

Benign lesions in the non-cirrhotic liver *Value of hepato-biliary agents*

Călin Vainak Adriana | Regional Institute of Gastroenterology and Hepatology "Octavian Fodor"



Key discussion points



- 1. Role of hepatobiliary contrast media in the diagnosis of benign liver lesions;
- 2. Imaging features of benign liver lesions;
- 3. Management of incidental liver lesions.



MRI principles



- Multiparametric approach, due to multitude of sequences: T1 IP/OOP (fat), T2, DWI, MRCP (when needed), CE-MRI;
- Non-invasive tool;
- Contrast agents containing Gd shorten relaxation on T1 sequences (either extracellular or hepatobiliary);
- Detection of focal lesions;
- Assessment of the liver background;
- Biliary pathology;



Benign liver lesions



- Are frequently encountered in clinical practice;
- They can arise from epithelial cells (hepatocytes and biliary cells) or non epithelial cells (mesenchymal cells);
- Contrast-enhanced MRI is the best method to characterize liver lesions;
- Advanced techniques, such as DWI and hepatobiliary contrast can improve confidence;
- Some lesions may be confidently diagnosed with MRI, making biopsy unnecessary;



Hepatobiliary contrast agents



- Gadoxetic acid (Gd EOB DTPA Primovist®; Bayer Schering, Berling, Germany);
- 0.025mmol/kg;
- Absorbed by hepatocytes via organic anion transporting polypeptides (OATP 1) transporter and excreted by multidrug resistance protein 2 (MRP 2);
- A fraction is excreted in the biliary canaliculi 50%;
- Transitional phase (3-5 min) and hepatobiliary phase (20 min);
- Enhancement pattern of lesions depending on the content of functioning hepatocytes;



- Gadobenate dimeglumine (Gd-BOPTA MultiHance®; Bracco, Milan, Italy);
- 0.1mmol/kg;
- 2 fold T1 relaxivity compared to Gadoxetic acid;
- Only 2-4% is excreted via biliary canaliculi;
- HBP at 60-90 min.



MRI contrast agent



Category	Molecule	Structure	Ioniity	Relaxivity	Recommended dose (mmol/kg)	Excretion
ECAs	Gadoterate meglumine (Dotarem)	Macrocyclic	Ionic	Standard	0.1	Renal
ECAs	Gadobutrol (Gadavist)	Macrocyclic	Non-ionic	Standard	0.1	Renal
ECAs	Gadoteridol (Prohance)	Macrocyclic	Non-ionic	Standard	0.1	Renal
ECAs	Gadopentetate dimeglumine (Magnevist)	Linear	Ionic	Standard	0.1	Renal
ECAs	Gadoversetamide (OptiMark)	Linear	Non-ionic	Standard	0.1	Renal
ECAs	Gadodiamide (Omniscan)	Linear	Non-ionic	Standard	0.1	Renal
HBA	Gd-EOB-DTPA (Eovist/Primovist)	Linear	Ionic	High	0.025	50% renal, 50% biliary
HBA	Gd-BOPTA (MultiHance)	Linear	Ionic	High	0.1	5% biliary, 95% renal
BPA	Gadofosveset trisodium (Ablavar)	Linear	Ionic	High	0.03	Renal

ECAs: Extracellular agents; HBA: Hepatobiliary agents; BPA: Blood pool agents.

Gatti M, Maino C, Tore D, Carisio A, Darvizeh F, Tricarico E, Inchingolo R, Ippolito D, Faletti R. Benign focal liver lesions: The role of magnetic resonance imaging. World J Hepatol. 2022 May 27;14(5):923-943. doi: 10.4254/wjh.v14.i5.923. PMID: 35721295; PMCID: PMC9157713.

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MRI protocol



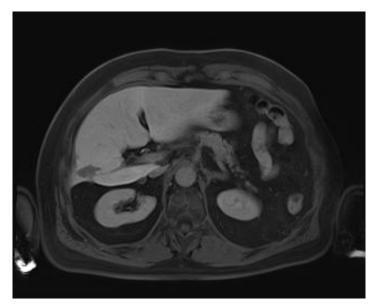
- T1, T2, DWI, multiphase contrast enhanced T1 sequences
- T2 and DWI may be acquired after contrast injection, after the TP (may improve lesion-liver CNR, due to shortened T2 relaxation time)
- Diffusion coefficients and shear liver stiffness may also be evaluated after contrast injection
- HBP usually at 20 min/60-90 min HYPER parenchyma, HYPO vessels, HYPO kidneys, contrast excretion via bile ducts
- Increased flip angle (30-35);



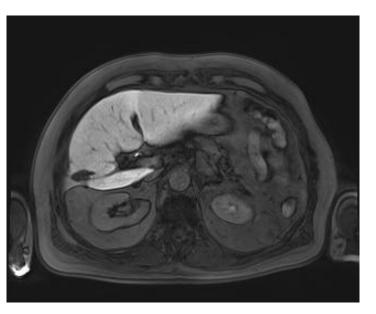
Different flip angles



Flip angle = 10



Flip angle = 30



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Classification of benign liver lesions



Gatti M, Maino C, Tore D, Carisio A, Darvizeh F, Tricarico E, Inchingolo R, Ippolito D, Faletti R. Benign focal liver lesions: The role of magnetic resonance imaging. World J Hepatol. 2022 May 27;14(5):923–943. doi: 10.4254/wjh.v14.i5.923. PMID: 35721295; PMCID: PMC9157713.

