

ESPR | 2022

Liver cirrhosis in children – role of imaging in the diagnostic pathway (US, CT, MRI)

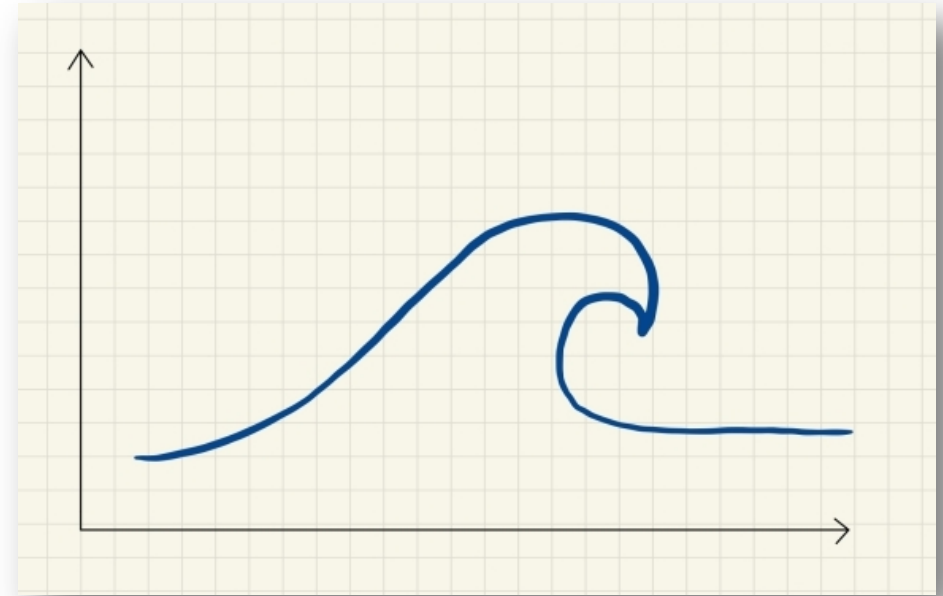
PD Dr. med. Jochen Herrmann

Conflicts of interest

None regarding the subject

Overview

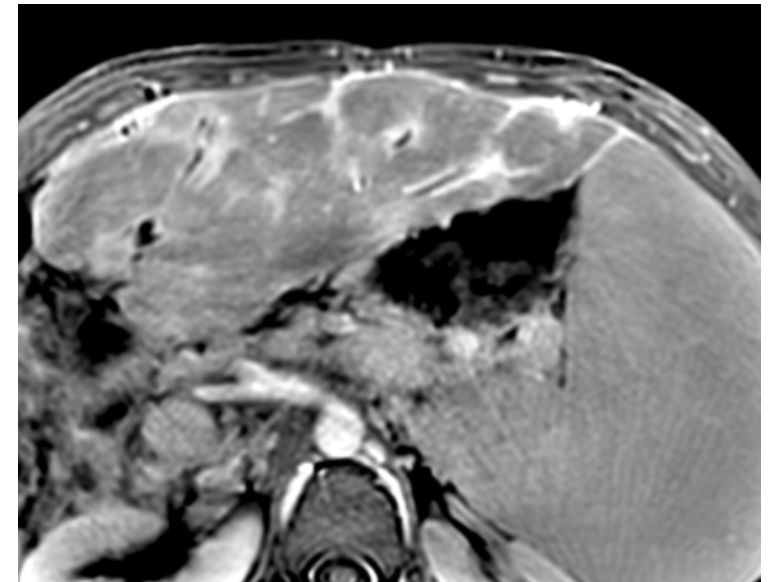
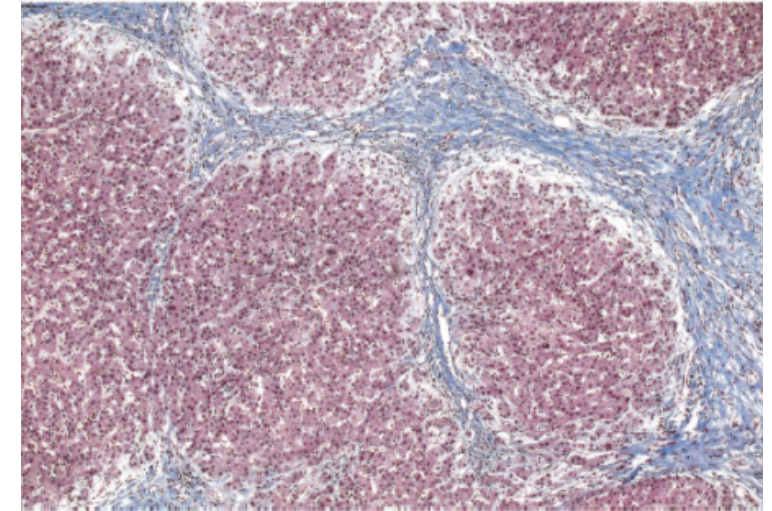
- ▶ Definition of cirrhosis & temporal course
- ▶ **Modalities**
- ▶ Morphologic changes (uniform parenchymal response)
- ▶ Tissue characterization (fat, iron, etc)
- ▶ Hemodynamics
- ▶ Grading of fibrosis
- ▶ Assessing treatment response
- ▶ Monitoring disease evolution (Portal hypertension)
- ▶ Nodular lesions (HCC)



Definition of cirrhosis and temporal course

Definition of cirrhosis

- Diffuse, uniform process
- Fibrosis und nodular regeneration
- Desorganisation of the liver architecture



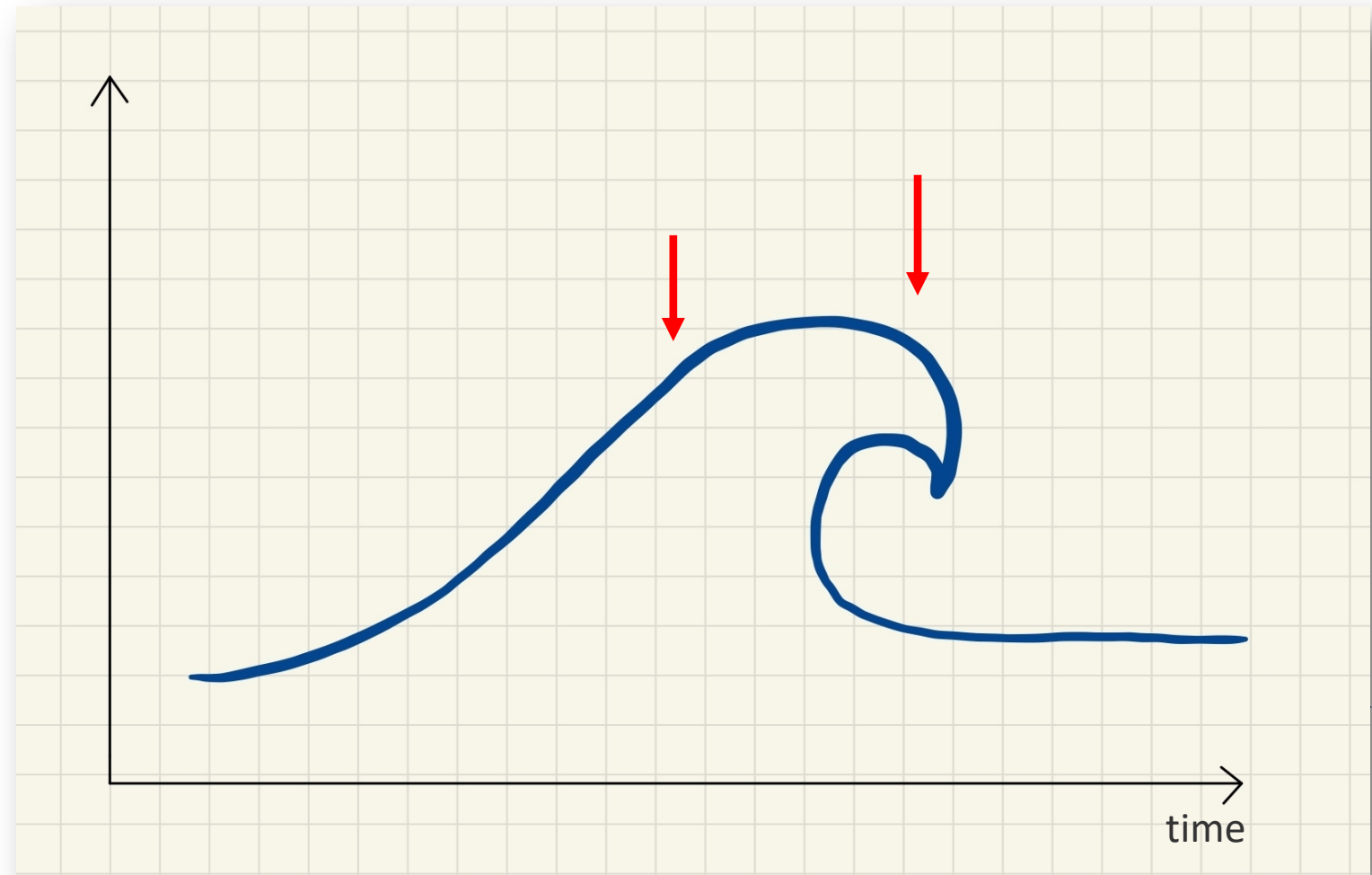
Underlying causes & ages

- Distinct from adults
- Multifactorial causes
- Cholestatic, viral, inherited genetic-metabolic disorders, autoimmune, vascular
- Very young patients (and grow older)
- Adolescent

▶	Biliary obstruction
	Biliary atresia
	Choledochal cysts
	Gallstones
	Bile duct stenosis
	Familial intrahepatic cholestasis
	Alagille syndrome
	FIC1 deficiency (ATP8B1)
	BSEP deficiency (ABCB11)
	MDR3 deficiency (ABCB4)
	Defects of bile acid synthesis
	Hepatotropic viral infections
	Hepatitis B and D
	Hepatitis C
	Hepatitis E
	Inherited genetic-metabolic diseases
	α-1-antitrypsin deficiency
	Glycogenosis type III and IV
	Galactosemia
	Fructosemia
▶	Tyrosinemia type 1
	Wilson's disease
	Mitochondrial hepatopathies
	Late cutaneous porphyria
▶	Cystic fibrosis
▶	Hemochromatosis
	Wolman disease
	Drugs and toxins
	Total parenteral nutrition
	Isoniazid
	Methotrexate
	Vitamin A intoxication
▶	Autoimmune diseases
	Autoimmune hepatitis
	Primary sclerosing cholangitis
▶	Vascular alterations
	Budd-Chiari syndrome
	Veno-occlusive disease
	Congenital cardiopathy
	Congestive heart failure
	Constrictive pericarditis
	Other: Fatty liver disease, Neonatal hepatitis, Zellweger disease

Natural course

- Usually a late diagnosis
- Progressive

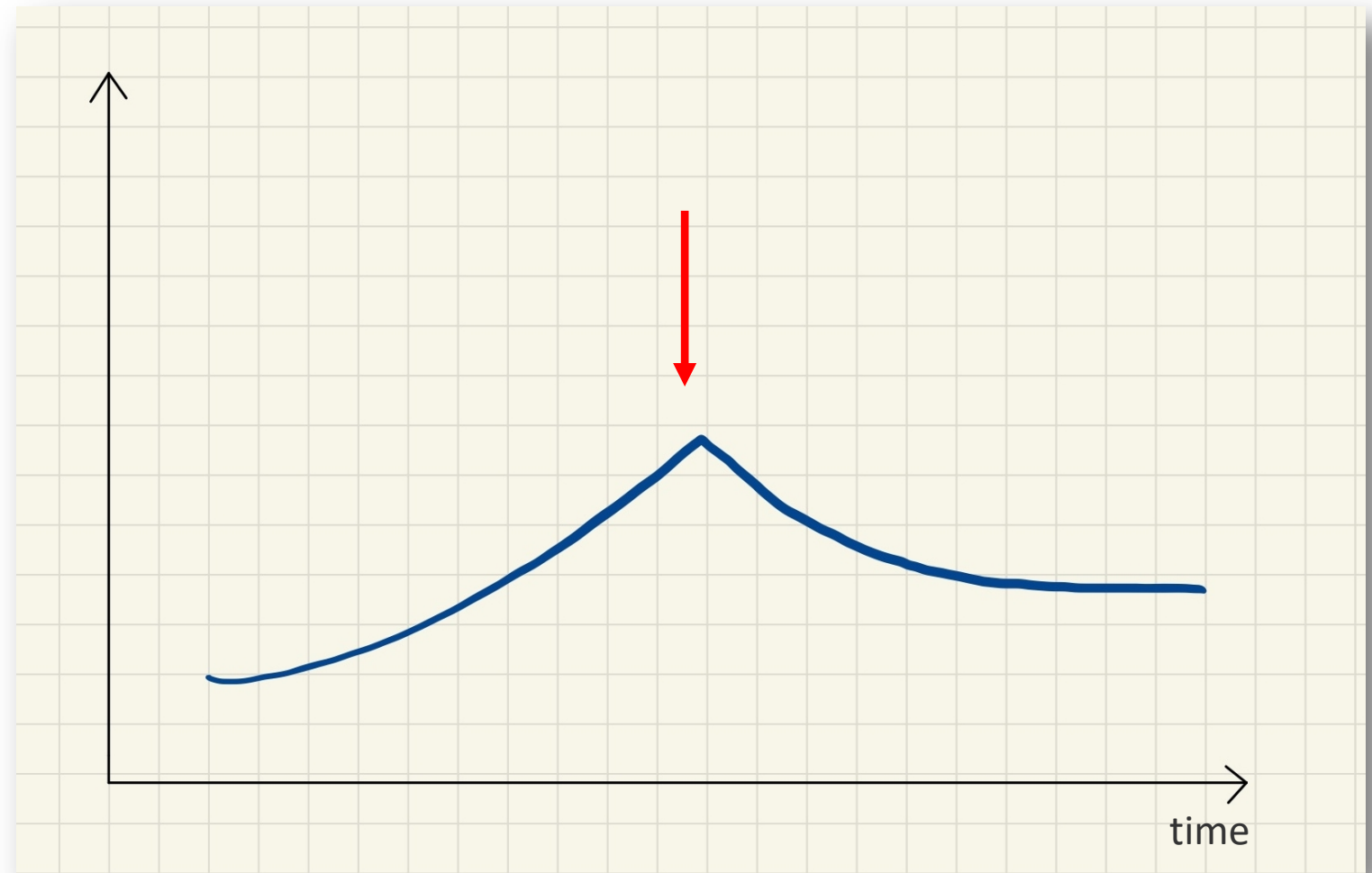


Natural course

- Usually a late diagnosis
- Progressive

But

- Regressive
(if treated adequately)



Role of imaging

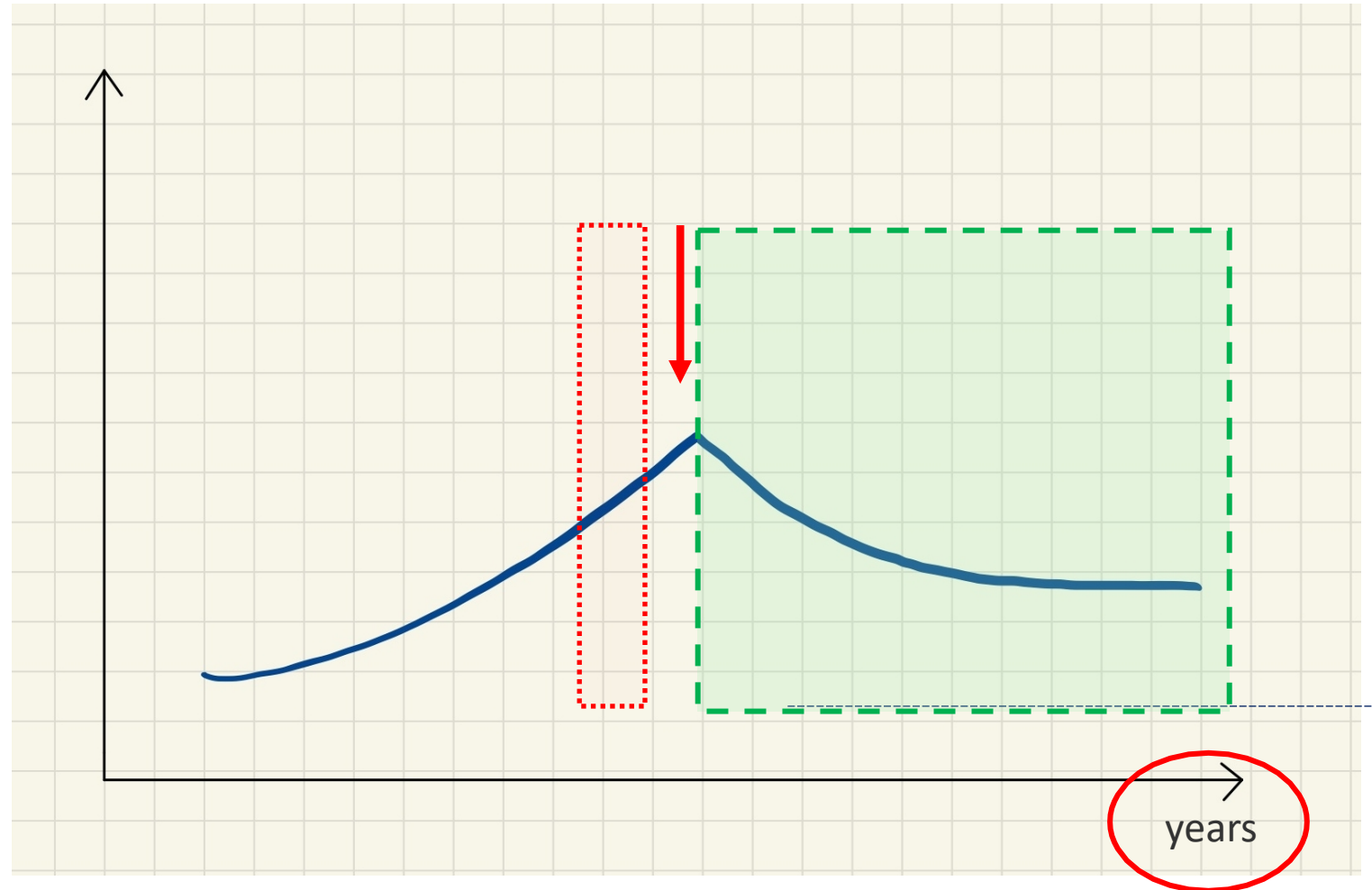
- Detect cirrhosis & causes
- Image guided biopsy

