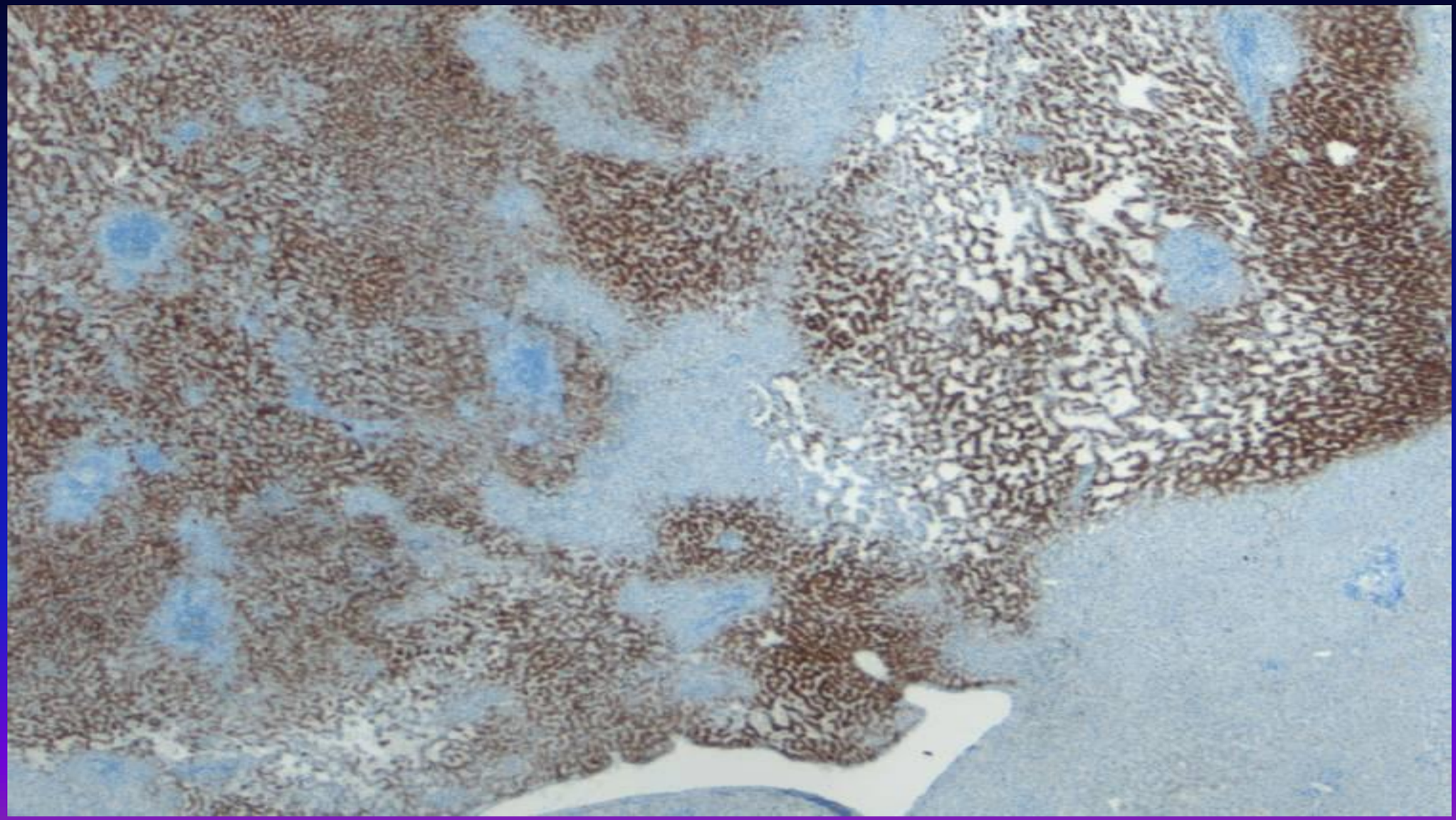