Epithelial tumors (hepatocellular and biliary)	Mesenchymal tumors	Pseudotumor
Hepatocellular adenoma	Hemangioma	Focal fatty infiltration
Focal nodular hyperplasia	Lymphangioma	Infection (liver abscess, Echinococcus granulosus)
Biliary cystadenoma	Solitary fibrous tumor	Inflammatory disorder of the liver (pseudotumor, sarcoidosis)
Biliary hamartoma (von Meyenburg Complex)	Mesenchymal hamartoma	

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Hepatocellular adenoma (HCA)



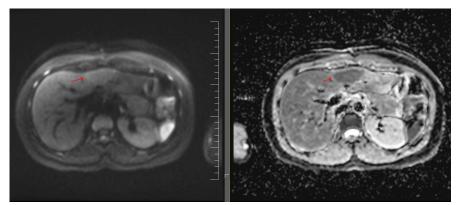
- Occurs mostly in women between 15-45 years;
- Strongly associated with oral contraceptive consumption (OCP), but also with anabolic androgenic steroids, glycogen storage disease, obesity, diabetes, Fanconi's anemia, FAP, beta thalassemia, tyrosinemia;
- Composed of hepatocytes;
- Perfused by peripheral arterial vessels high vascular nature;
- Adenomatosis >10 lesions;
- May undergo hemorrhage or malignant transformation;



Type 1: HNF-1α HCA



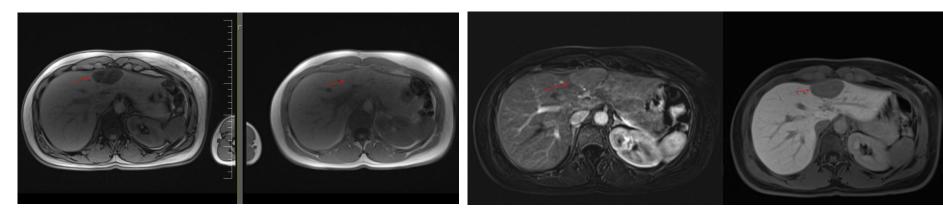
- 2nd most common subtype (30-35%);
- Almost only in women with a history of OCP;
- Lowest risk of malignant transformation;
- HYPER/ISO intense on T1, ISO/HYPER intense on T2;
- NO restricted diffusion;
- FAT content signal loss on T1 OOP compared to T1 IP 86,7% sensitivity and 100% specificity;
- **HYPER** enhancement in the arterial phase (AP), which doesn't persist in the portal venous phase (PVP).





F, 31, HNF-1α adenoma

DWI + ADC



T1 OOP + IP

T₁+C, hepatobiliary phase



Type 2: I-HCA



- Most frequent subtype (40-50%);
- Young women with OCP use, metabolic syndrome, obesity;
- Highest risk of bleeding (30%);
- Malignant transformation: 5-10%;
- Intralesional hemorrhage: acute (HYPER T1)/chronic (HYPO T1+T2);
- Atoll sign: heterogeneous **HYPER**intense on T2, particularly in the periphery;
- **HYPER**enhancement in the AP, persistence in the PVP, DP, **HYPO** in the HBP;

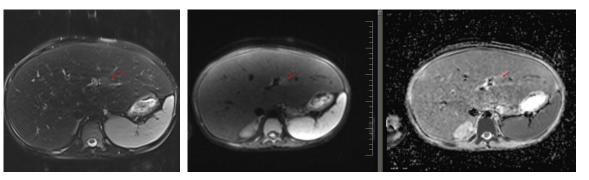


Type 3: β catenin activated HCA



- 10-15% of HCAs
- Continuous activation of the β-catenin protein, resulting in uncontrolled growth of hepatocytes
- More common in **men**
- Associated with anabolic androgenic steroids, glycogen storage disease, familial adenomatous polyposis
- Highest risk of **malignant transformation**
- May retain HB contrast agents and may be HYPER intense in the HBP

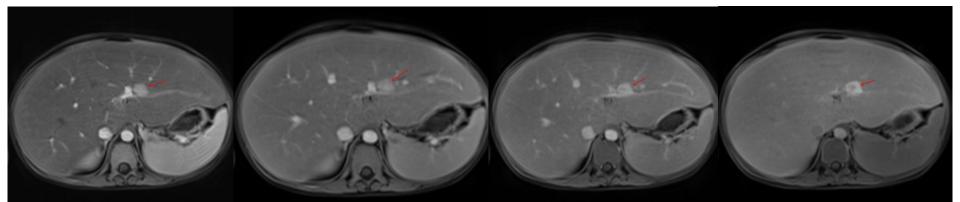




DWI + ADC

18, M, glycogenosis type B, β -catenin adenoma

T2



T1 + C, arterial

T1+ C, venous

T₁+ C, transitional

T₁+ C, hepatobiliary



Type 3: unclassified HCAs



- 10% of HCAs;
- Adenomas, but with no particular characteristics, including genetics, clinical appearance or imaging features.



FNH



- Second most common benign liver lesion (8-9%);
- Predilection for female patients, 3rd-5th decade;
- No relation to OCP;
- Hepatocytes + fibrous septa + central scar;
- Hypervascular due to rich capillaries;
- Associated with other vascular conditions (HA, arteriovenous malformations, shunts etc);



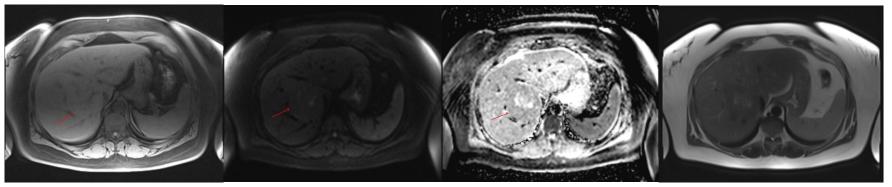
- **ISO**intense on T1 and T2 due to the presence of hepatocytes;
- Homogeneous and strong contrast enhancement in the AP, excepting the central scar;
- **ISO**intense in the PV phase, while the scar remains slightly hypointense;
- **ISO- to HYPER**intense in the HBP, scar mainly HYPO, sometimes HYPER;
- When atypical difficult to distinguish from HCA;



- Central scar better depicted on MRI (HYPER T2; DDx in HCC: HYPO);
- Extracellular contrast agents and CT: scar enhances in the DP;
- Gd-BOPTA MultiHance®; Bracco, Milan, Italy scar is HYPERintense in the LP;
- Gadoxetic acid (Gd EOB DTPA Primovist®; Bayer Schering, Berling, Germany) - scar is always HYPOintense, due to the overlap of the late PV and the HBP (everything not containing hepatocytes will be HYPO, including fibrous tissue).