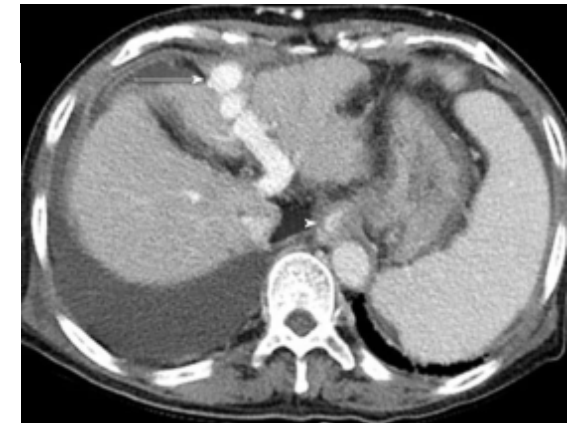
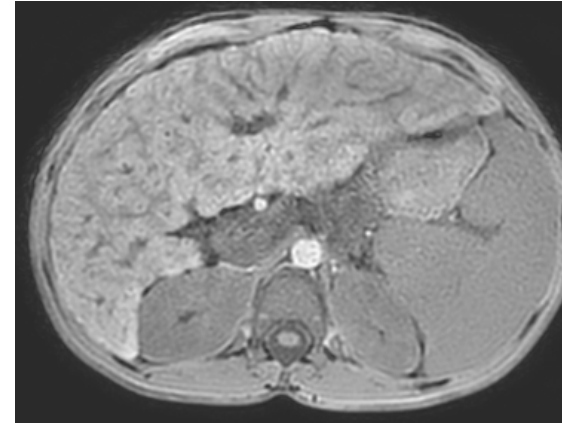
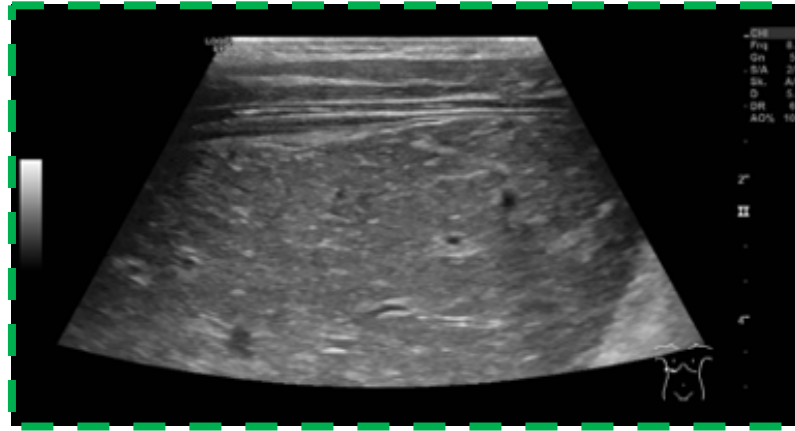


Role of imaging

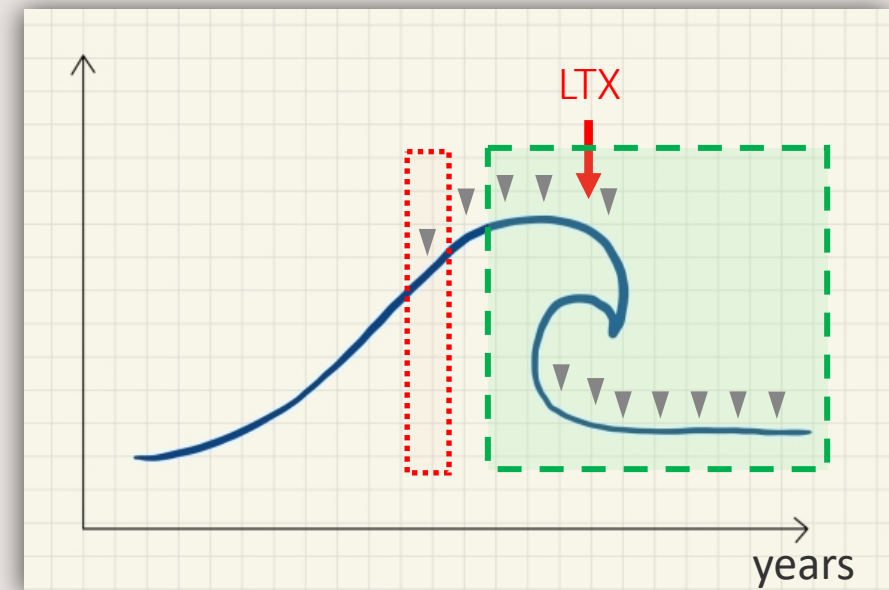
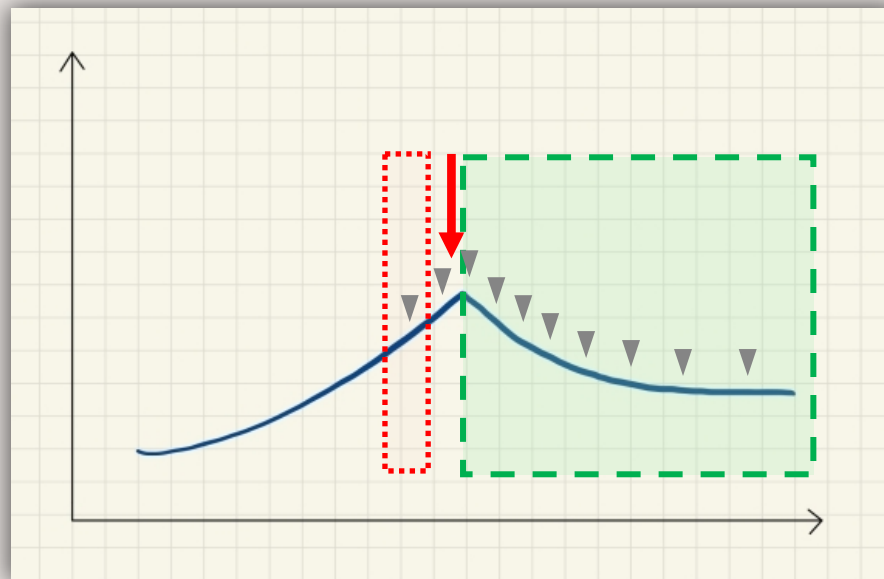
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- Image guided biopsy

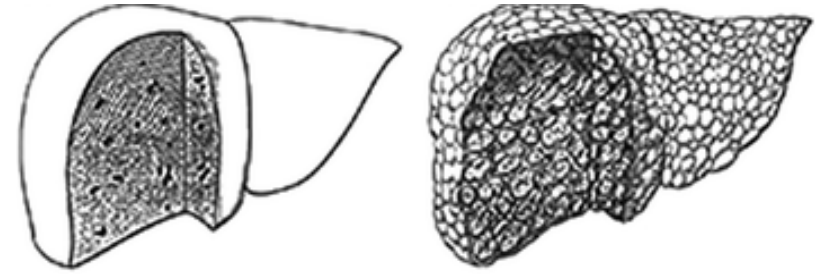
- Monitor disease evolution
- Find complications
- Direct treatment
- Prepare for LTX





Modalities



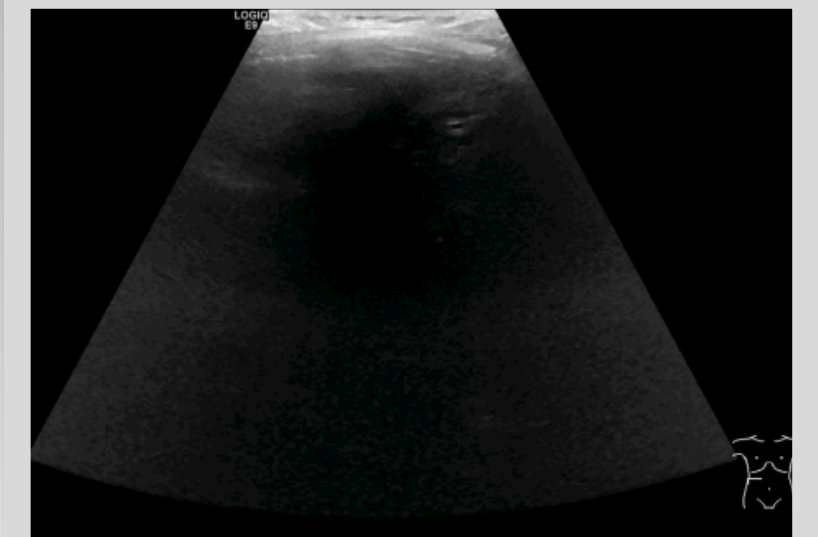
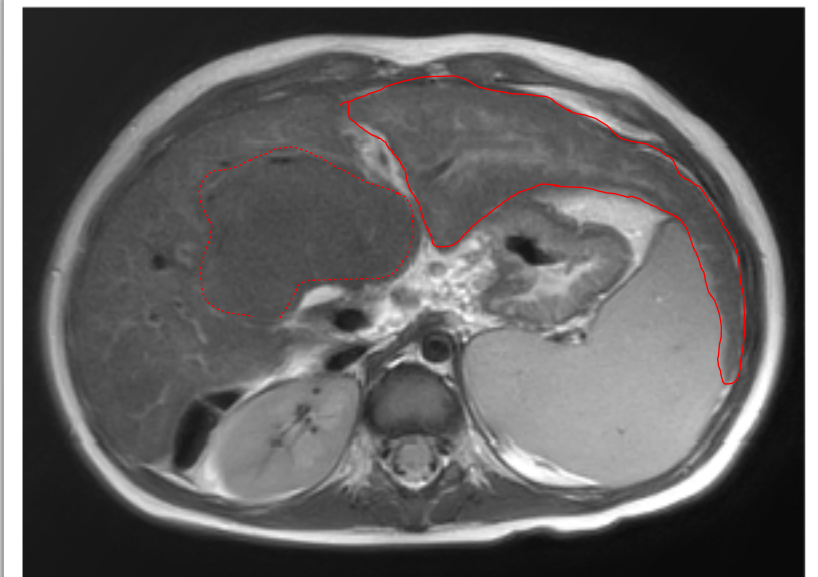


http://digestive.niddk.nih.gov/ddiseases/pubs/cirrhosis_ez

Morphologic changes of cirrhosis

Sizes

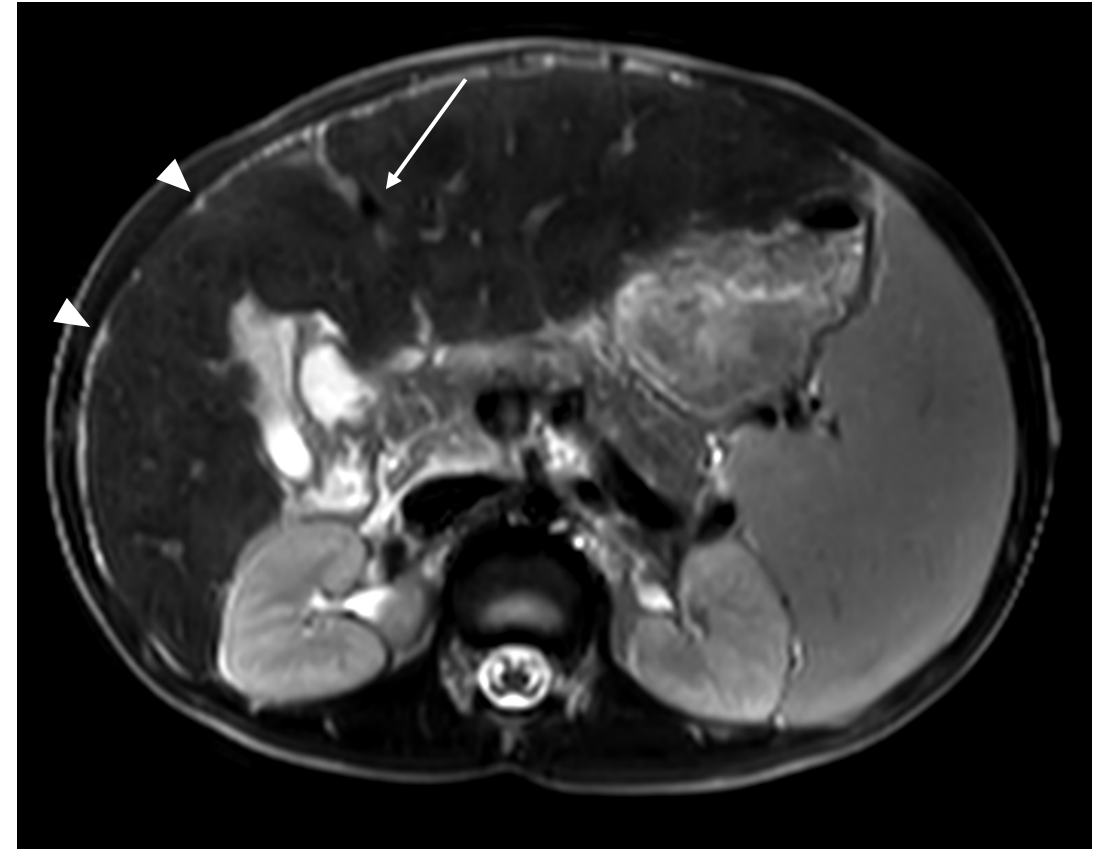
- Hepatomegaly (early)
- Hypotrophy (late)
- Combination of hypertrophy & hypotrophy
- Hypertrophy left lateral (LS 2/3) & LS 1
- Hypotrophy right lobe



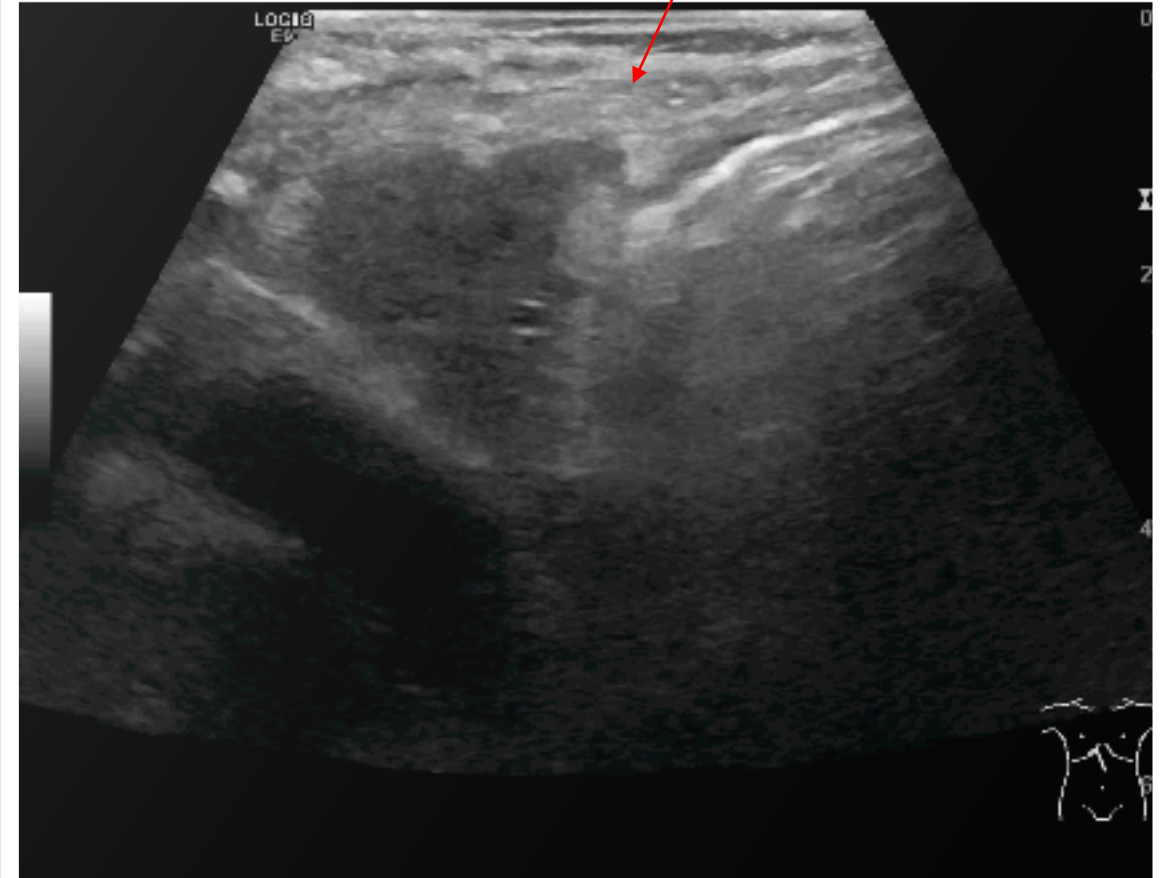
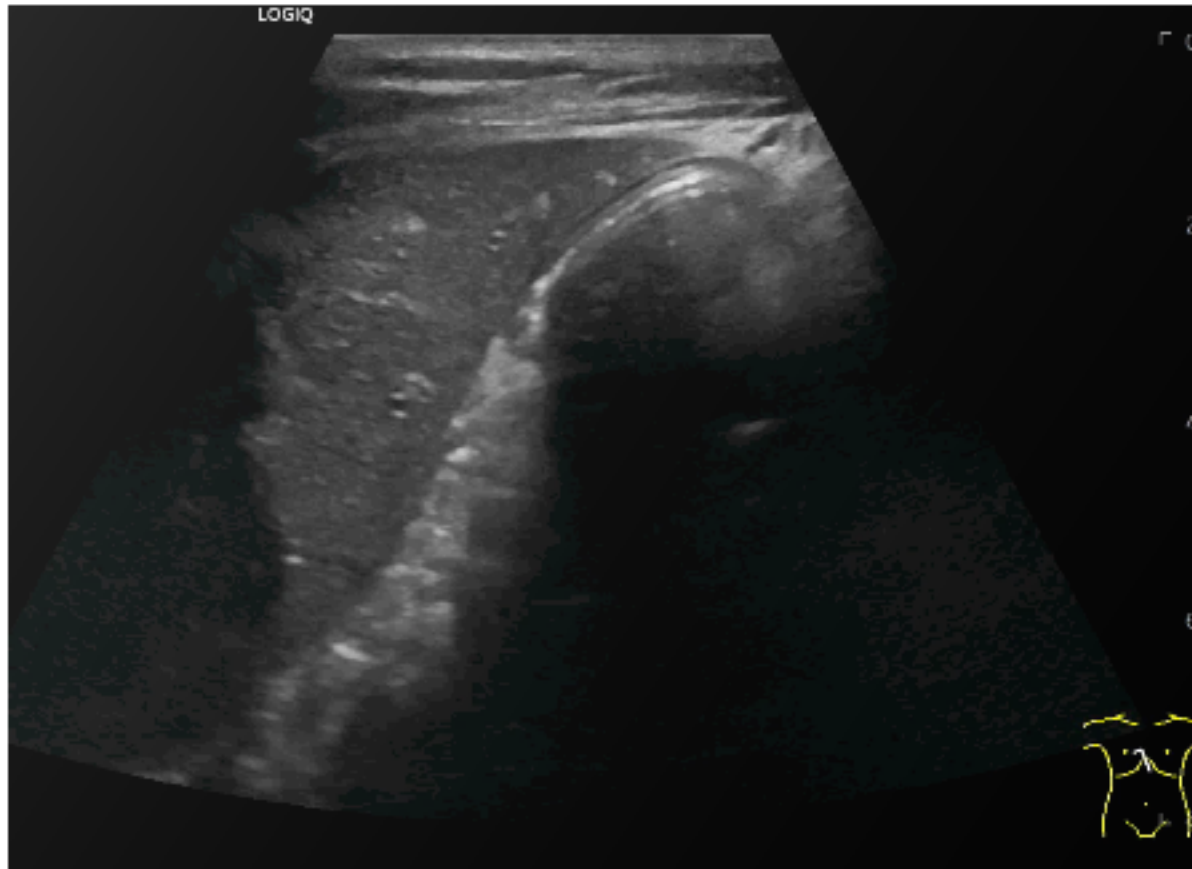
Shape and contour