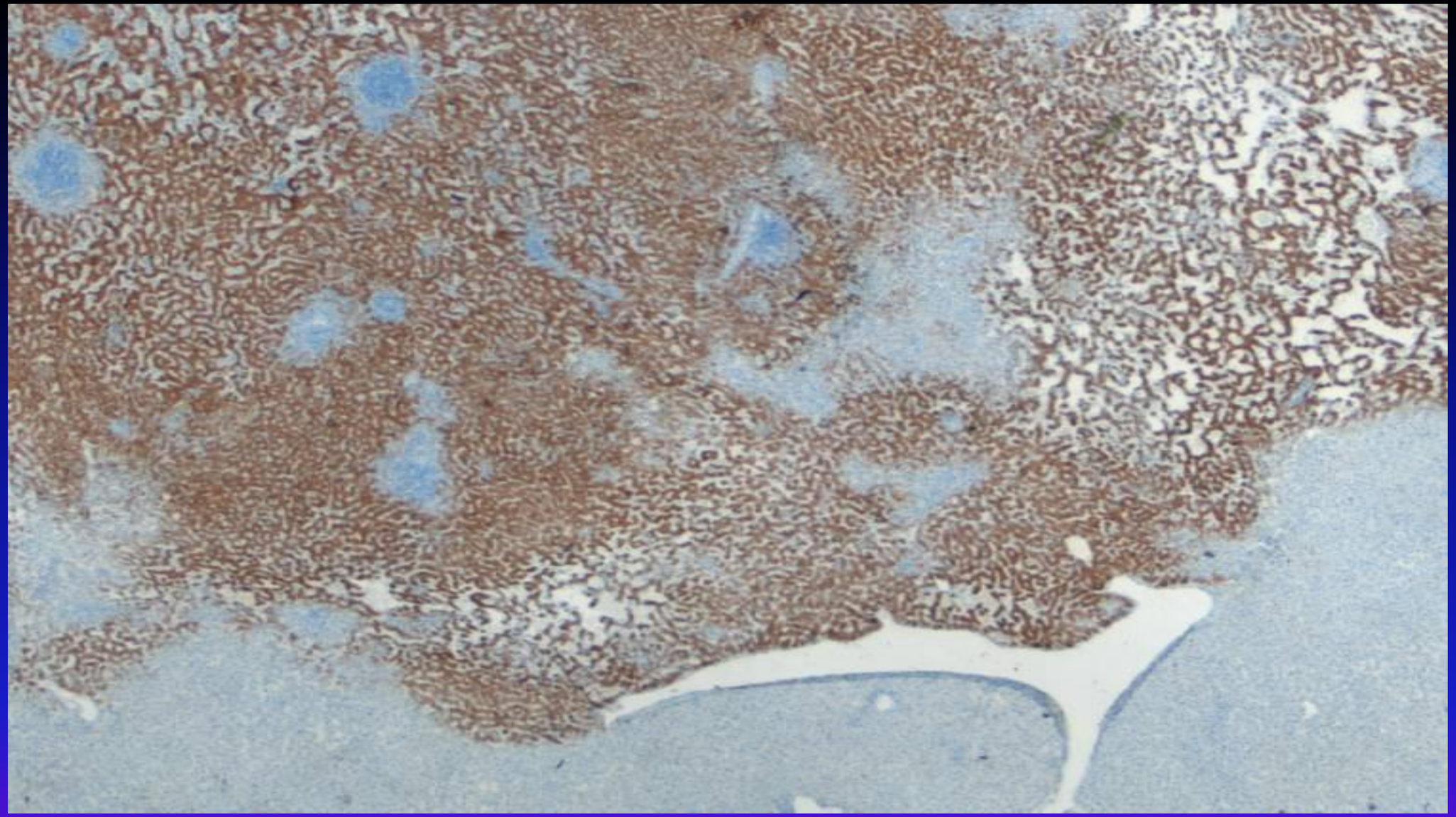