FNH – 35, F



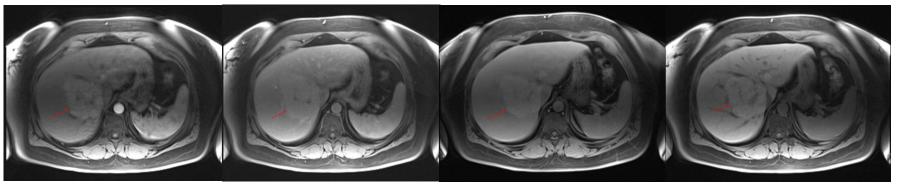


T₁ pre contrast

DWI

ADC

T2



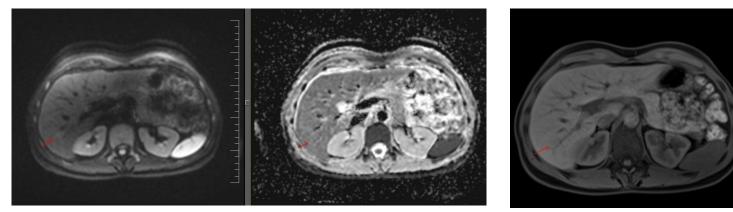
T1+C, arterial

T1+C, venous

T1+C, transitional

T1+C, hepatobiliary

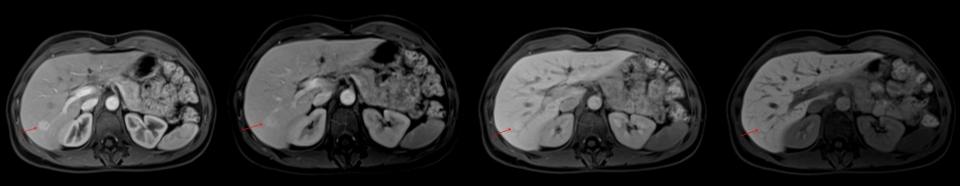
FNH- 34, M



DWI+ADC







T1+C, arterial

T1+C, venous

T1+C, transitional

T1+C, hepatobiliary



Atypical:

- No central scar;
- Large central scar;
- Intralesional fat;
- Pseudocapsule;
- Sinusoidal distension.



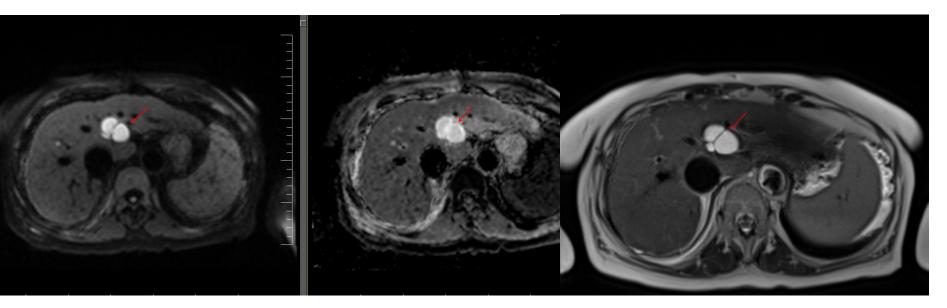
Biliary cystadenoma



- Rare, benign hepatic tumor
- Origin from the intrahepatic bile ducts
- Almost always in **women**
- Predilection for the **right hepatic lobe**
- Fluid-containing lesion with septa, various signal intensity depending on proteinaceous content
- Risk of malignancy: nodular growth, hemorrhage, vascularized septa

Biliary cystadenoma- 74, F





DWI + ADC

T2



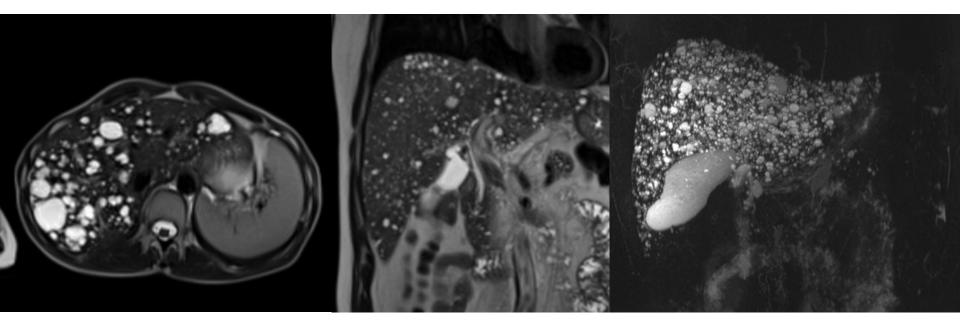
Biliary hamartomas (von Meyenburg complex)



- Rare biliary malformations
- Mostly occur in women (~48 years)
- More common in chronic liver disease
- Small, infracentimetric, subcapsular
- **HYPOintense** on T1, **HYPERintense** on T2
- May present mural nodules with PVP enhancement
- MRCP: "starry sky" appearance, with no communication with bile ducts, HBP may demonstrate the lack of connection to bile ducts

Biliary hamartomas (von Meyenburg complex)