With progressive hepatic remodeling

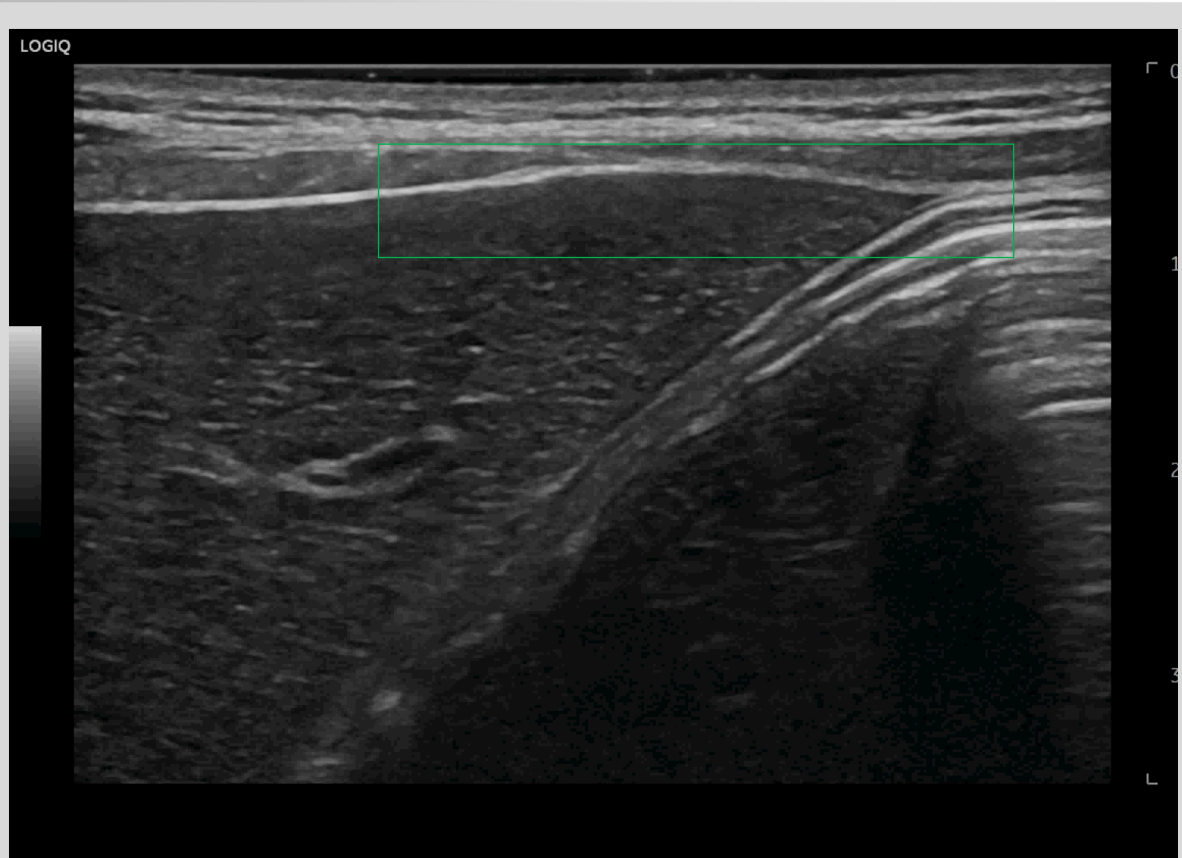
- Loss of shape
- Nodular rounding
- Capsular retraction (confluent fibrosis)



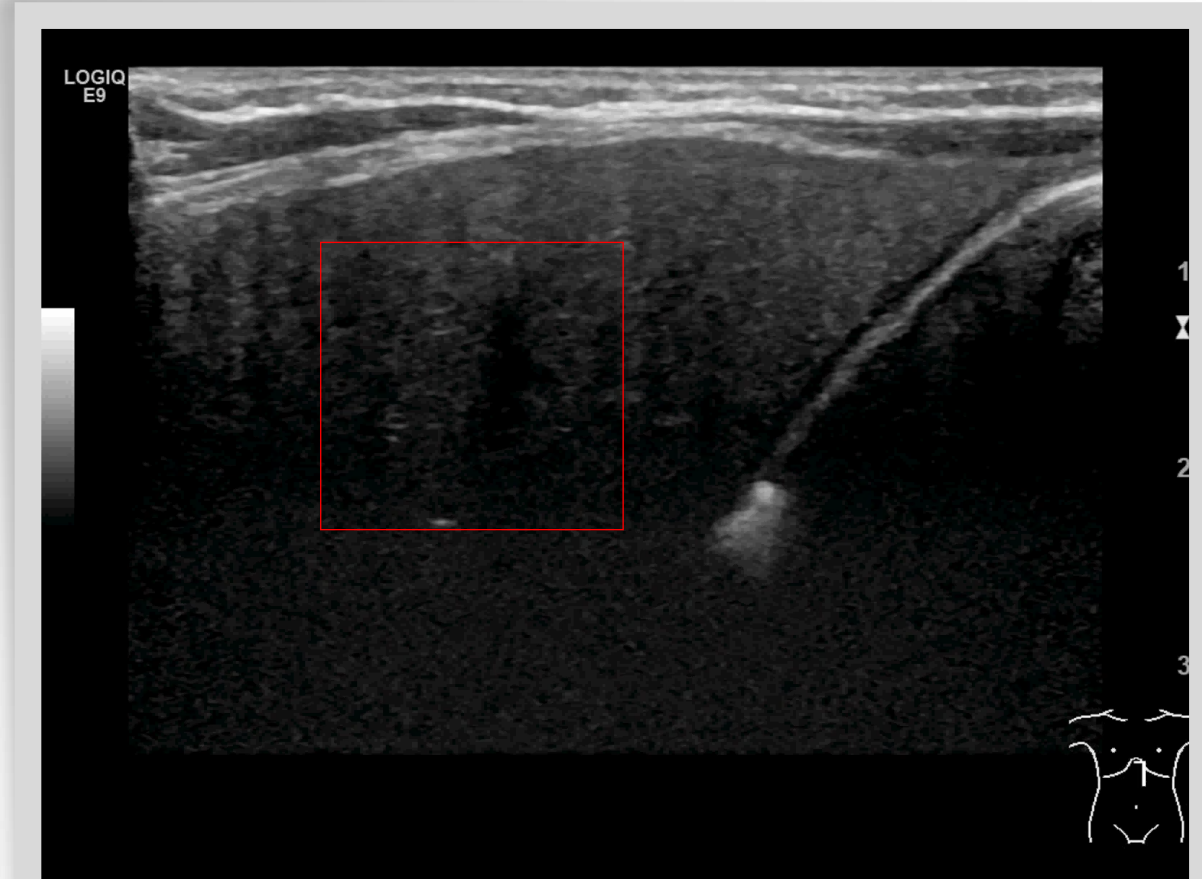
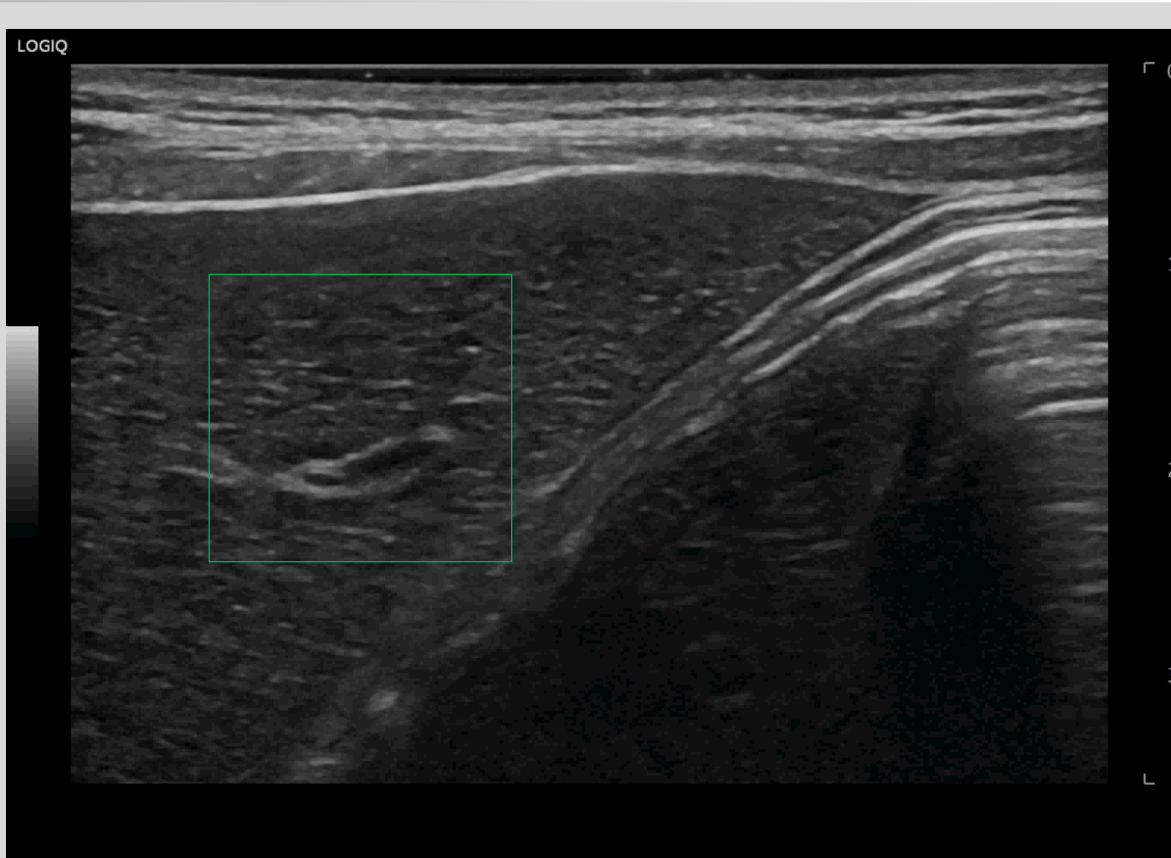
Contural changes



Contural changes (fine)



Textural changes



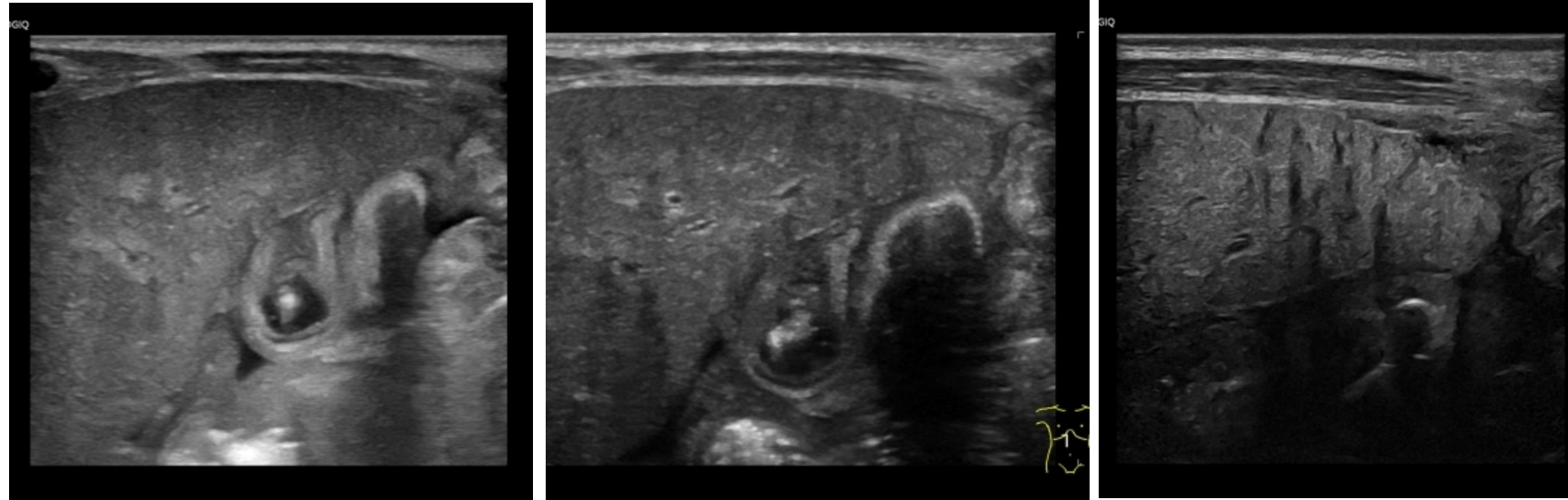
Textural changes

- Important part of report
- Differences in echogenicity between pixel

But

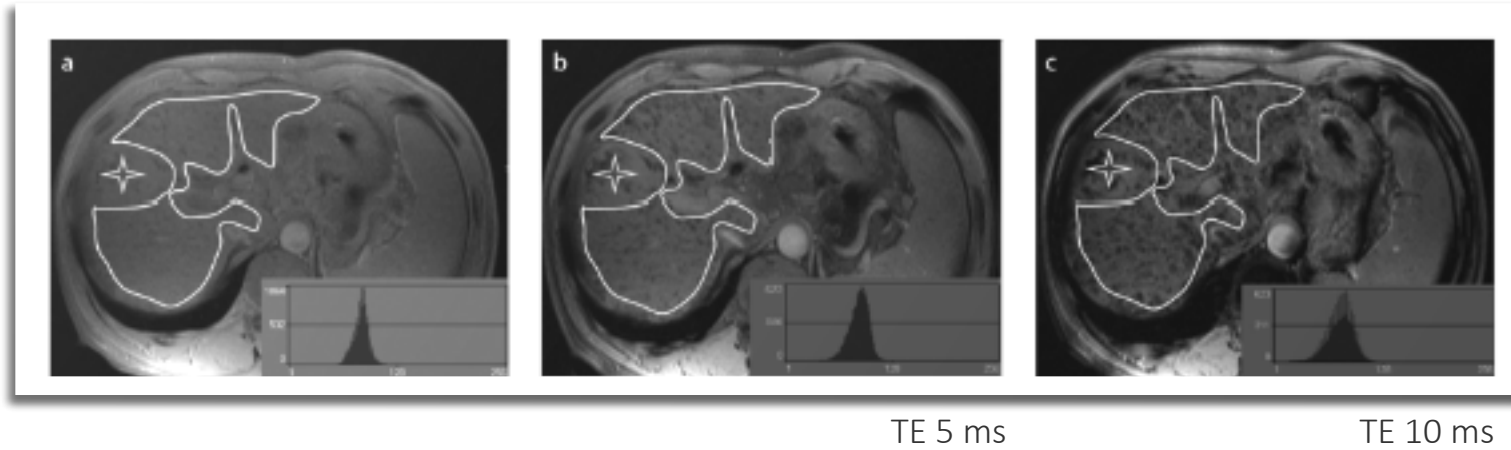
- Description is subjective
- Depends on equipment

3 month old boy with biliary atresia

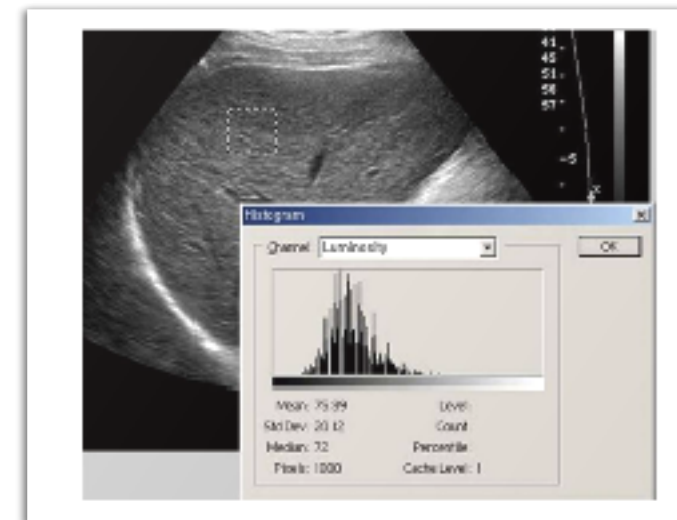


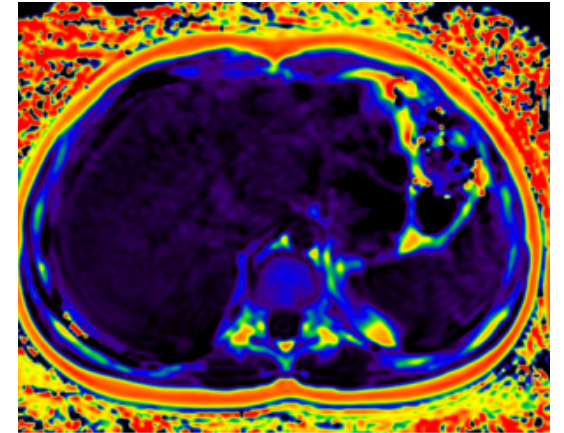
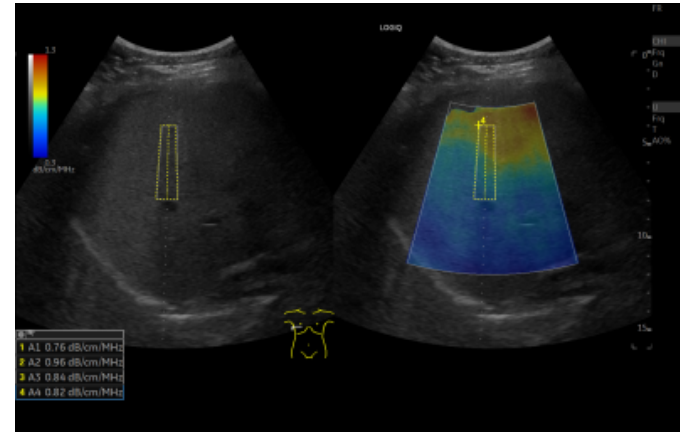
Automatic textural analysis Quantification

- Research attempts using AI / neuronal networks
- Can detect or grade fibrosis
 - US (differences echogenicity, grey-scale values)
 - MRI (T1, T2, DWI, SWI)
 - CT (CE-CT, surface nodularity)



Susceptibility-weighted MRI histogram analysis of liver fibrosis.
Yang ZX. Diagn Interv Radiol 2016; 22:301–307





Tissue composition

Fat

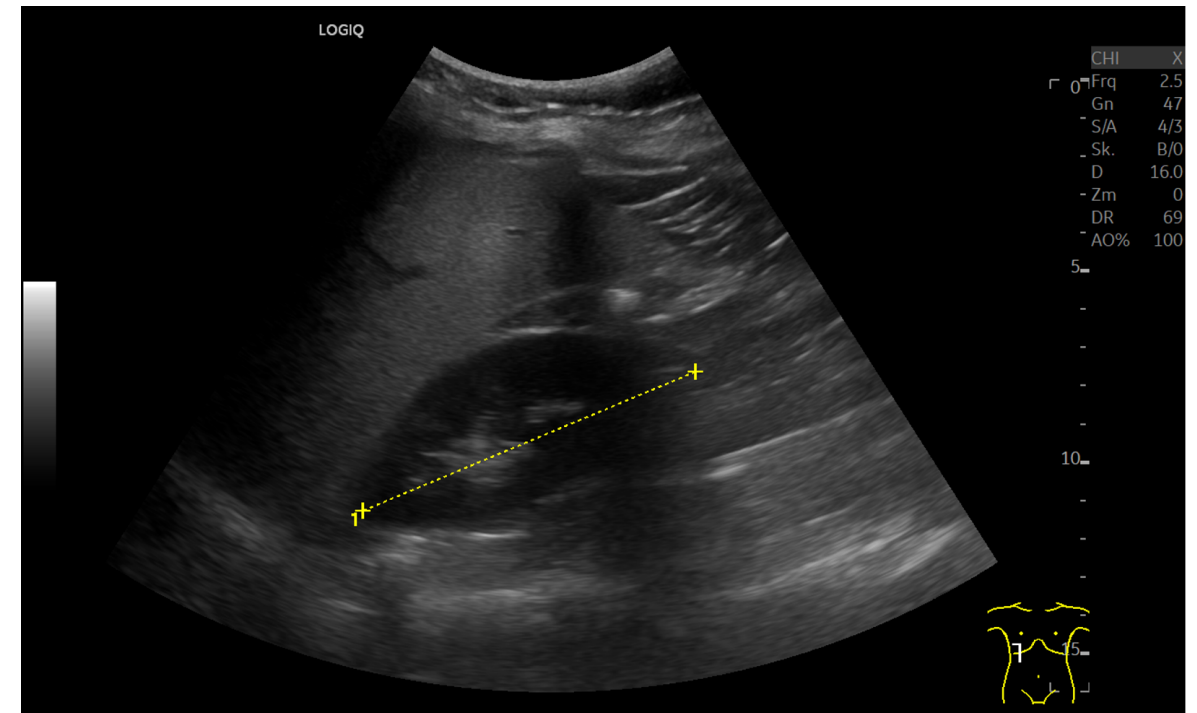
Iron

(DWI)