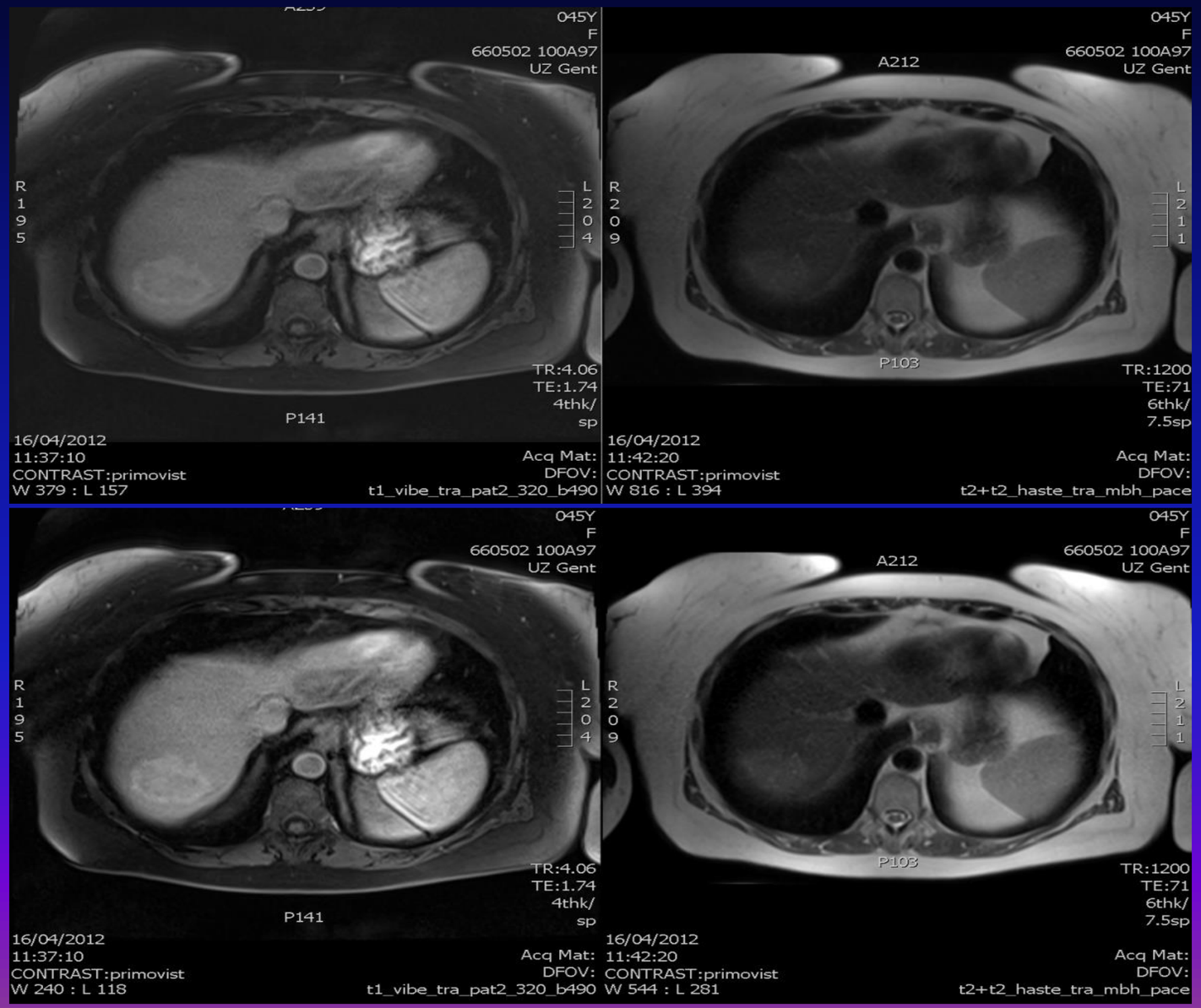