44, F, T2 axial

66, M, T2 Haste Coronal, MIP reformat

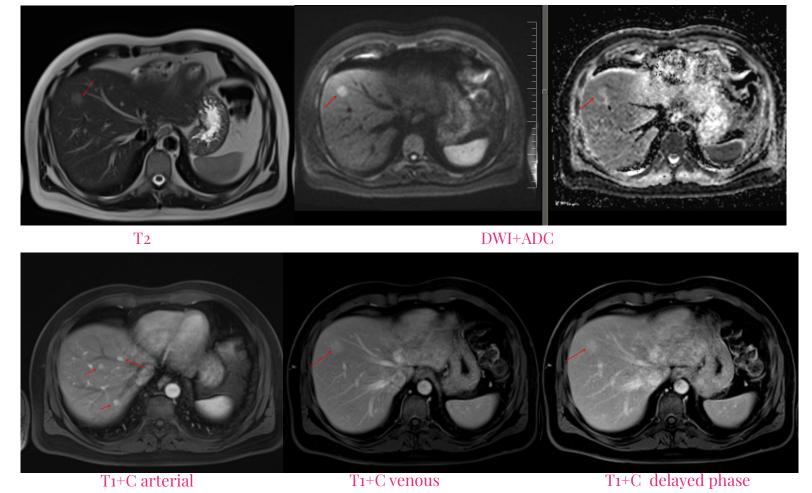


FNH-like lesions



- Histologically and radiologically identical, but in an abnormal liver
- Fontan associated liver disease (surgical technique for complex cardiac disease), Budd – Chiari syndrome, abnormal hepatic venous flow (congenital absence of PV, cavernoma, Osler-Weber-Rendu, chemotherapy)
- No risk of malignant transformation
- DDx: HCC (some of the conditions are risk factors for HCC)

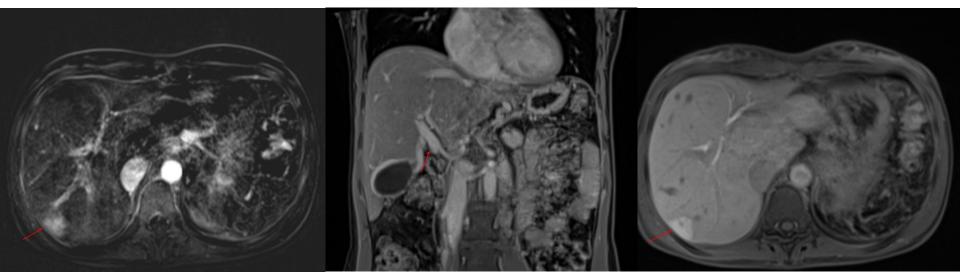
FNH – like lesions after chemotherapy – 43, M





FNH – like in Portal Vein Thrombosis – 32, F





T₁+C, arterial subtraction

T1+C venous

T1+C hepatobiliary



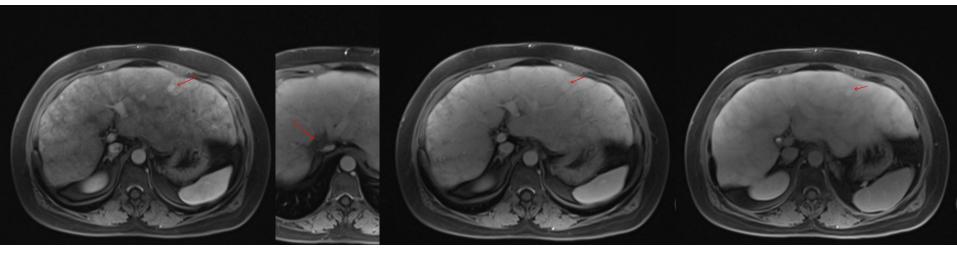
Nodular regenerative hyperplasia



- Multiple regenerative nodular lesions, ~1mm diameter
- Associated with impaired venous flow
- Hematologic (lymphoproliferative, myeloproliferative, immunodeficiency, HIV), autoimmune, vascular (congenital absence of PV, Budd-Chiari syndrome, PV thrombosis), medications
- DD cirrhosis: no fibrosis

Nodular regenerative hyperplasia – Budd – Chiari syndrome, 52, F





T1+C, arterial

T1+C venous

T1+C transitional

T1+C hepatobiliary



Hemangioma (HA)



- Most common benign liver lesion (20%), incidental findings
- More common in women
- Small:1-2 cm, typical: 2-10cm, giant: >10cm
- Cavernous vascular spaces, lined by endothelium + fibrous stroma
- 3 different subtypes
- Most commonly diagnosed with extracellular contrast agents, NOT and indication for hepatobiliary contrast agents!



Cavernous HA

- Most common type
- <3cm, large vascular spaces
- Homogeneous **HYPER** T2, may contain a hypointense hyalinized/thrombosed area or calcifications (diffuse hypointensity)
- DWI **high signal on b0**, decrease at higher b values, sometimes residual hyperintensity on high b values = "**T2 shine through**"
- ADC higher than surrounding liver
- Peripheral nodular enhancement, centripetal and progressive filling on PVP and DP, "**blood-pool**" sign similar to aorta in all phases
- No hepatocytes = > **HYPO**intensity on HBP



Capillary HA

- 16% of all HA
- Mostly <1cm
- HYPER T2 and HYPO T1
- Steatosis **HYPER T1** on OOP, due to peritumoral fatty sparing
- Early enhancement, similar to the aorta
- Transient perilesional enhancement
- Persistence of contrast enhancement in DP, compared to metastases (hypointensity)