(Mapping)

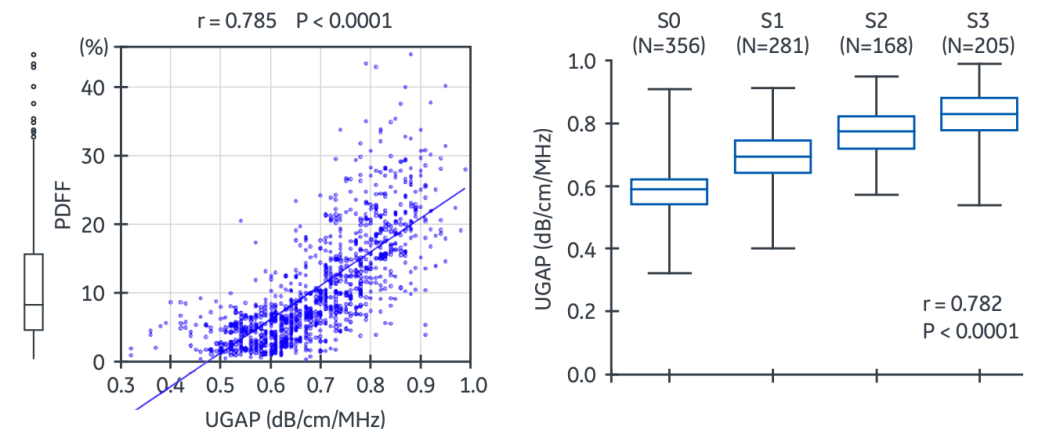
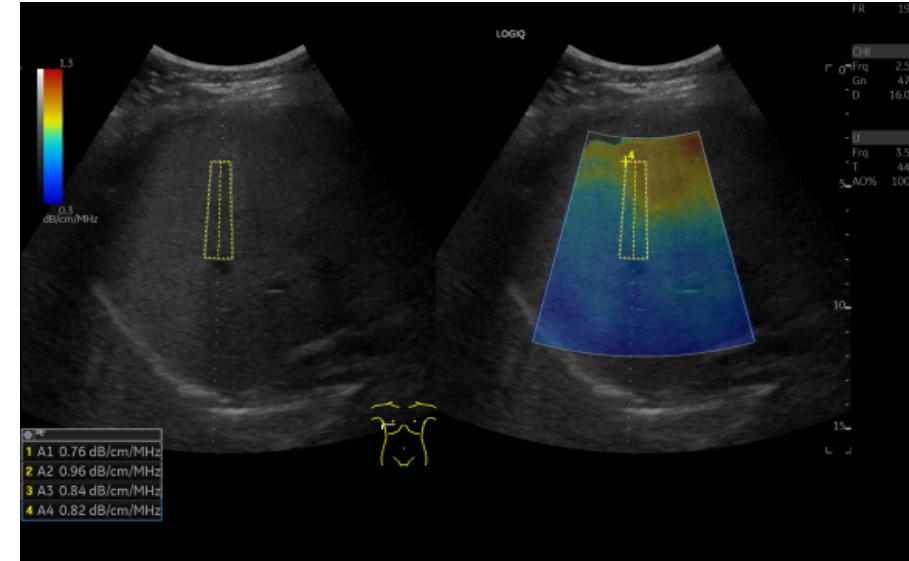
Fat quantification

- Steatosis often coexists with fibrosis
- Viral infections, metabolic disorders, non-alcoholic fatty liver disease (NAFLD)
- NAFLD described in 8% of pediatric population (can result in cirrhosis in late childhood)
- Exact measurement of fat deposition important to direct treatment



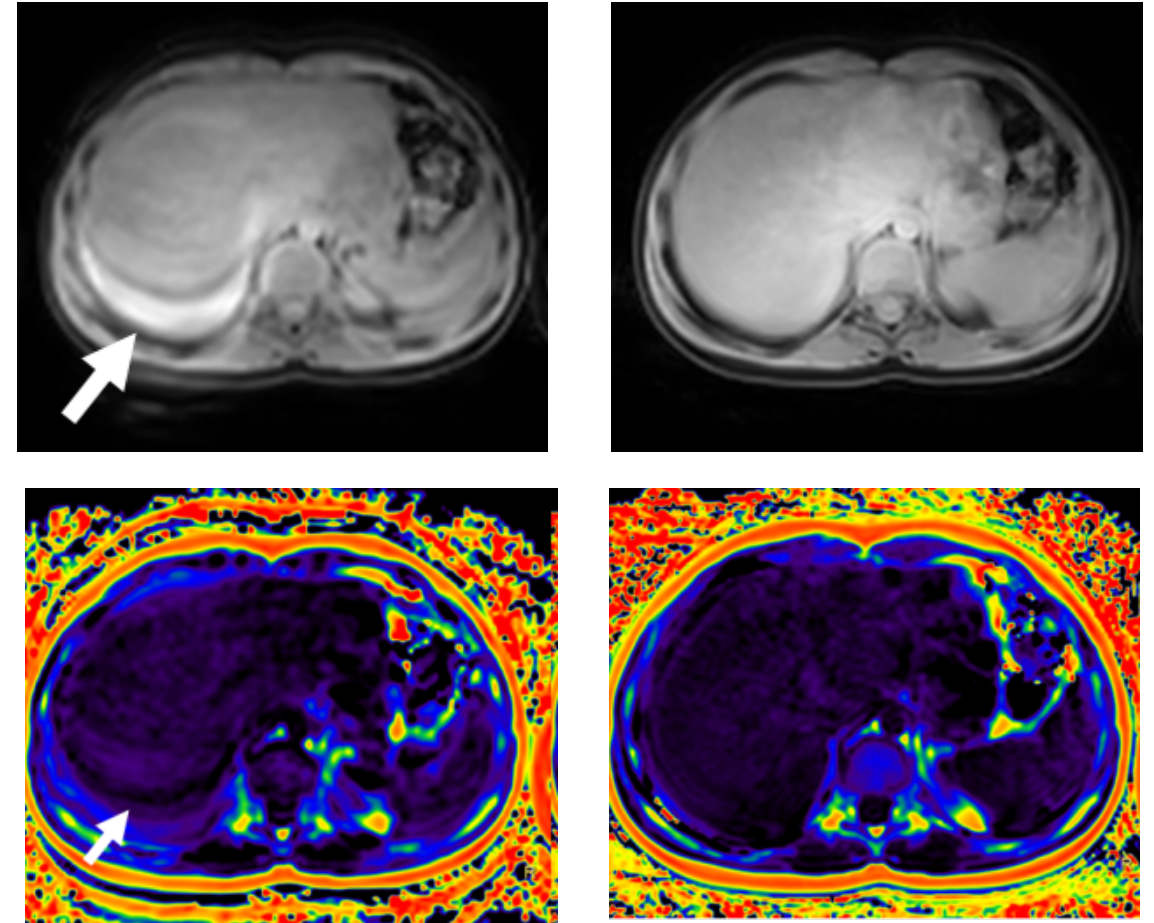
Fat quantification US-based methods

- Different methods commercialised by different vendors (complicated comparability)
- CAP (with TE), Attenuation coeff., Backscatter coeff., Computerized hepatorenal index, ...
- Good performance of fat quantification in a bedside manner
- Inflammation and fibrosis are confounders
- So far, not sufficiently adapted for children



Fat quantification Chemical shift encoded MRI

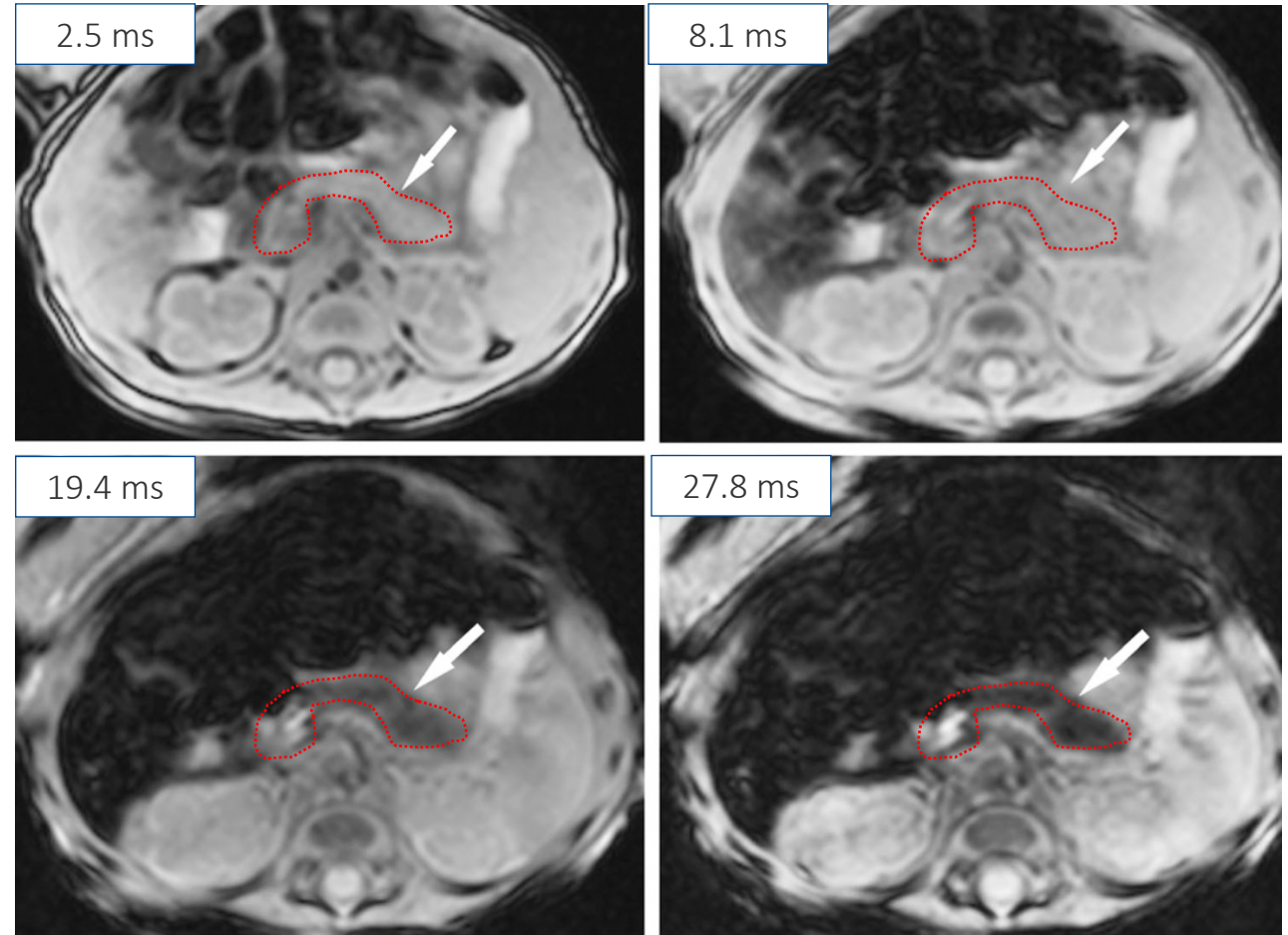
- Current *non-invasive* standard for fat quantification
- Proton-density fat fraction (PDFF)
- Multi-echo mDixon MRI, breath holding required
- Free-breathing radial stack of stars
Under evaluation for children

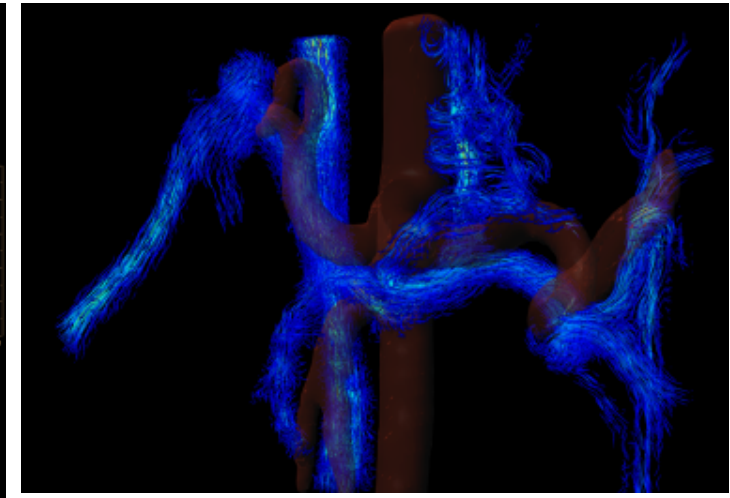
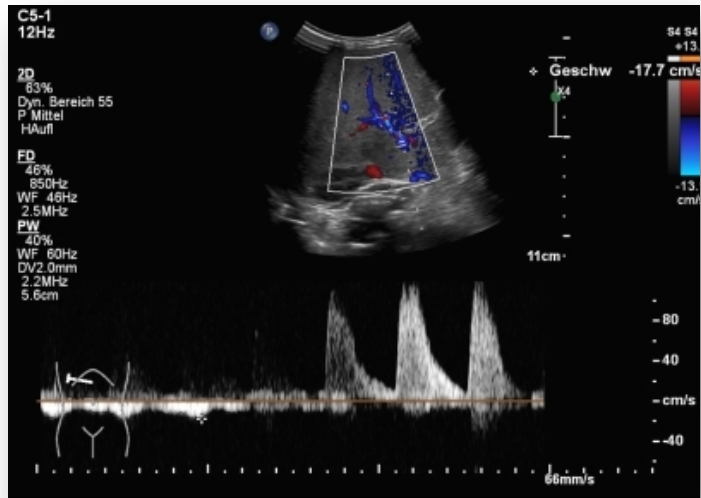


Iron deposition

Gestational alloimmune liver disease (GALD)

- Maternal antibodies directed against fetal liver (hepatocyte loss, fibrosis, nodules)
- Pattern of **extrahepatic** siderosis similar to hereditary hemochromatosis
- T2*MRI with multiple echotimes used for semiquantitative detection of iron
- Role in *non-invasive* work-up (buccal biopsy can be risky)
- Treatment with exchange transfusion and Immunoglobulins

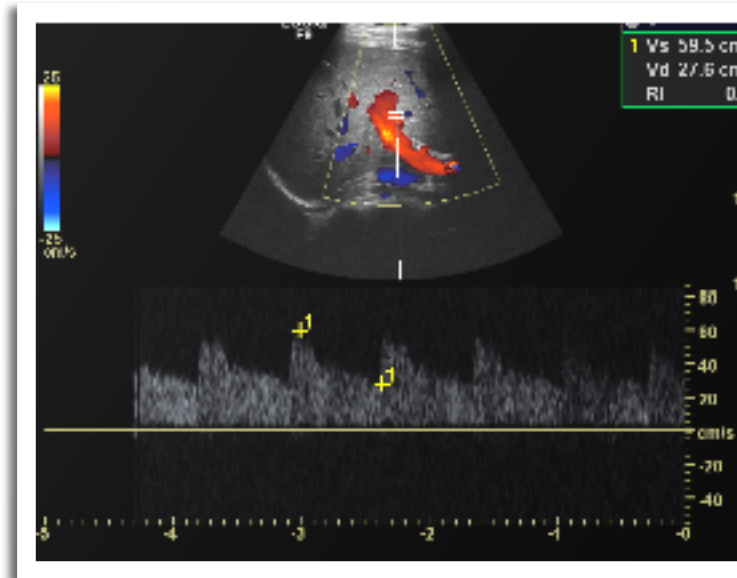




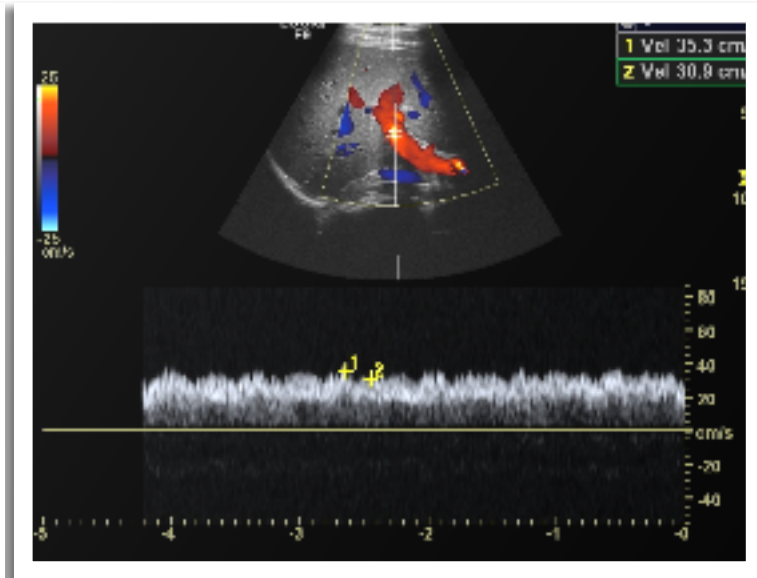
Hemodynamics

Liver hemodynamics

- Hepatic remodelling affects perfusion
- Evaluation of flow is part of work up
- US is first-line
- In young children, US has better capability to provide dynamic information on small vessels than MRI/CT