SAA



CRP

Inflammatoir adenoma



"Atoll sign "

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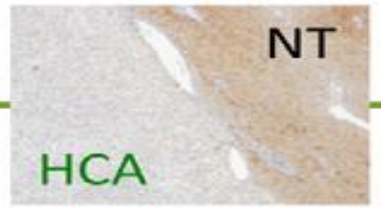

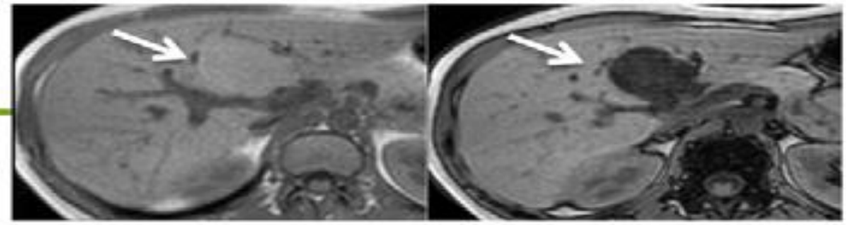

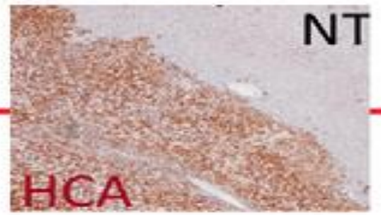

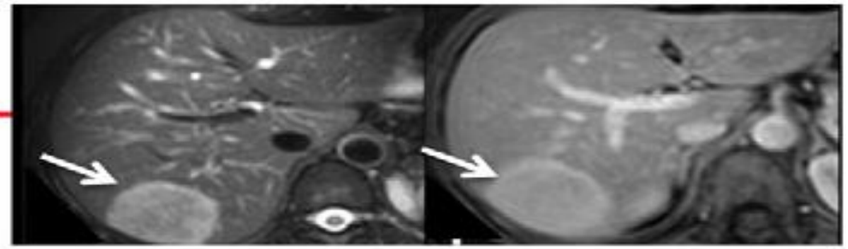

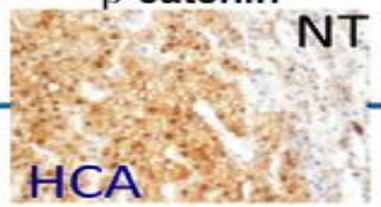

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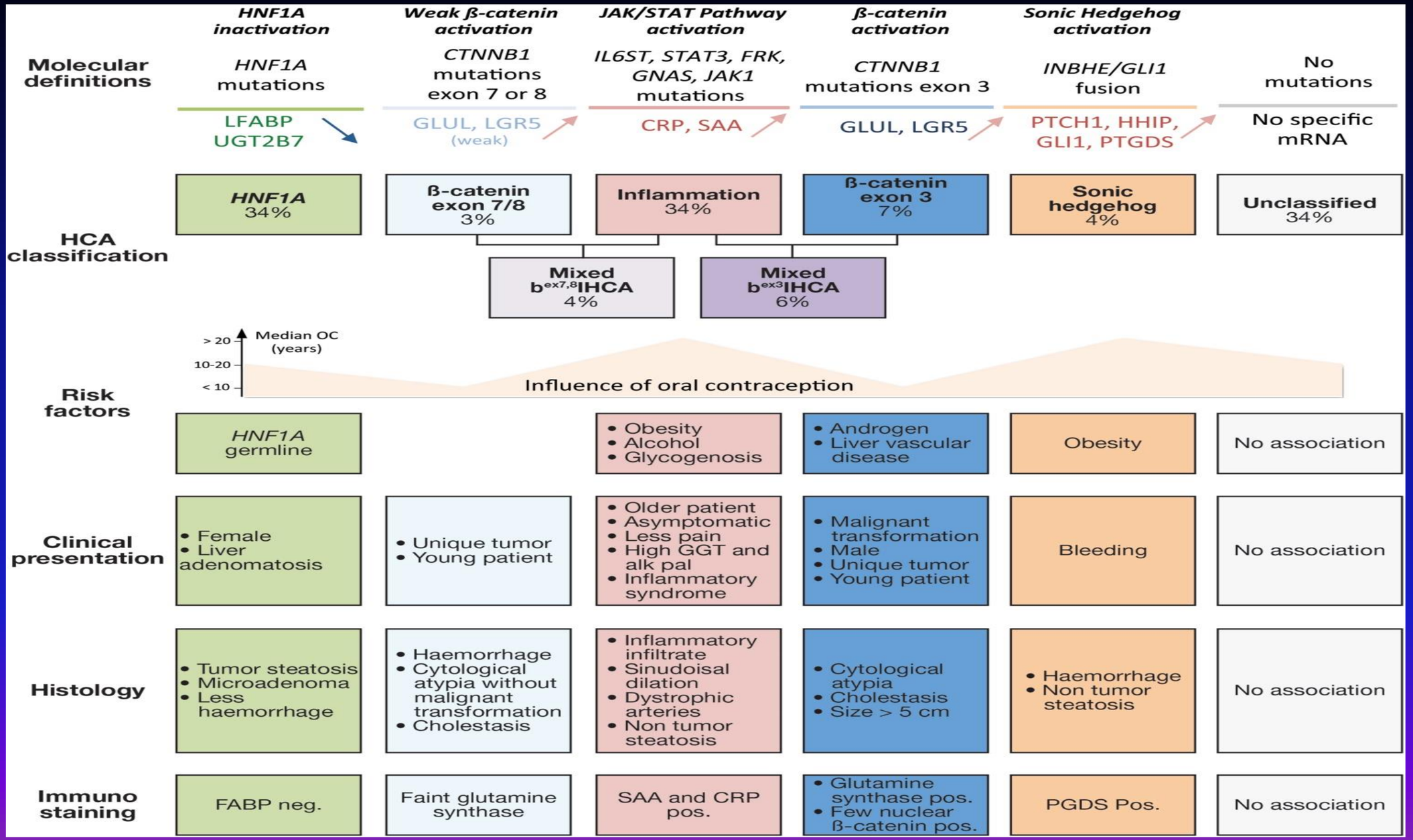