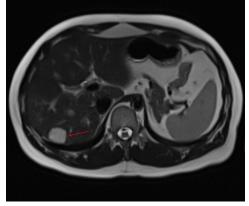


Sclerosed/hyalinized HA

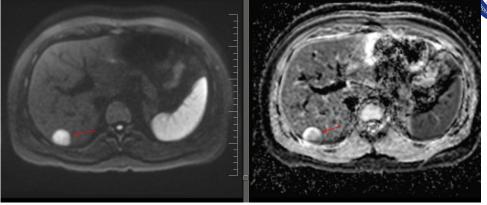
- Presence of fibrosis
- Slight HYPER T2 signal
- Slow and heterogeneous enhancement in the later phases
- Late centripetal filling may be seen

Hemangioma – hepatobiliary contrast, 36, M

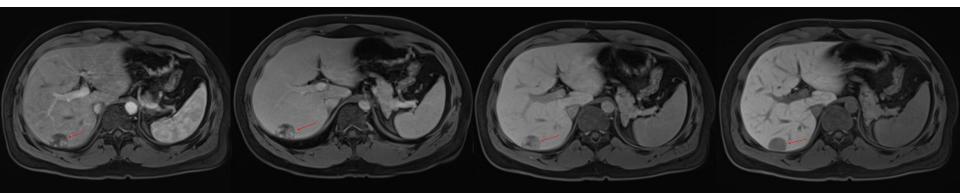




T2



DWI+ADC



T1+C, arterial

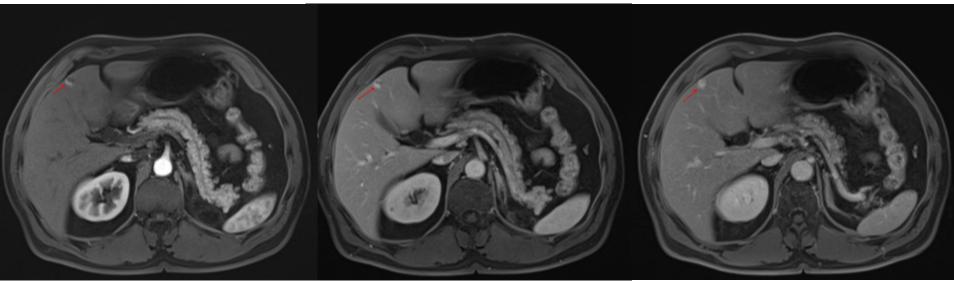
T1+C, venous

T1+C, transitional

T1+C, hepatobiliary

Hemangioma – extracellular contrast





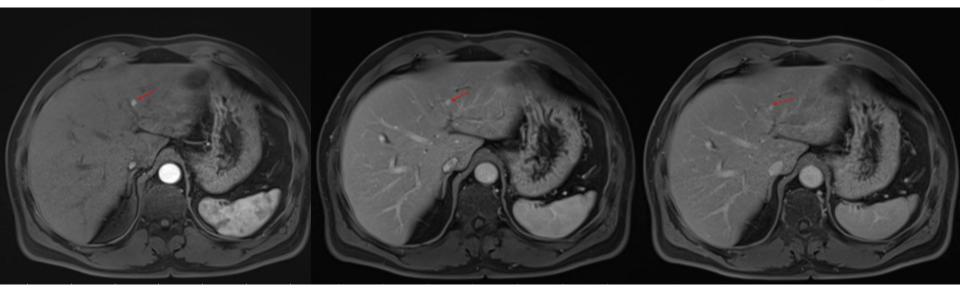
T1+C, arterial

T₁+C, venous

T1+C, delayed phase

European Society ESCAR BUILDING INTERNATION

Flash filling hemangioma



T1+C, arterial

T1+C, venous

T1+C, delayed phase



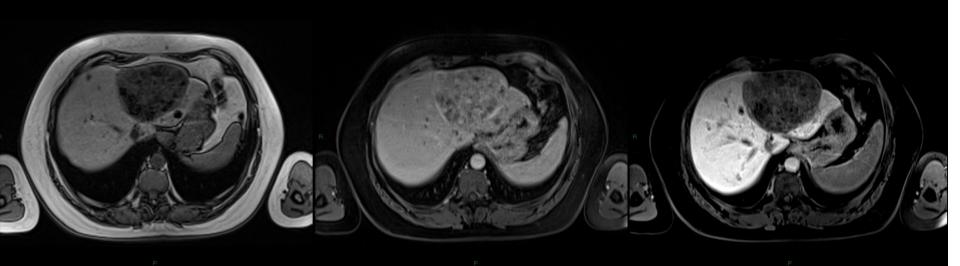
Angiomyolipoma



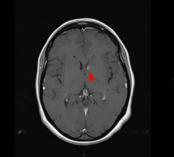
- Arteries + fat + smooth muscle cells
- 4 subtypes: mixed, lipomatous, myomatous, angiomatous
- Associated with Tuberous Sclerosis
- Fat containing: **HYPER T1**, signal loss on **T1 OOP**
- Low fat content: **HYPER T2, HYPO T1**, heterogeneous contrast enhancement, difficult to distinguish from HCC
- **Higher ADC** values than HCC with fat component
- No hepatocytes **HYPO**intensity on HBP

Angiomyolipoma in a patient with tuberous sclerosis





T1 Out-of-Phase





T1+C venous



T1+C, hepatobiliary

Case courtesy of Dr. Caraiani Cosmin



Lymphangioma



- Rare benign tumor
- Rarely seen in liver, mostly in lymphangiomatosis
- Women, >30 years
- Mixed solid and cystic mass, septa, nodules
- Intermediate signal due to intralesional bleeding