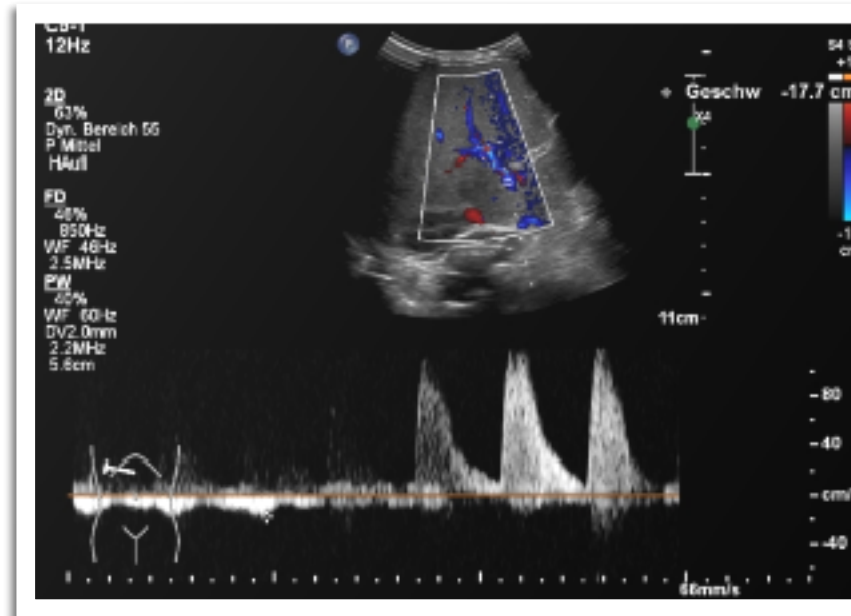
Norm: RI < 0.8
PSV 40-80 cm/s



monophasic, postive inflow
> 15 cm/s

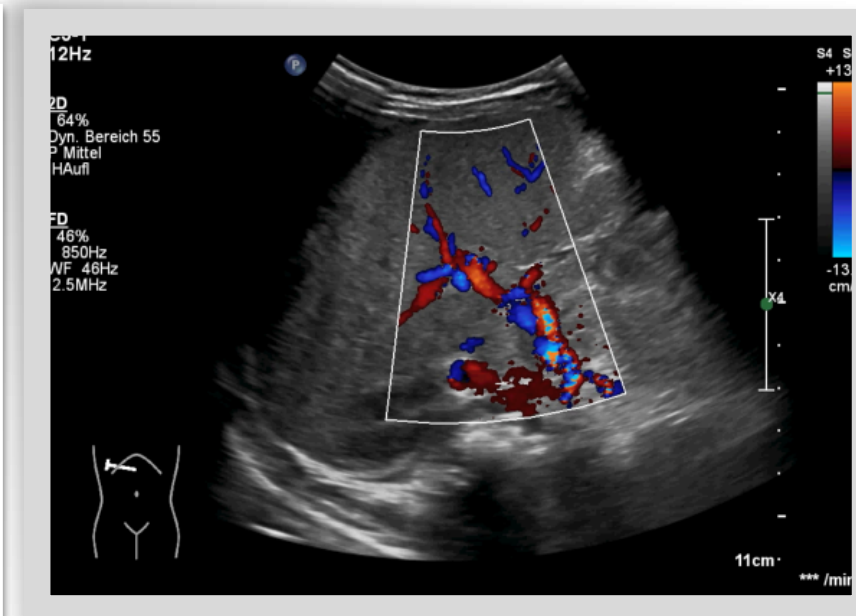
Hepatic vessels (inflow)

- PV flow is a low pressure, low gradient system
- Decrease of PV flow
- Reversed flow in advanced stages
- PV hypoplasia (< 4 mm) in BA
- Increased risk for PV thrombosis
- Compensation by high HA flow (hepatic buffer response)



BA fibrosis:

RI > 0.9
High PSV
Hypertrophy of HA



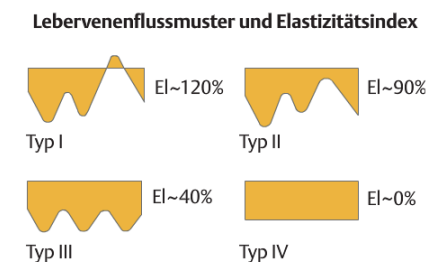
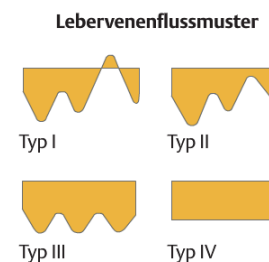
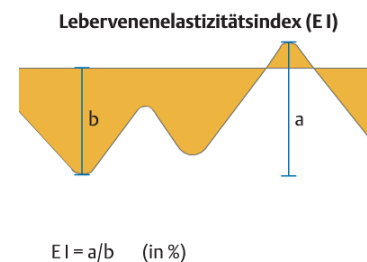
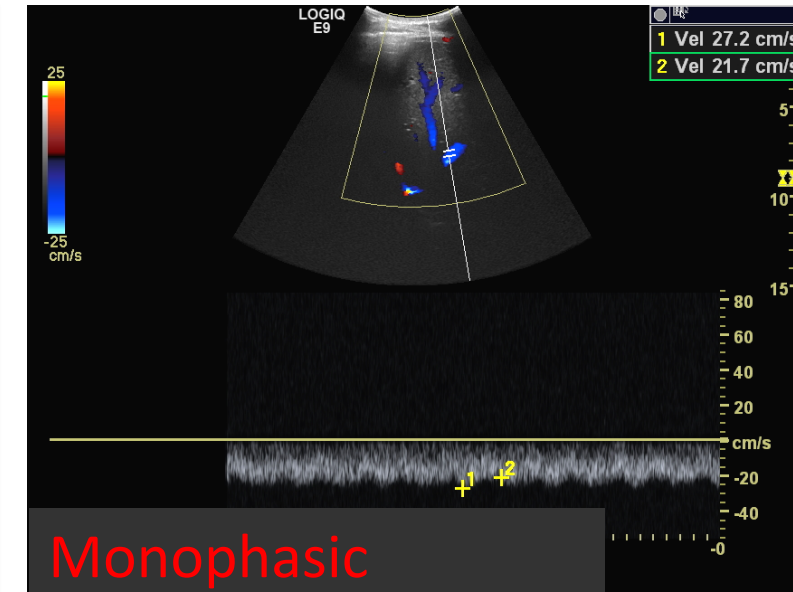
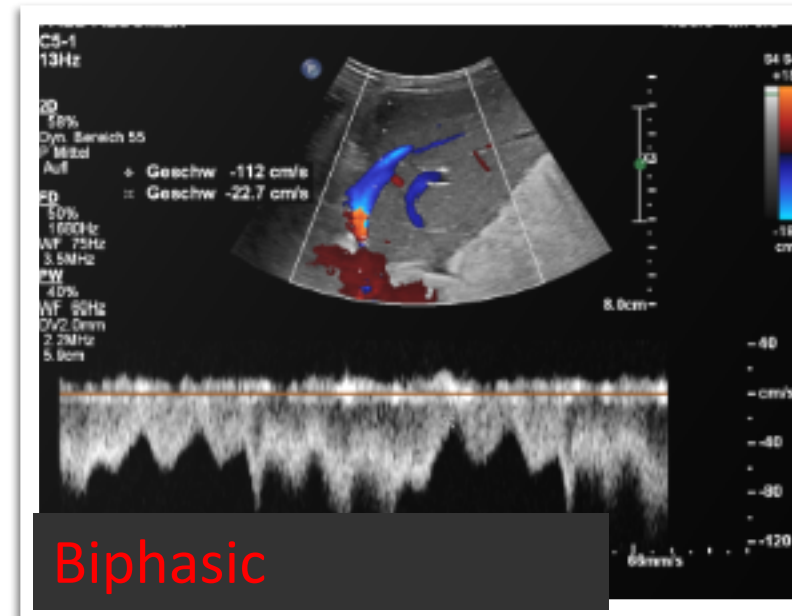
Retrograde PV flow

Liver veins (outflow)

- Triphasic or biphasic (normal)
- Monophasic flow („typical for cirrhosis“)
- But can be normal (especially infants)

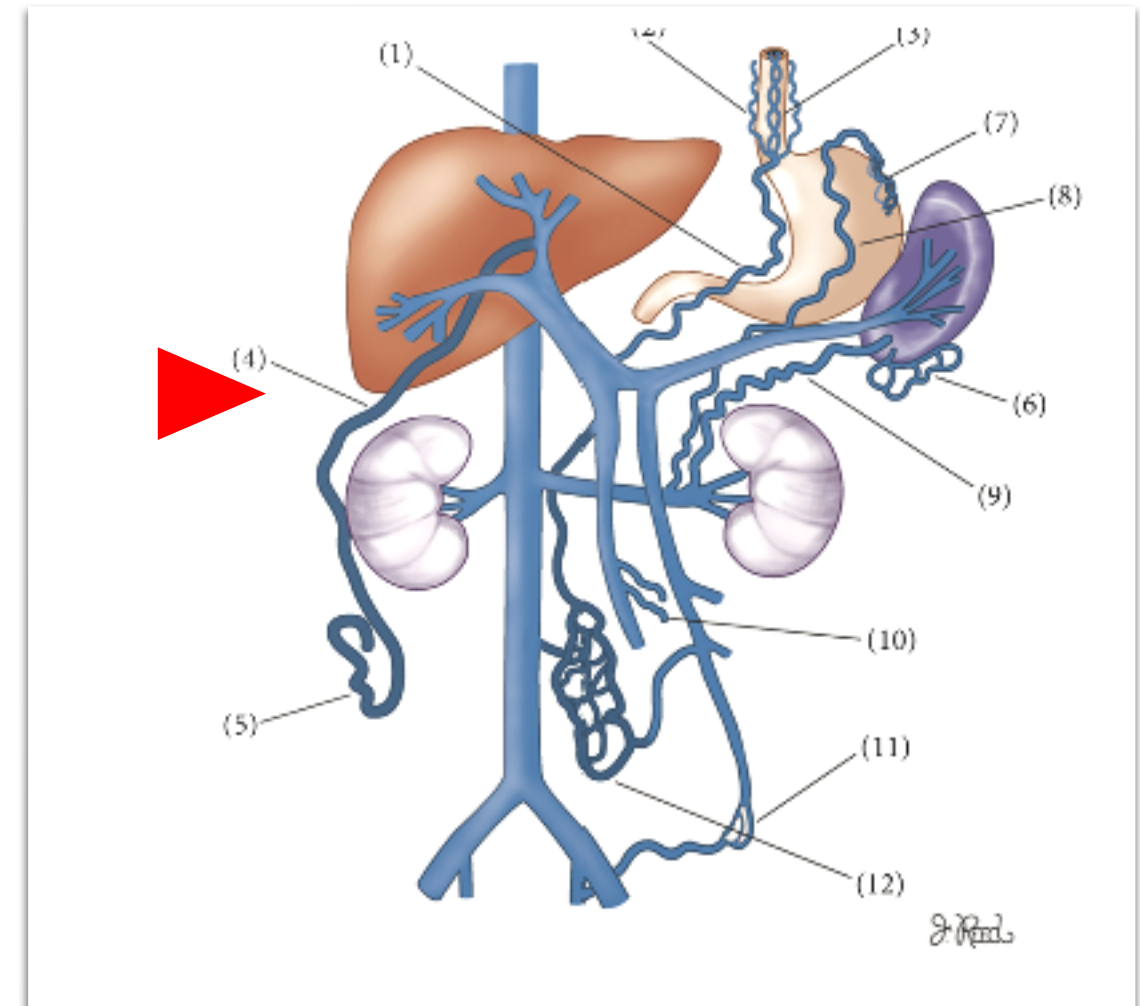
None of the flow indices has been shown be a sensitive predictor of cirrhosis

Don't use for staging!



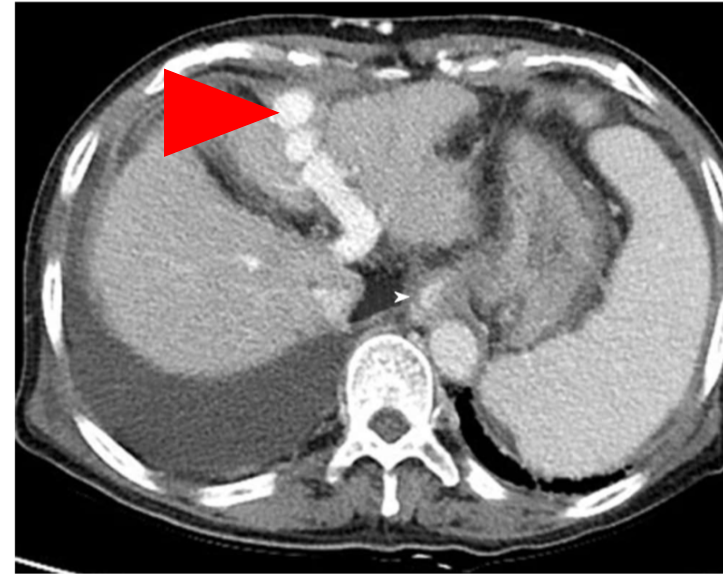
Portosystemic communications

- Reaction to increased intrahepatic pressure gradient
- Bypass of blood from the splenic and mesenteric circulation
- Intrahepatic or extrahepatic shunts:
 - Recanalized umbilical vein
 - Persisting ductus venosus
 - Venous splenic collaterals



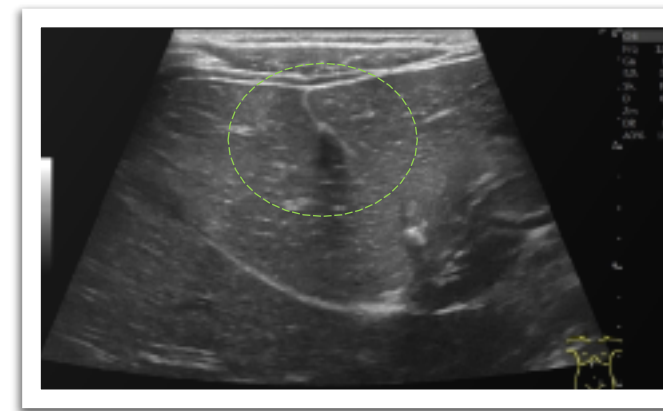
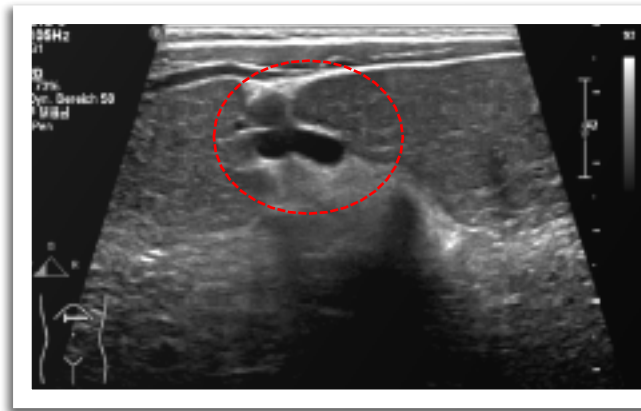
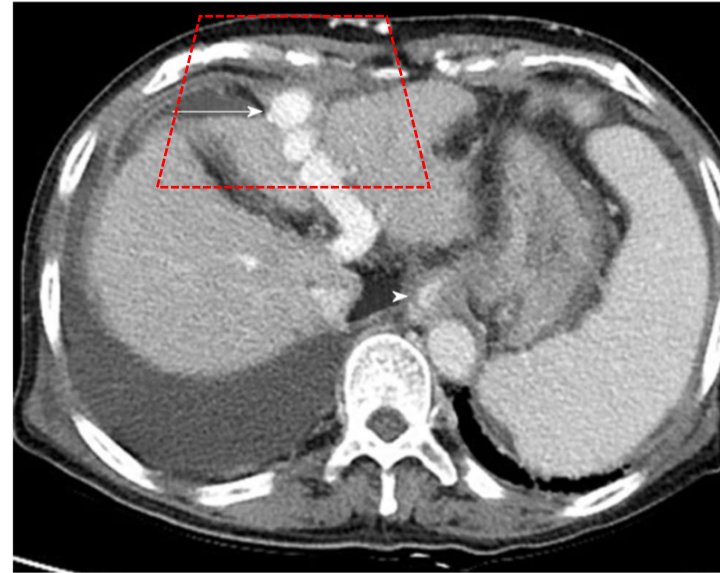
Re-opened umbilical vein

- Drains blood from the umbilical recess to the systemic circulation
- Can be easily identified by US
- Runs within the falciform ligament
- Hepato-fugal flow pattern