Nault JC, Gastroenterology 2017;152: 880-894

Complications of HCA (1)

Bleeding

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

Complications of HCA (2)

Bleeding

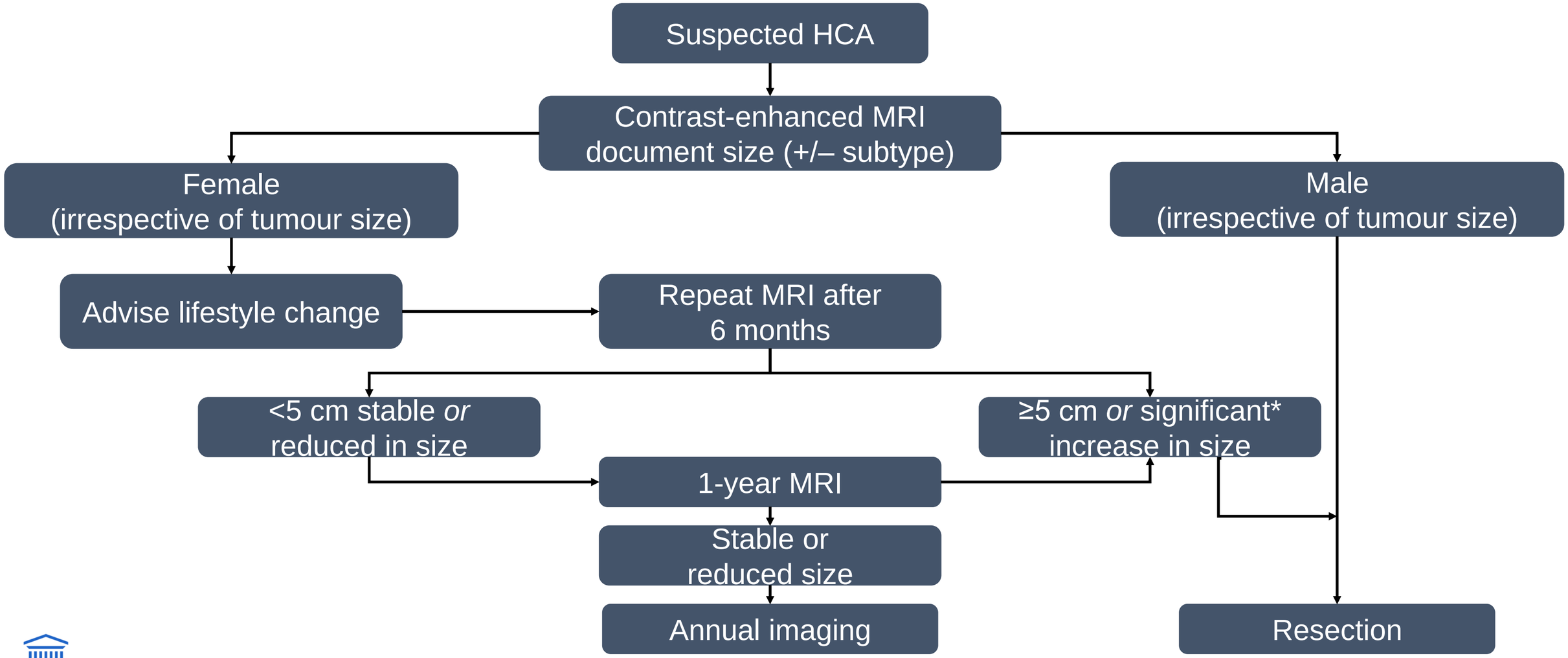
- Risk across the subtypes of HCA : IHCA (30%) > H-HCA (8%) / higher risk in new classification sonic-Hedgehog HCA
- All subtypes bear this intrinsic risk, which diminishes the utility of subtype classification in clinical management of prevent bleeding
- Size remains the most important marker to predict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