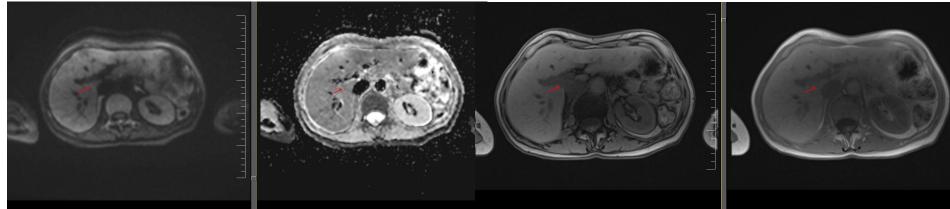
Focal fatty infiltration



- **Signal drop** on T1 OOP in comparison to T1 IP
- **HYPO**intensity on T2
- Reduced number of functioning hepatocytes **HYPO**attenuating
- Wedge-shaped
- Lack of mass effect
- Round DDx with fat-containing liver masses
- Fat spared areas no signal drop, **HYPER**attenuating on HBP, due to normally functioning hepatocytes

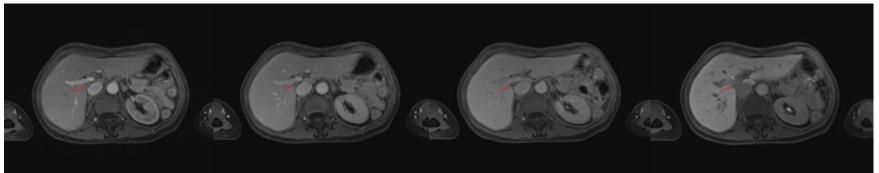


Focal fatty infiltration – 46, F



DWI+ADC

T1 Opposed Phase + In Phase



T1+C, arterial

T1+C, venous

T1+C, transitional

T1+C, hepatobiliary



Liver abscess



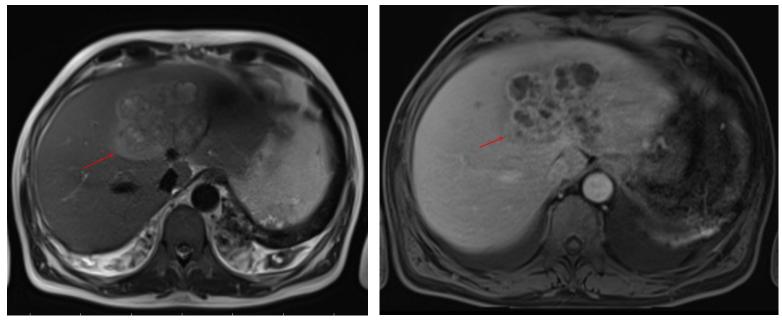
- MRI best depicts lesions
- ISO/HYPER T1 hemorrhage, proteinaceous content, no signal drop
- Edema/peripheral inflammation seen on T2
- High restricted diffusion, **centrally** (DDx: tumor, more peripherally)
- Peripheral rim enhancement in PVP and TP
- Periphery is **HYPO/ISO** in the HBP, due to edema in the surrounding functioning hepatocytes
- Main DDx: metastases

Liver abscess – 74, M



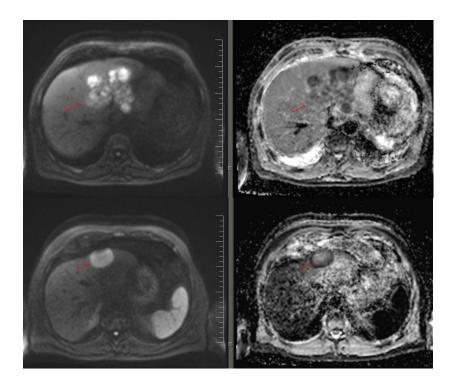


T1+C, venous



Liver abscess versus tumor











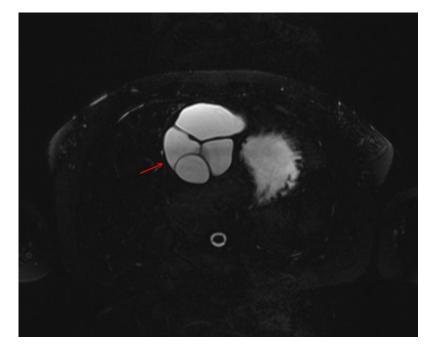
Echinococcosis

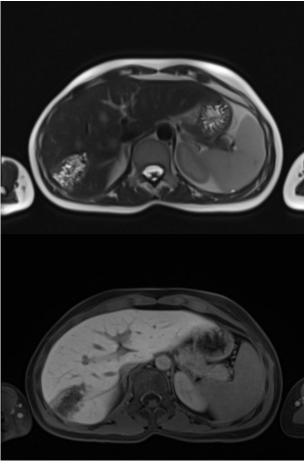


- **Cystic** (E. granulosus) or **alveolar** (E. multilocularis)
- From sheep and pigs/fox
- Cystic lesion, varying size, two layers (germinal layer and outer layer)
- First stage: simple cyst, peripheral enhancement in PVP
- Daughter cysts: honeycombing appearance
- Possible rupture into bile ducts
- End stage: solid component and calcifications