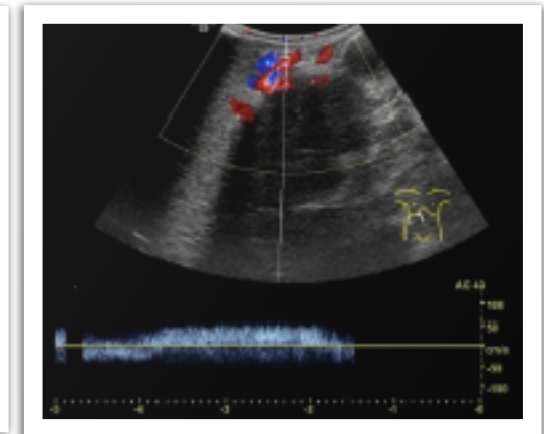
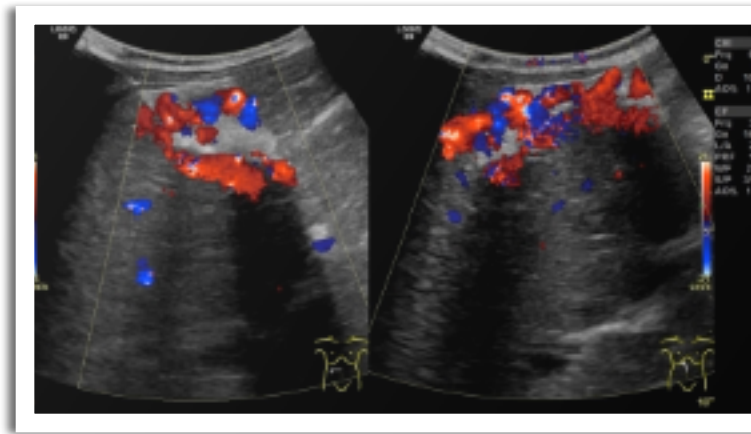
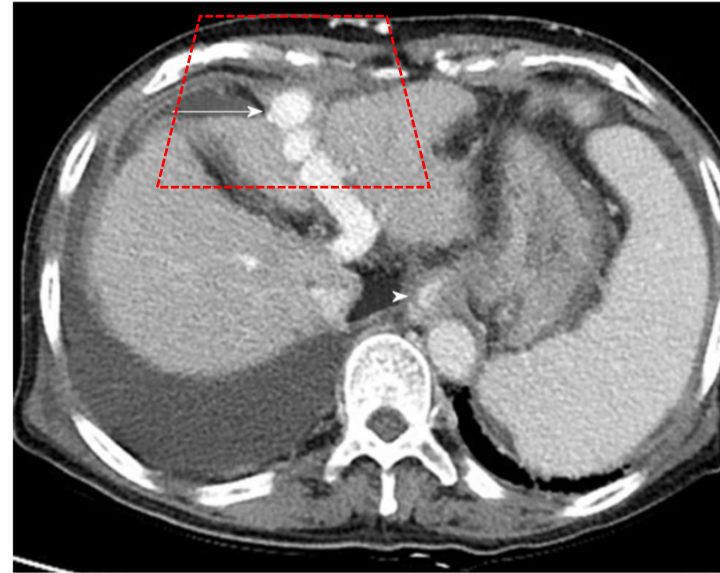
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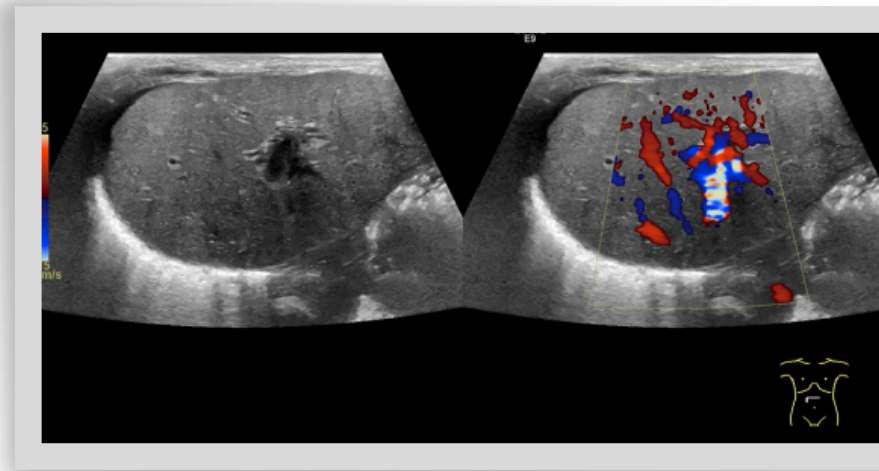
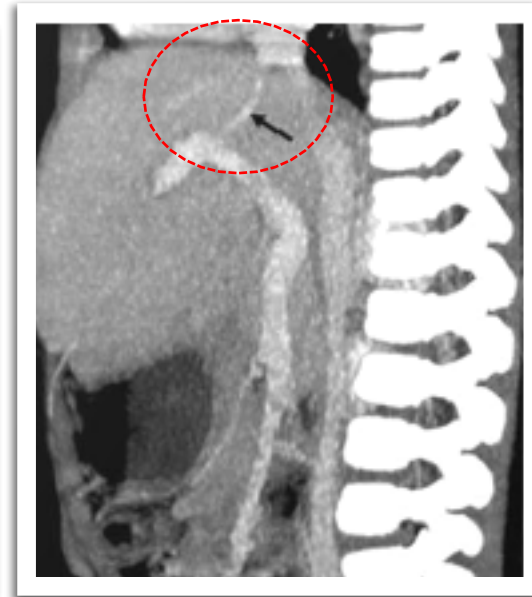
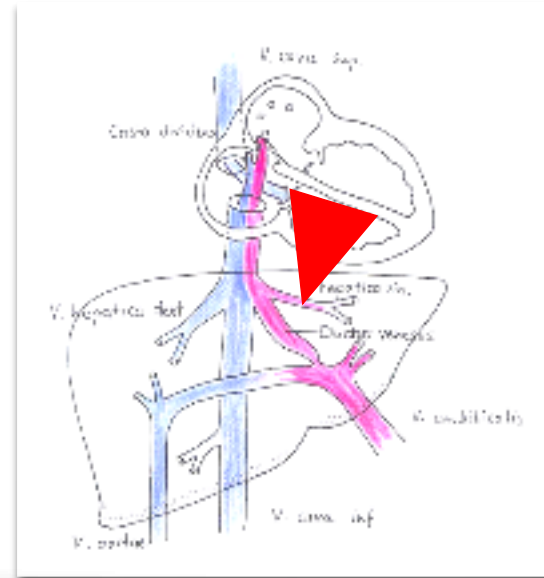
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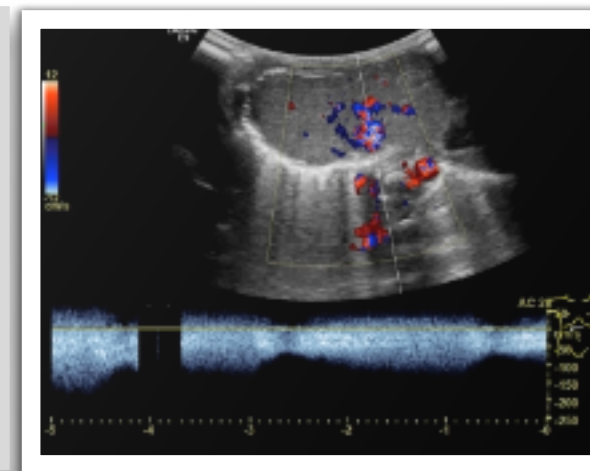
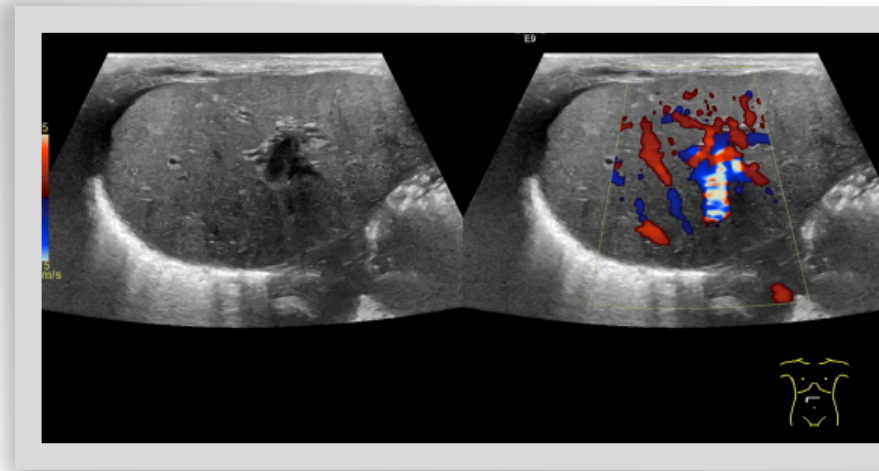
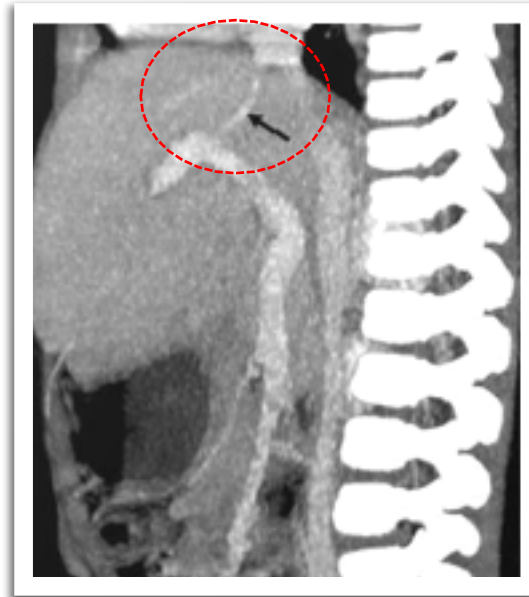
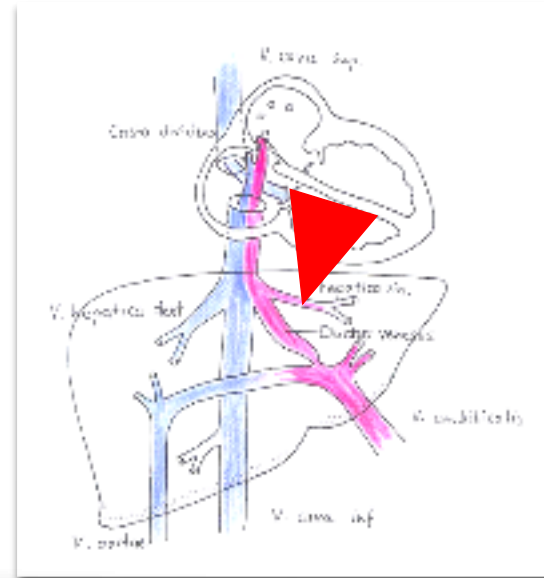
Persistent ductus venosus

- Part of fetal circulation
- From umbilical recess to venous confluence
- Closes shortly after birth (term < 2 weeks after birth)
- Persistent ductus venosus in neonatal hemochromatosis and other forms of diffuse liver disease



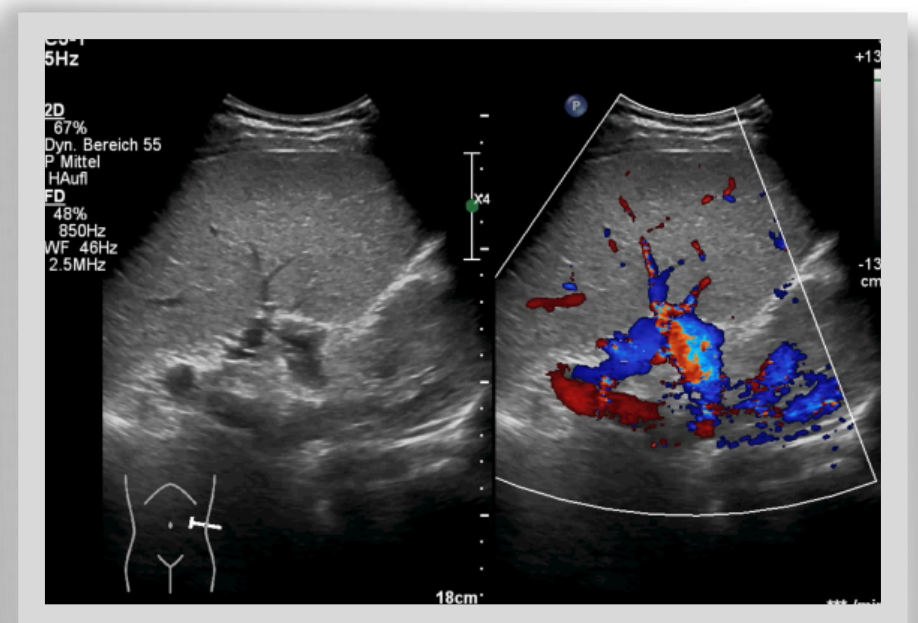
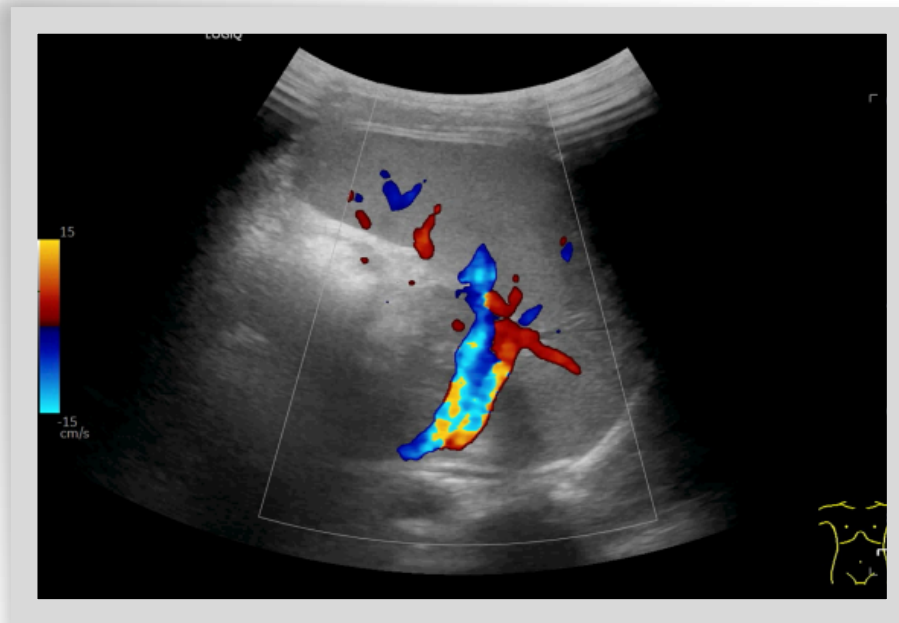
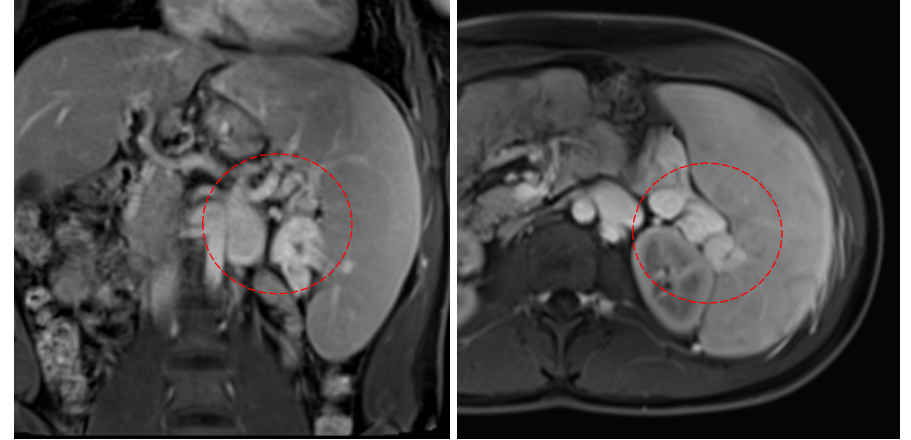
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Perisplenic collaterals

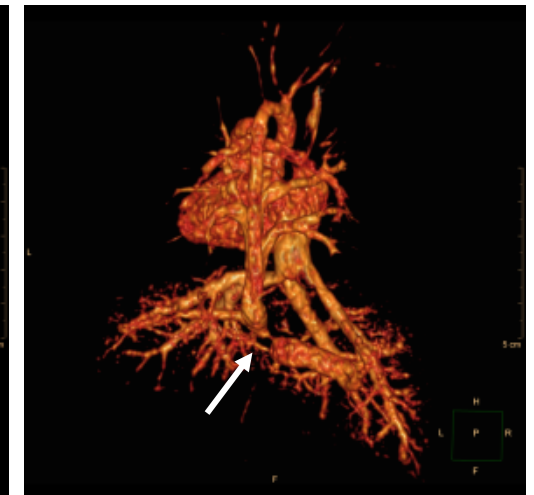
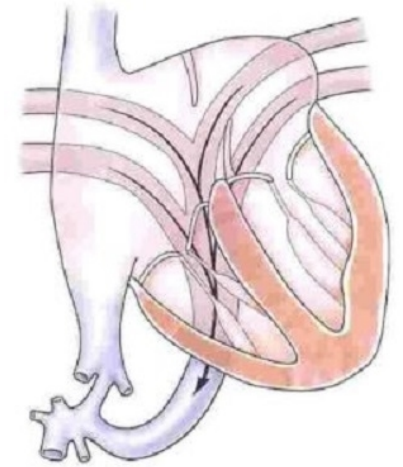
7 year old girl with hereditary
cholestasis syndrome



Complex vascular anatomy

- Cannot be fully delineated with US
- MRI or CT helpful
- Complex shunts
- High-resolution vascular anatomy to plan surgery (tumor, LTX)

Newborn ,
total anomalous
pulmonary venous return
(TAPVR),
Infracardiac type



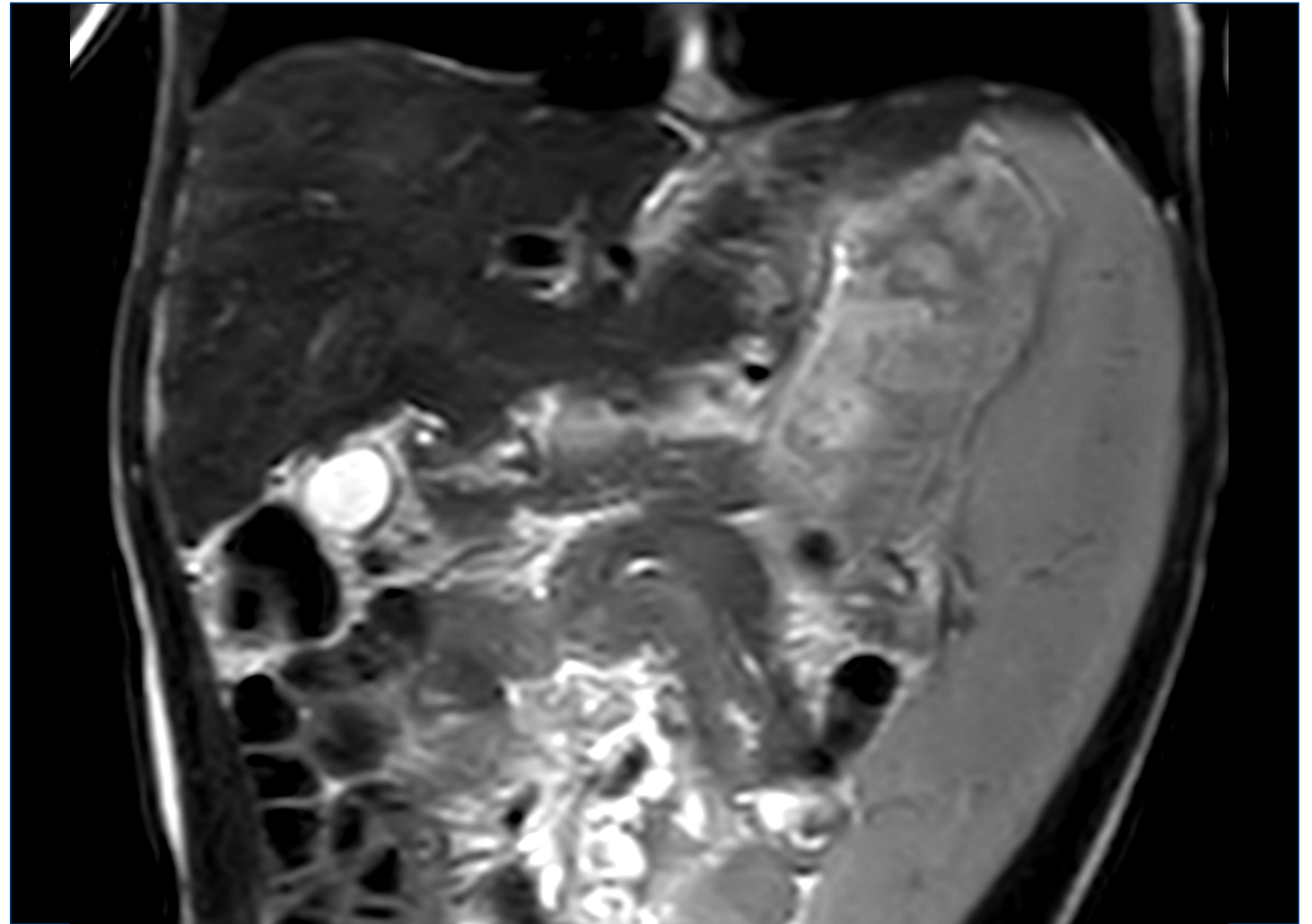
*Bove EL, Hirsch JC. Total anomalous pulmonary venous drainage and cor triatriatum. Operative Cardiac Surgery, London: 2004:581–592.