Complications of HCA (3)

Malignant transformation

- 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

HCA: MANAGEMENT ALGORITHM



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PS: Biopsy IN cases of doubt: B-catenin +: indication for resection irrespective of size

*≥20% diameter

EASL CPG benign liver tumours. J Hepatol 2016;65:386–98

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

Patients with multiple lesions

Key recommendations

MULTIPLE LESIONS: KEY RECOMMENDATIONS

The term ‘multiple HCAs’ has replaced ‘liver adenomatosis’

- >10 HCAs

Risk of bleeding and malignant transformation:

- Does not differ in patients with multiple HCAs versus a single HCA
- Driven by the size of the largest nodule

Recommendations		
Base management of multiple HCAs on the size of the largest tumour	III	2
Hepatic resection may be considered in unilobular disease For widespread HCA, resection of the largest adenomas may be an option	III	2
LTx is not recommended in multiple HCA LTx may be considered in case of underlying liver disease	III	2

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EASL CPG benign liver tumours. J Hepatol 2016;65:386–98

CASUS

- Female 22 years old
- Diagnosis 2010: diagnosis of adenomatosis
- 2012: Diagnosis of MODY type 3 (diabetes- liver adenomatosis)
- Episodes of bleeding/ growth of lesions
- Listing for liver transplantation
- 24/09/2014: livertransplant
- Explant liver: full of nodules morfological and immunohistological HNF1α-inactivated adenoma

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CONCLUSIONS

- Benign does not always mean without risk
- Your best partner in the management of benign liver tumours is first the radiologist and if doubt the pathologist
- Liver surgery should always be justified and safe: however, in the case of benign liver tumors, be even more stringent

- Male sex and benign tumor: an a priori suspicious combination

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CHARACTERISTICS OF COMMON BENIGN LIVER LESIONS

	Haemangioma	FNH	HCA
Estimated prevalence	Common ~5%*	Less common 0.03%	Rare ≤0.004%
Age	30–50 years	20–40 years	All ages
Gender	F > M	F ~ M	F >> M
US	Hyperechoic	Varied	Varied
CT	Centripetal enhancement	Central scar	Varied
MRI	Centripetal enhancement Hyperintense T2-w	Central scar	Varied
Calcification	Yes	No	No
Rupture	Rare	No	Yes