Hydatid cyst, F, 33

SPACE sequence

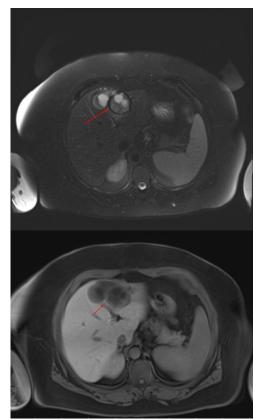






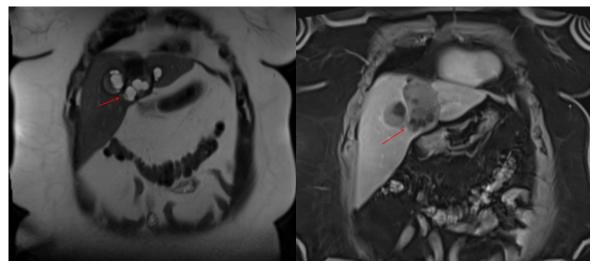
T2

T1+C, HBP



T1+C HBP

Hydatid cyst with daughter cysts – 49, F

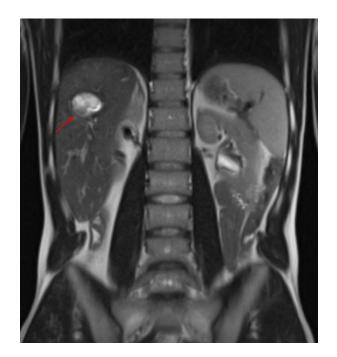


T₂ coronal



Hydatid cyst with floating membrane – 24, M

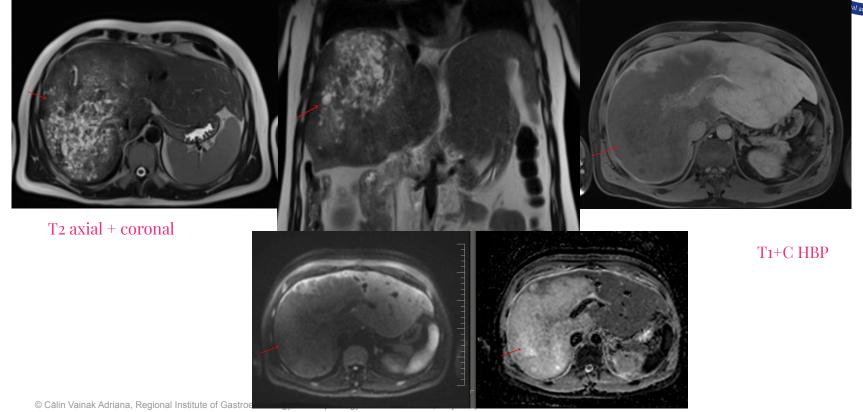




T₂ coronal

Diffuse alveolar hydatidosis – 42, M





DWI+ADC



Management of benign liver lesions

Suspected hepatocellular adenoma

7.	Oral contraceptives, hormone-containing IUDs, and anabolic steroids are to be avoided in patients with hepatocellular adenoma (strong recom- mendation, moderate quality of evidence).
8.	Obtaining a biopsy should be reserved for cases in which imaging is inconclusive and biopsy is deemed necessary to make treatment decisions (strong recommendation, low quality of evidence).
9.	Pregnancy is not generally contraindicated in cases of hepatocellular adenoma <5 cm and an individualized approach is advocated for these patients (conditional recommendation, low quality of evidence).
10.	In hepatocellular adenoma ≥5cm, intervention through surgical or nonsurgical modalities is recommended, as there is a risk of rupture and malig nancy (conditional recommendation, low quality of evidence).
11.	If no therapeutic intervention is pursued, lesions suspected of being hepatocellular adenoma require follow-up CT or MRI at 6- to 12-month intervals. The duration of monitoring is based on the growth patterns and stability of the lesion over time (conditional recommendation, low quality of evidence).
Susp	vected hemangioma
12.	An MRI or CT scan should be obtained to confirm a diagnosis of hemangioma (strong recommendation, moderate quality of evidence).
13.	Liver biopsy should be avoided if the radiologic features of a hemangioma are present (strong recommendation, low quality of evidence).
14.	Pregnancy and the use of oral contraceptives or anabolic steroids are not contraindicated in patients with a hemangioma (conditional recommen- dation, low quality of evidence).
15.	Regardless of the size, no intervention is required for asymptomatic hepatic hemangiomas. Symptomatic patients with impaired quality of life can be referred for surgical or nonsurgical therapeutic modalities by an experienced team (conditional recommendation, low quality of evidence).
Susp	vected focal nodular hyperplasia
16.	An MRI or CT scan should be obtained to confirm a diagnosis of FNH. A liver biopsy is not routinely indicated to confirm the diagnosis (strong recommendation, low quality of evidence).
17.	Pregnancy and the use of oral contraceptives or anabolic steroids are not contraindicated in patients with FNH (conditional recommendation, low quality of evidence).
18.	Asymptomatic FNH does not require intervention (strong recommendation, moderate quality of evidence).
19.	Annual US for 2–3 years is prudent in women diagnosed with FNH who wish to continue OCP use. Individuals with a firm diagnosis of FNH who are not using OCP do not require follow-up imaging (conditional recommendation, low quality of evidence).
Susp	pected nodular regenerative hyperplasia
20.	Liver biopsy is required to confirm the diagnosis of NRH (strong recommendation, moderate quality of evidence).
21.	Pregnancy and the use of oral contraceptives or anabolic steroids are not contraindicated in patients with an NRH (conditional recommendation, low quality of evidence).
22.	Asymptomatic NRH does not require intervention (conditional recommendation, low quality of evidence).
23.	Management of NRH is based on diagnosing and managing any underlying predisposing disease processes (strong recommendation, low quality evidence).

Cystic FLL

Suspect simple hepatic cysts

24.	A hepatic cyst identified on US with septations, fenestrations, calcifications, irregular walls, or daughter cysts should prompt further evaluation with
	a CT or MRI (strong recommendation, low quality of evidence).

- 25. Asymptomatic simple hepatic cysts should be observed with expectant management (strong recommendation, moderate quality of evidence).
- 26. Aspiration of asymptomatic, simple hepatic cysts is not recommended (strong recommendation, low quality of evidence)
- Symptomatic simple hepatic cysts may be managed with laparoscopic deroofing rather than aspiration and sclerotherapy, dictated based on availability of local expertise (conditional recommendation, low quality of evidence).