Functional hemodynamics 4D flow MRI

- 3 dimensional, time-resolved
- Visualize and quantify blood flow
- **dysproportional flow** can identify patients with esophageal varices and risk of bleeding

(Sens. 100%, Spec. 94%)

$$PV < SV + SMV$$



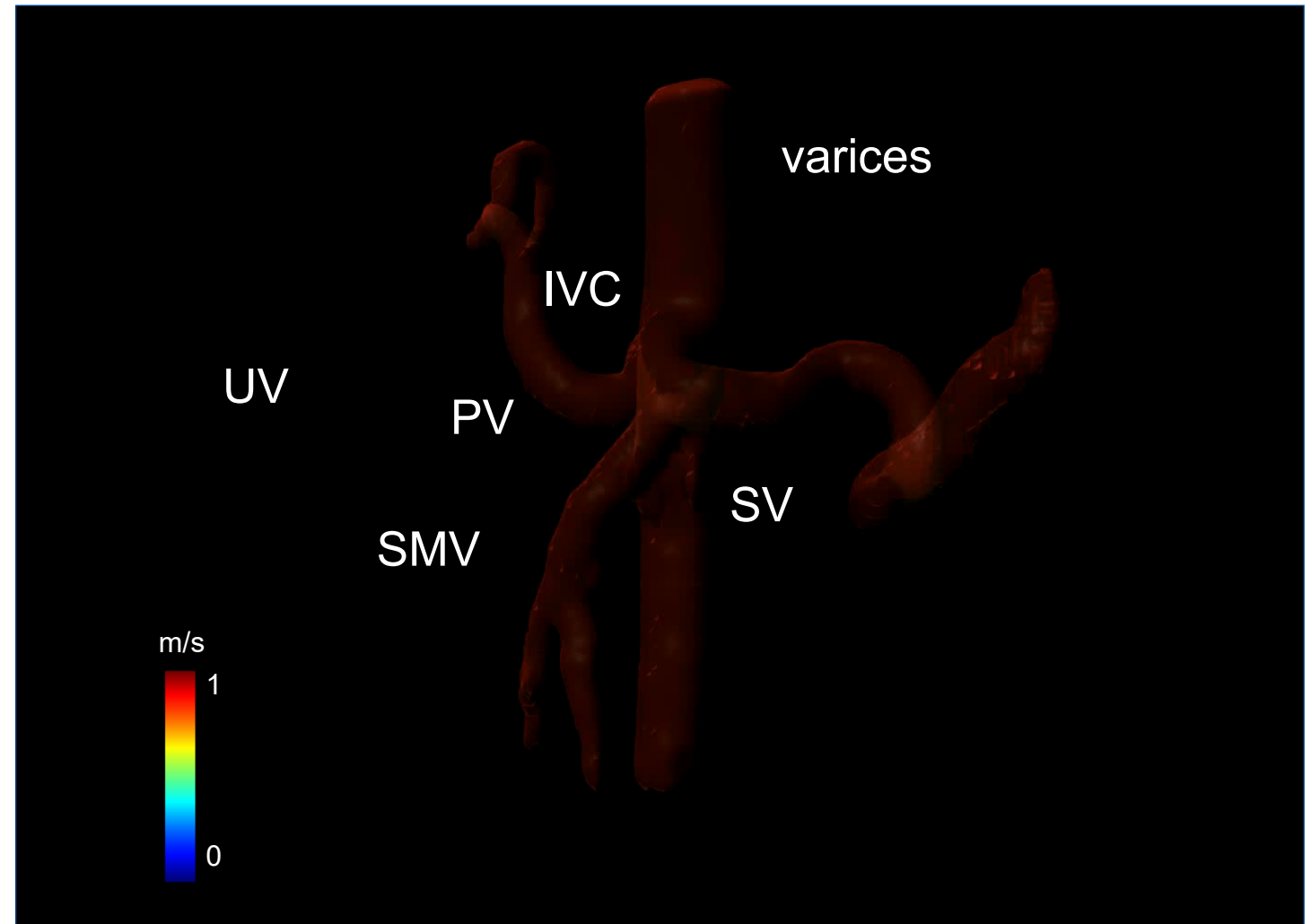
9 year old girl with nephronophtosis, hepatic fibrosis and esophageal varices

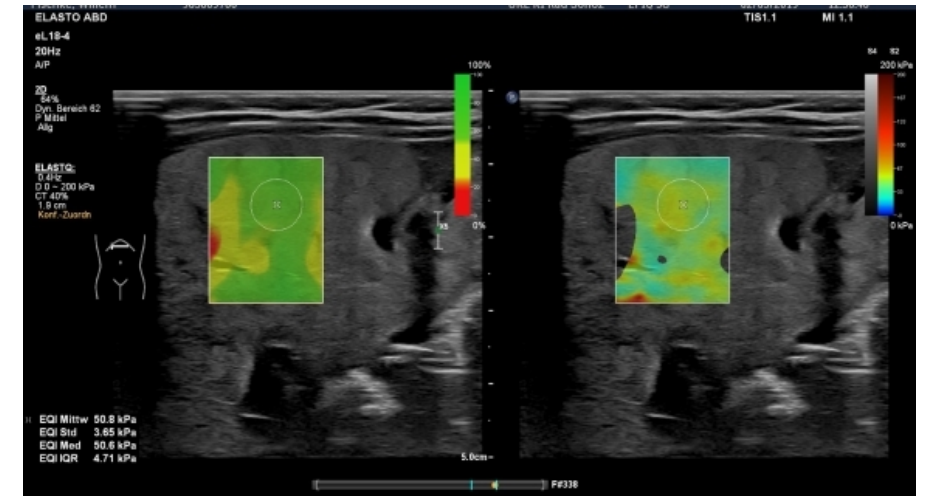
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Elastography

Fibrosis staging

Scoring systems

Histology

„Gold Standard“

Different fibrosis scores:

Metavir, Knoddel-Ishak Score, LAFs

Additional information (e.g., inflammation)

but

US guided liver biopsy (invasiv)

Small sample size

HISTOLOGIC SCORING SYSTEMS		
Stage	Metavir System [43]	Ishak System [44]
0	No fibrosis	No fibrosis
1	Periportal fibrosis expansion	Fibrous expansion of some portal areas, with or without short fibrous septa
2	Portal-portal septae (>1 septum)	Fibrous expansion of most portal areas, with or without short fibrous septae
3	Portal-central septae	Fibrous expansion of most portal areas with occasional portal-portal (P-P) bridging
4	Cirrhosis	Fibrous expansion of portal areas with marked bridging (P-P or portal-central P-C)
5	—	Marked bridging (P-P or P-C) with occasional nodules (incomplete cirrhosis)
6	—	Cirrhosis

Abraldes JG et al, Diagnosing and monitoring cirrhosis: Liver biopsy, hepatic venous pressure gradient and elastography. Gastroenterol Hepatol 2012;
Venturi, Am J Transplantation 2012

Fibrosis staging Elastography

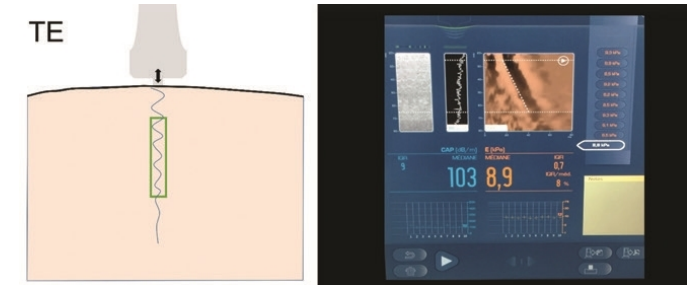
Pros

- Non-invasive*
- Repeatable (monitoring)
- Larger sample volume (2D SWE, MRE)

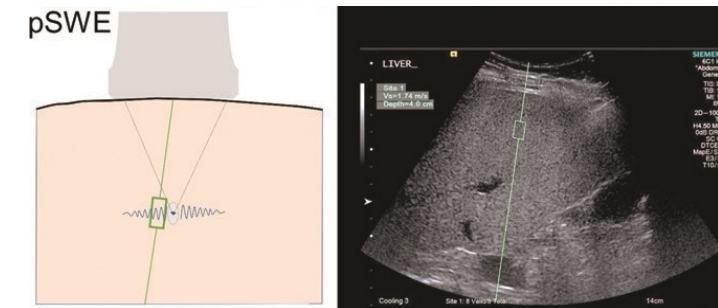
Cons

- Different methods (variation)
- In smaller children less well evaluated
- Higher failure rate
 - Small size
 - Movement (no-breathhold)

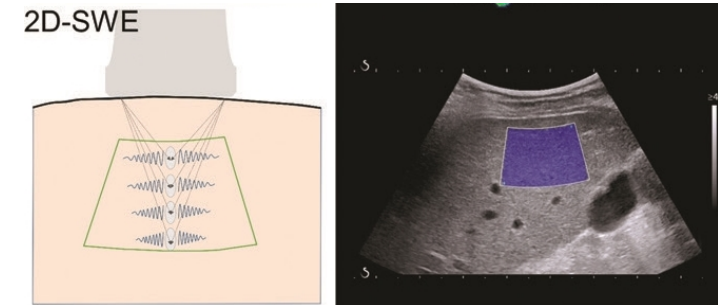
Transient Elastography



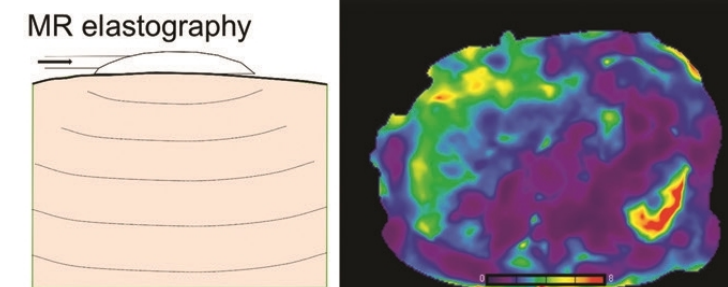
Point Shear Wave Elastography (pSWE)



2-dimensional SWE



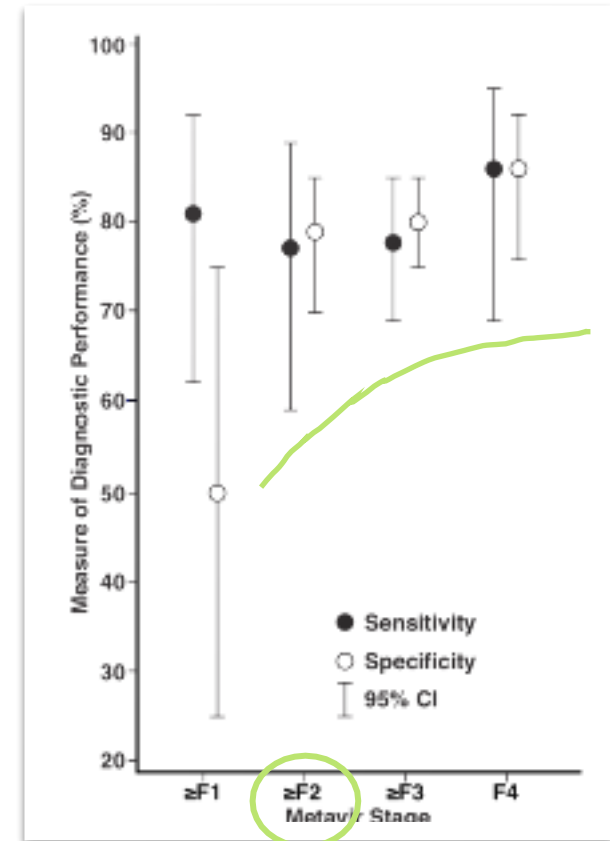
MRE



US Elastography

Children with chronic liver disease (mixed etiologies)

- Metaanalysis for Transient Elastography (TE)
- 723 children, 11 studies
- Significant fibrosis ($\geq F2$ METAVIR, $\geq F3$ Knodell–Ishak)
- Good Performance
- Cut off 10.6 kPa
(Sensitivity 90%, specificity 90%)



US Elastography

Children with chronic liver disease

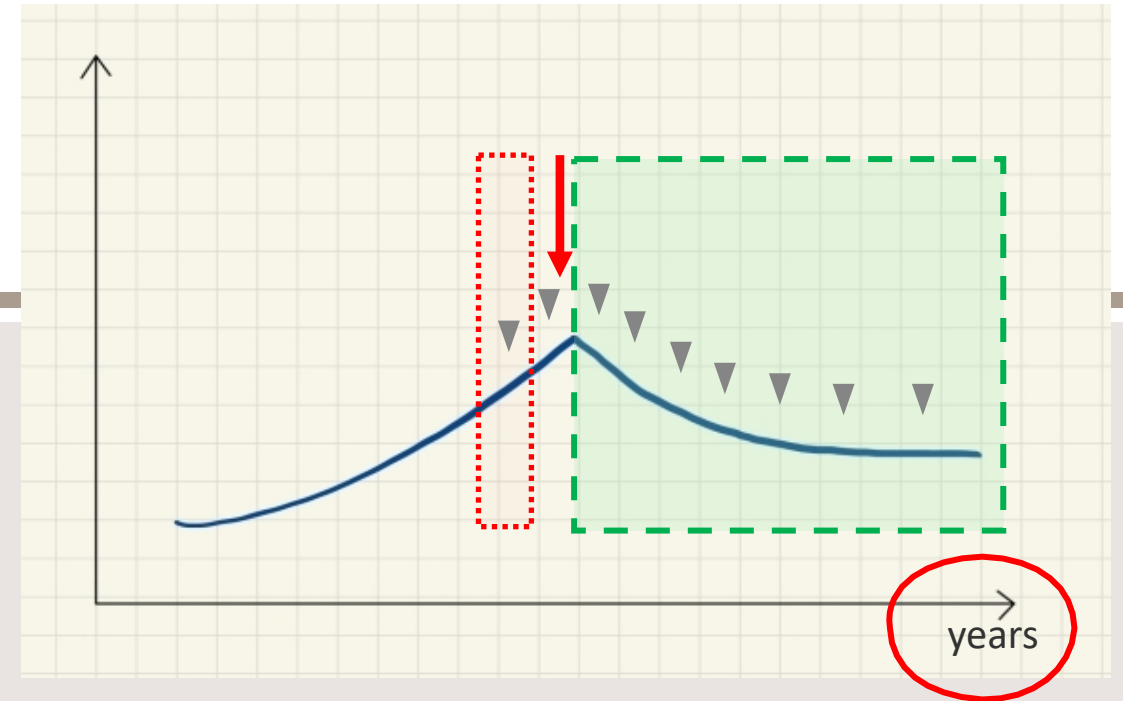
- Metanalysis for 2D-SWE vs. ARFI
- Detektion significant fibrosis ($\geq F2$)
- Good performance
- Cut off 9.4 kPa
(Sensitivity 81%, specificity 91%)

Subgroup	Number of studies	Number of studies per SWE technique*	Median cut-off value*	Range of cut-off value (kPa)	Meta-analytic summary est	
					Sensitivity, % (95 % CI)	Specificity, % (95 % CI)
Staging of fibrosis						
≥ F1	6	3	1.34 m/s	1.31–1.70 m/s	82 (70–90)	91 (71–98)
		3	7.90 kPa	5.1–10.6 kPa		
≥ F2	10	5	1.57 m/s	1.39–2.15 m/s	81 (71–88)	91 (83–96)
		5	9.40 kPa	6.70–12.14 kPa		
≥ F3	4	2	1.85 m/s	1.70–2.00 m/s	86 (70–94)	90 (46–99)
		2	14.20 kPa	10.8–17.60 kPa		
≥ F4	4	2	2.13 m/s	2.0–2.25 m/s	97 (50–100)	94 (85–98)
		2	23.94 kPa	23.48–24.40 kPa		
Modality of shear wave imaging						
ARFI	5		1.57 m/s	1.39–2.15 m/s	74 (59–85)	85 (71–93)
SSI	5		9.40 kPa	6.70–12.14 kPa	87 (75–93)	96 (91–98)

Normal values 3.4-6.6 kPa (variation, different US methods, different vendors).

Assessment of response

US Elastography

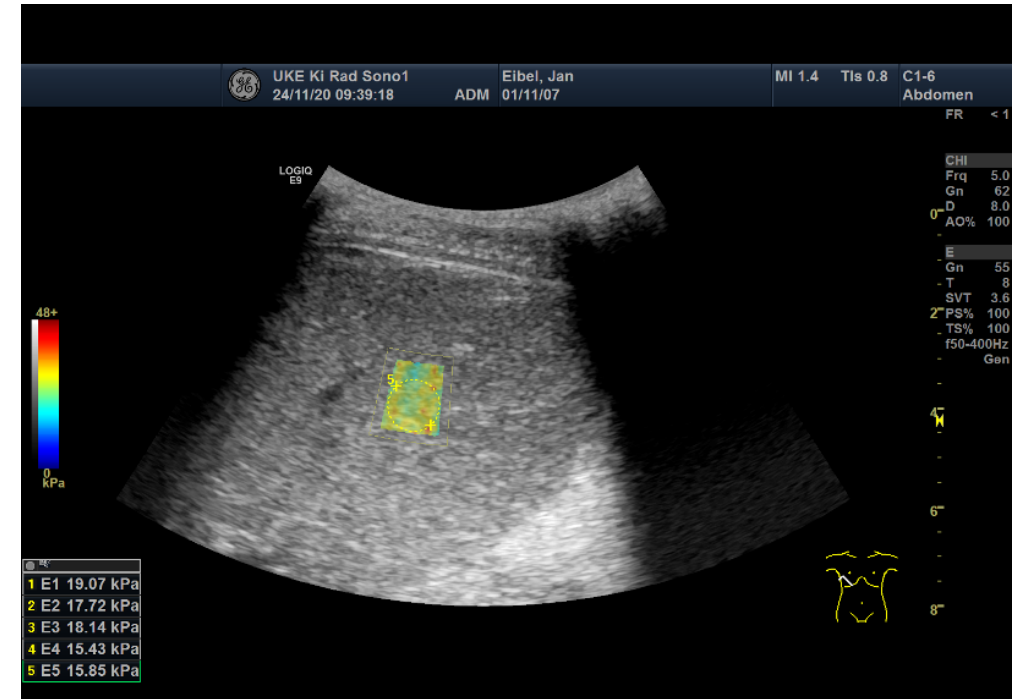


US Elastography

Autoimmune hepatitis (AIH)

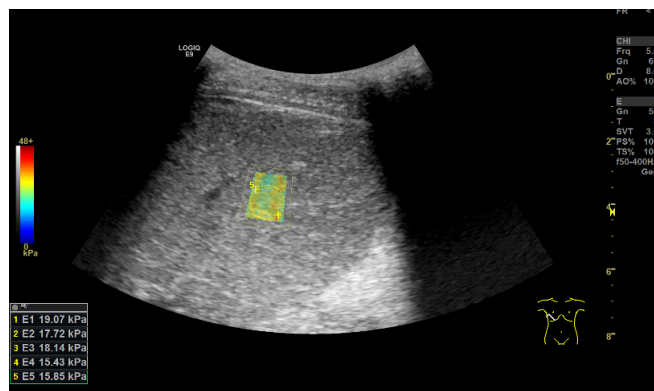
- In children often late diagnosis (adolescence)
- Autoimmune cellular infiltrates & significant fibrosis (biopsy)
- Liver stiffness at diagnosis reflects inflammatory & fibrotic changes
- After 6 mo. of treatment & biochemical remission liver stiffness reflects true fibrotic changes

13-year-old boy with AIH

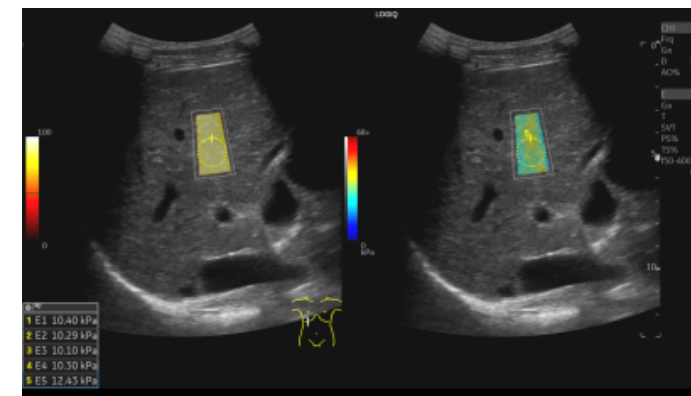
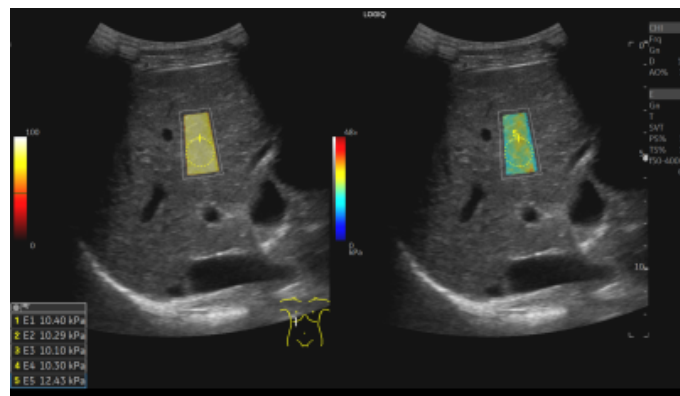