Suspected biliary cystadenoma or cystadenocarcinoma

- Routine fluid aspiration is not recommended when BCA is suspected because of limited sensitivity and the risk of malignant dissemination (strong recommendation, low quality of evidence).
- Imaging characteristics suggestive of BC or BCA, such as internal septations, fenestrations, calcifications, or irregular walls, should lead to referral for surgical excision (strong recommendation, low quality of evidence).
- 30. Complete surgical excision, by an experienced team, is recommended if BC or BCA is suspected (strong recommendation, low quality of evidence)

Suspected polycystic liver disease

- Routine medical therapy with mammalian target of rapamycin inhibitors or somatostatin analogs is not recommended (strong recommendation, low quality of evidence).
- 32. Aspiration, deroofing, resection of a dominant cyst(s) can be performed based on the patient's clinical presentation and underlying hepatic reserve (conditional recommendation, low quality of evidence).
- 33. Liver transplantation with or without kidney transplantation can be considered in patients with refractory symptoms and significant cyst burden (conditional recommendation, low quality of evidence).

Suspected hydatid cysts

- 34. MRI is preferred over CT for concomitant evaluation of the biliary tree and cystic contents (conditional recommendation, low quality of evidence).
- Monotherapy with antihelminthic drugs is not recommended in symptomatic patients who are surgical or percutaneous treatment candidates (strong recommendation, moderate quality of evidence).
- 36. Adjunctive therapy with antihelminthic therapy is recommended in patients undergoing PAIR or surgery, and in those with peritoneal rupture or billary rupture (strong recommendation, low quality of evidence).
- Percutaneous treatment with PAIR is recommended for patients with active hydatid cysts who are not surgical candidates, who decline surgery, or who relapse after surgery (strong recommendation, low quality of evidence).
- 38. Surgery, either laparoscopic or open, based on available expertise, is recommended in complicated hydatid cysts with multiple vesicles, daughter cysts, fistulas, rupture, hemorrhage, or secondary infection (strong recommendation, low quality of evidence).

Marrero JA, Ahn J, Rajender Reddy K; American College of Gastroenterology. ACG clinical guideline: the diagnosis and management of focal liver lesions. Am J Gastroenterol. 2014 Sep;109(9):1328–47; quiz 1348. doi: 10.1038/ajg.2014.213. Epub 2014 Aug 19. PMID: 25135008.



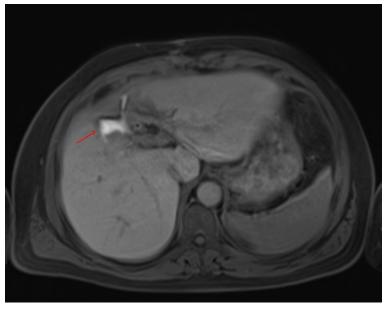
Biliary leaks/bilomas



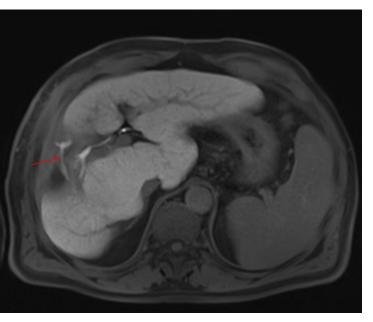
- latrogenic/non iatrogenic
- latrogenic after cholecystectomy or hepatic surgery
- Usually suspected clinically
- US, CT, MRCP are useful tools for diagnosis
- CE-MRI with hepatobiliary agents hyperintense bile will extravasate outside the biliary tree/T1 hyperintense collections
- Additional delayed phases may be useful for detection (up to 180 min)



46, M, biliary leak visible on T1+C, hepatobiliary phase



60, M, biliary leak and biloma visible on T1+C, hepatobiliary phase

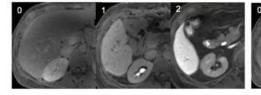




Assessment of liver function

Parameter	Explanation	Score		Explanation Score Par		Parameter	Explanation
1- Graft Parenchymal Enhancement (EnQS)	SI graft parenchyma relative to kidney on HBP	0	Hypointense	Vein Sign	PV SI relative to liver parenchyma SI on HBP		
		1	Isointense				
		2	Hyperintense				

Score PV > Liver PV = Liver PV < Liver



Parameter	Explanation	Score		
2- Contrast	CM in bile ducts on HBP	0	No biliary contrast excretion	
Excretion (ExQS)		1	Excretion into peripheral IHD or RHD and/or LHD	
		2	Excretion into the CHD, CBD or duodenum	
0	1	1	2	



Functional liver imaging score (FLIS)-Score

Poetter-Lang S, Bastati N, Messner A, Kristic A, Herold A, Hodge JC, Ba-Ssalamah A. Quantification of liver function using gadoxetic acid-enhanced MRI. Abdom Radiol (NY). 2020 Nov;45(11):3532-3544. doi: 10.1007/s00261-020-02779-x. Epub 2020 Oct 9. PMID: 33034671; PMCID: PMC7593310.

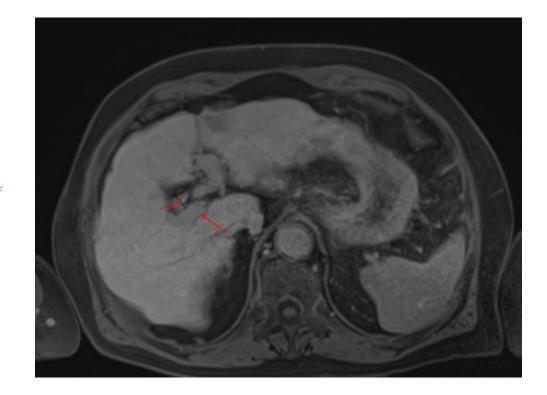


- Gadoxetic acid is considered to be a noninvasive marker of hepatobiliary disorders
- NAFLD, fibrosis, cirrhosis, preoperative assessment
- FLIS score: parenchymal enhancement quality+ rate of biliary excretion + persistence of contrast in PV



Altered hepatic function





T1+C, hepatobiliary



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Thank you!