US Elastography

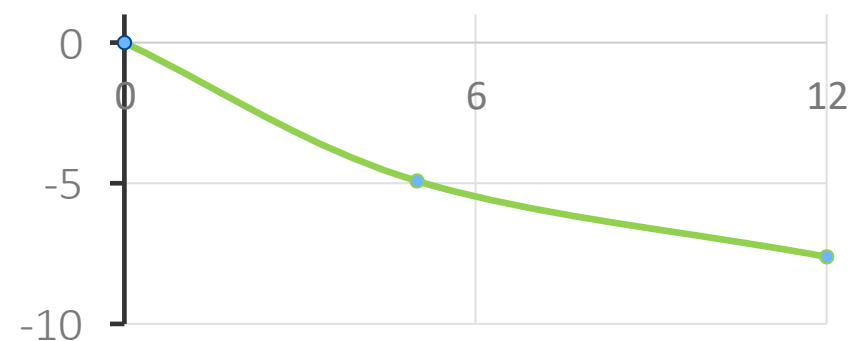
13 y/o boy, AIH



Laboratory:
Complete biochemical remission



Delta of liver stiffness

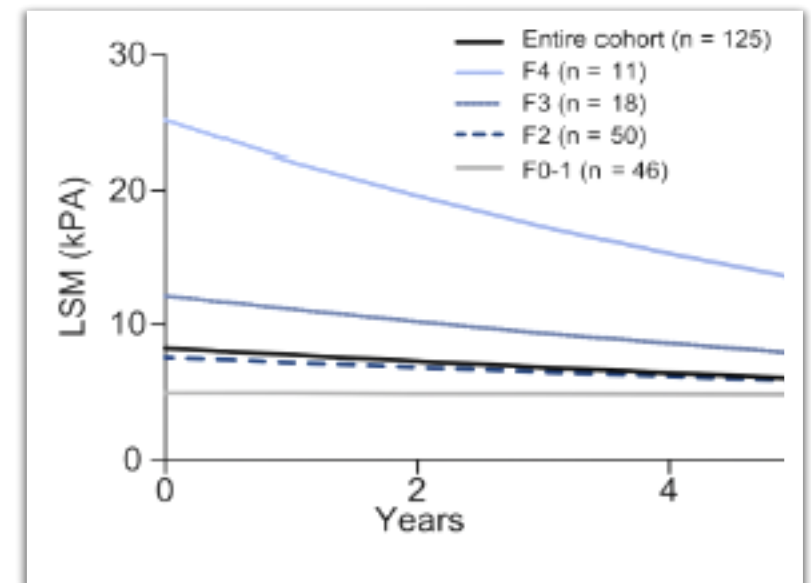
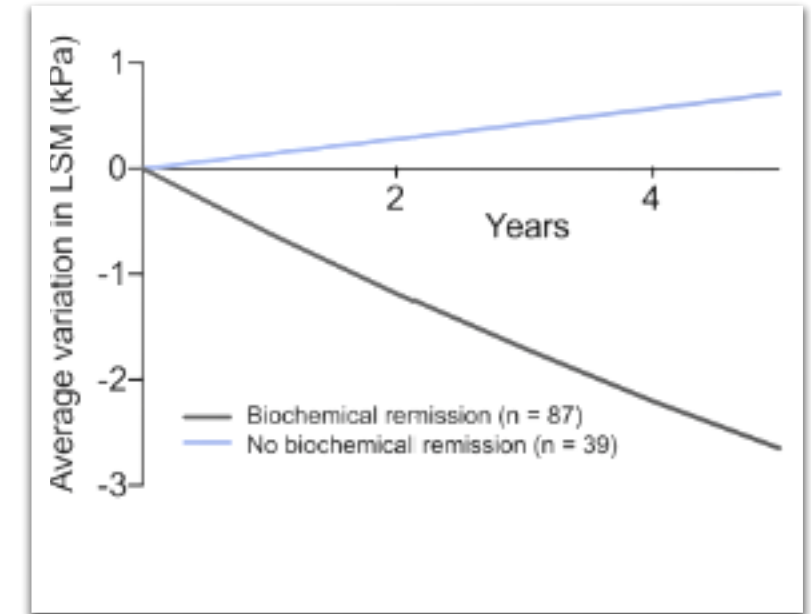


US Elastography

Autoimmune hepatitis (AIH)

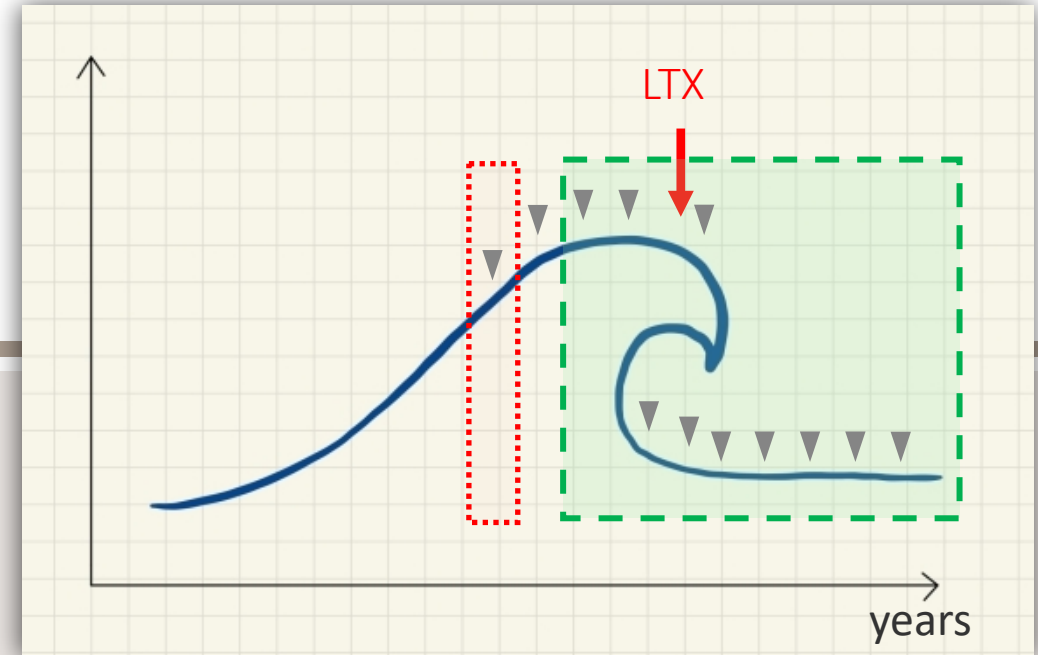
- Adult patients with AIH
- Follow-up with biopsy and TE
- **Full biochemical remission leads to a reduction of liver stiffness and regression of fibrosis**
- US elastography can identify patients with residual inflammatory activity

Delta of liver stiffness is a very sensitive marker for response



Disease evolution (PH)

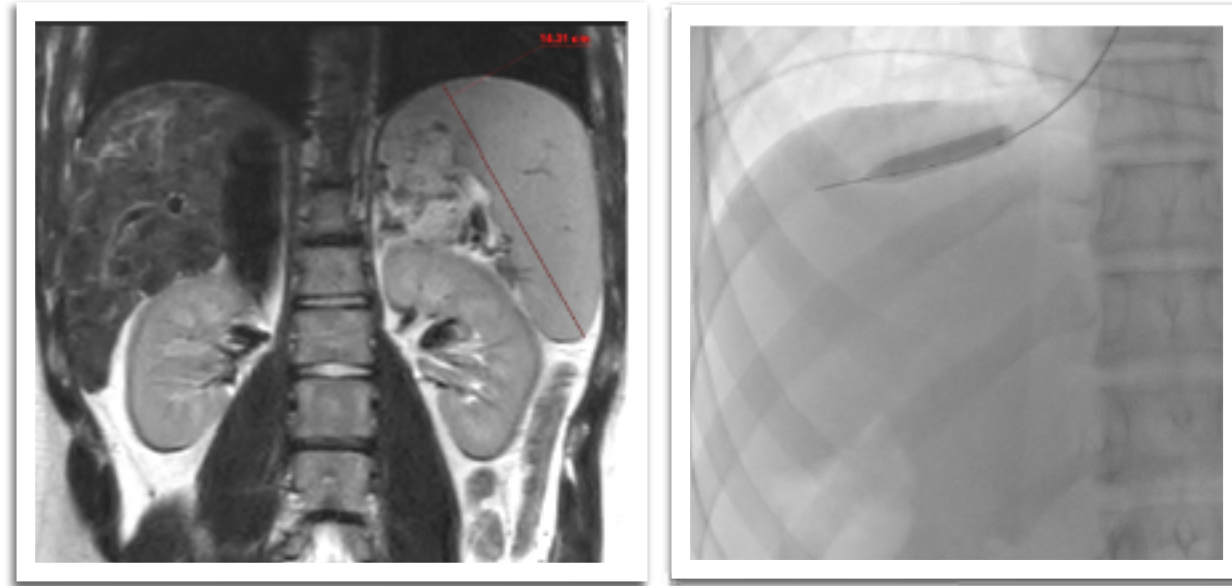
Elastography



Clinical significant portal hypertension (CSPH)

- Long-period of compensated disease (low symptoms)
- Difficult to predict decompensation (esophageal varices, bleeding, and HCC)
- Portal hypertension is best predictor
- Measured invasively by HVPG (rarely performed in children to assess clinical situation)

15 year-old boy with cirrhosis and splenomegaly



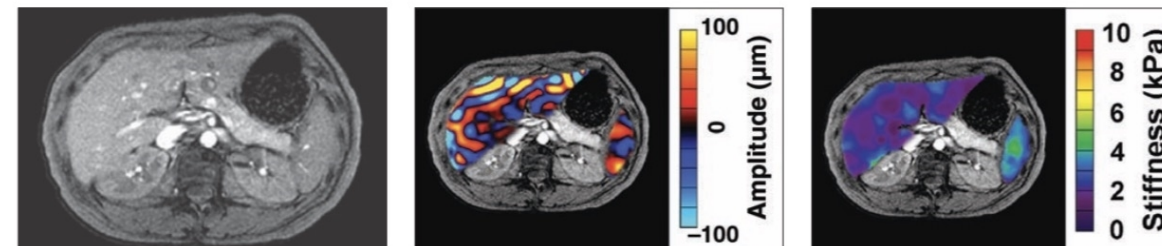
Search for *non-invasive* surrogate marker:

Platelet/spleen ratio, LSM; spleen diameter/platelet ratio score (LSPS), liver and spleen elastography

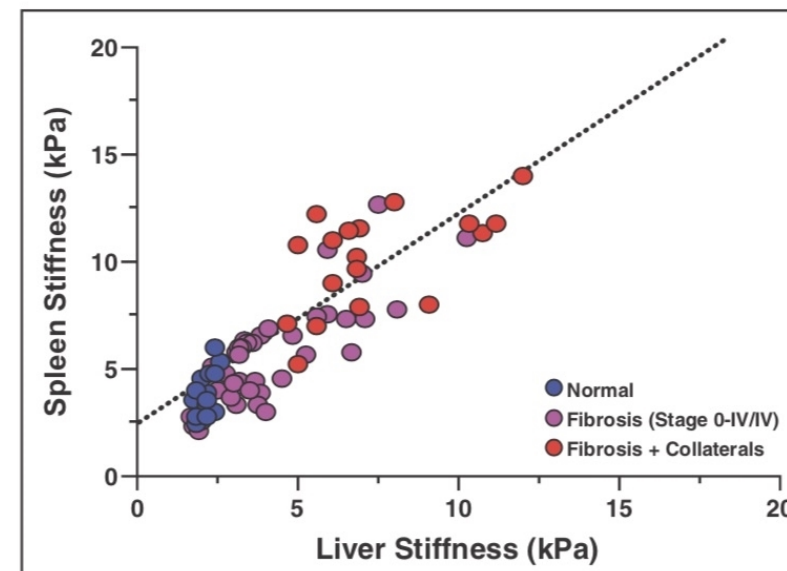
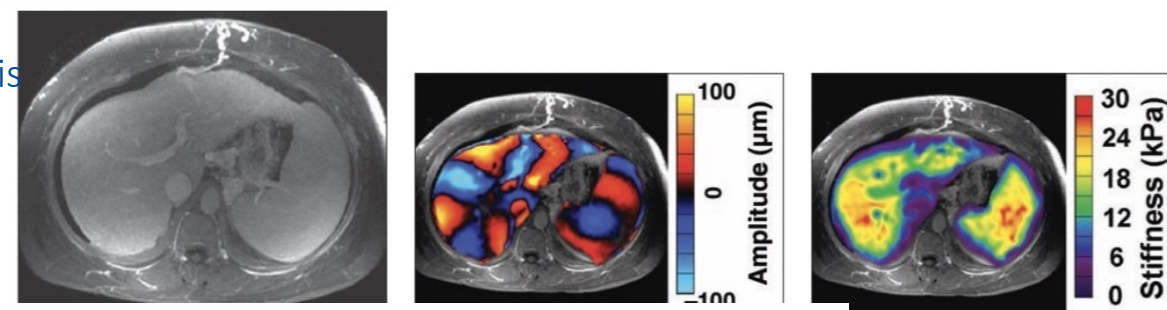
Liver stiffness and Spleen stiffness

- Proof of concept MRE Study
- Patients with hepatic fibrosis and hepato-venous collaterals
- Higher liver and spleen stiffness
- Splenic congestion & fibrosis

28 year old volunteer



54 year old with cirrhosis

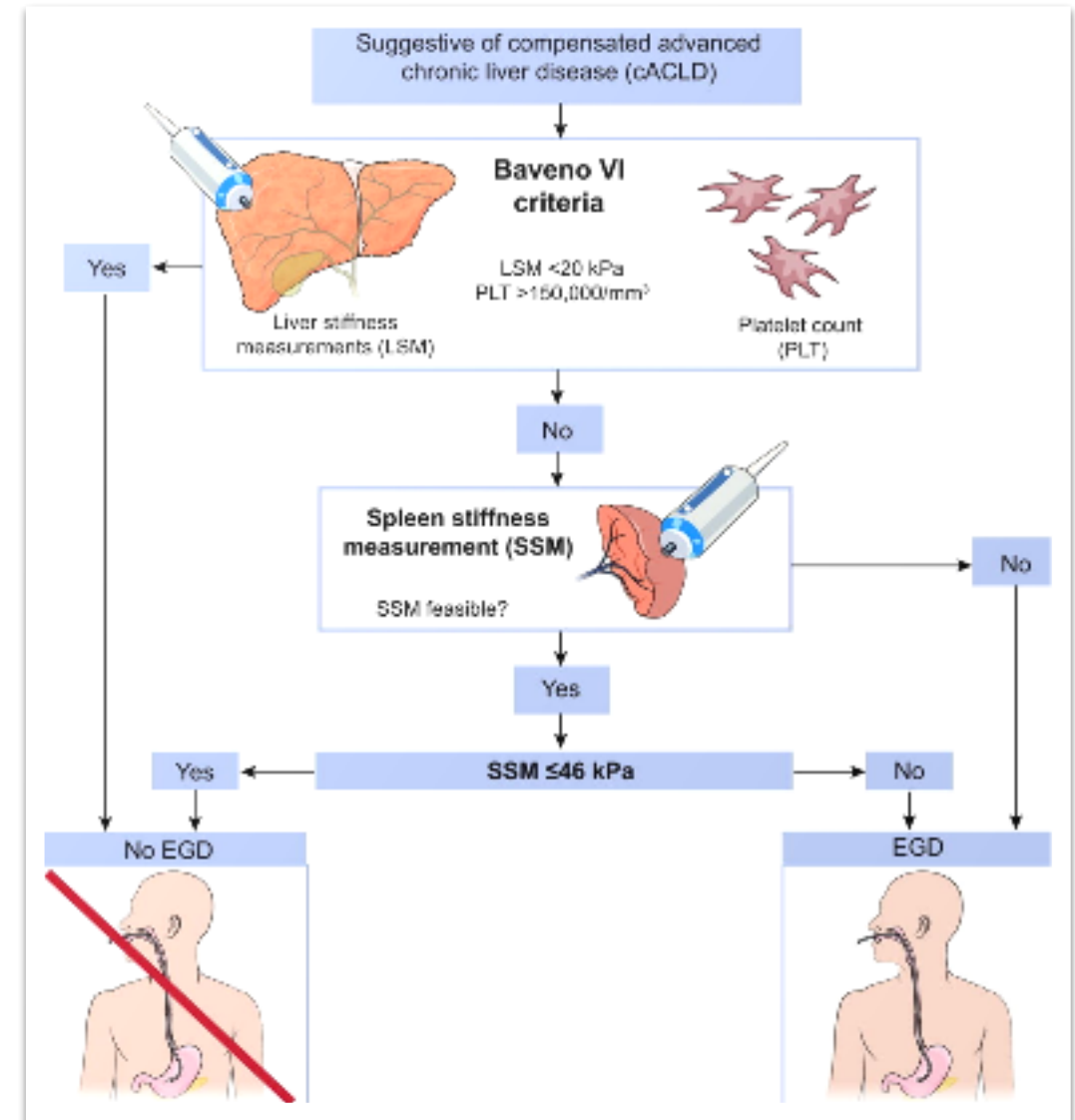


Talwalkar JA et al. Feasibility of In Vivo MR Elastographic Splenic Stiffness Measurements in the Assessment of Portal Hypertension. *AJR* 2009; 193:122–127

Spleen stiffness & liver stiffness Prediction of EV

- Adults
- Method: **Transient Elastography**
- High predictive value for absence of EV

- Liver stiffness < 20 kPa, PLT > 150 tsd
- Spleen stiffness < 46 kPa



Spleen stiffness & liver stiffness Predict EV

Method: Transient Elastography (TE)

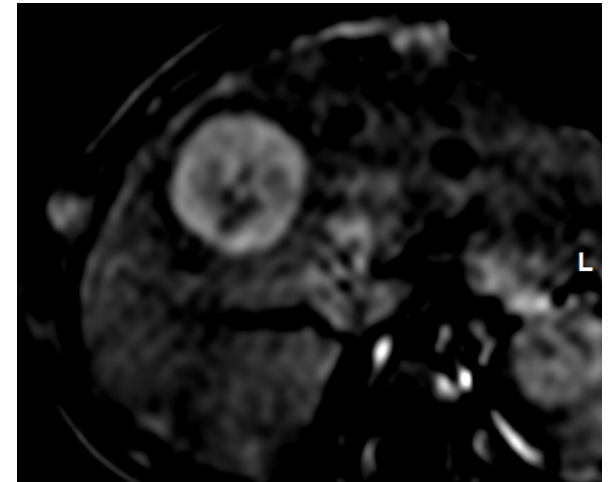
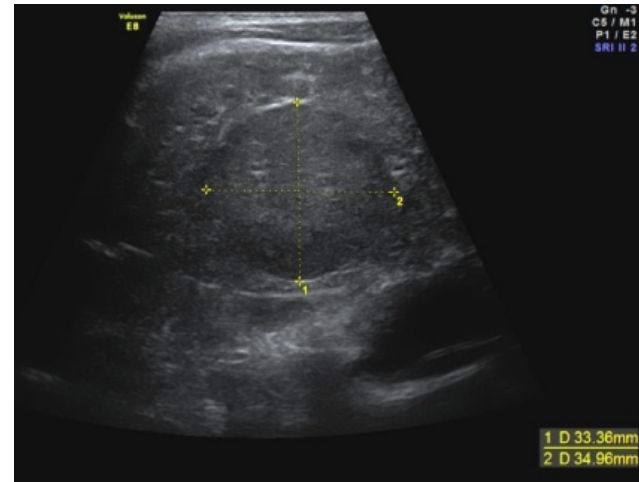
67 children with

- Chronic liver disorders (n=52)
- Portal venous thrombosis (n=15)

Good Performance to predict EV

Spleen stiffness better than liver stiffness

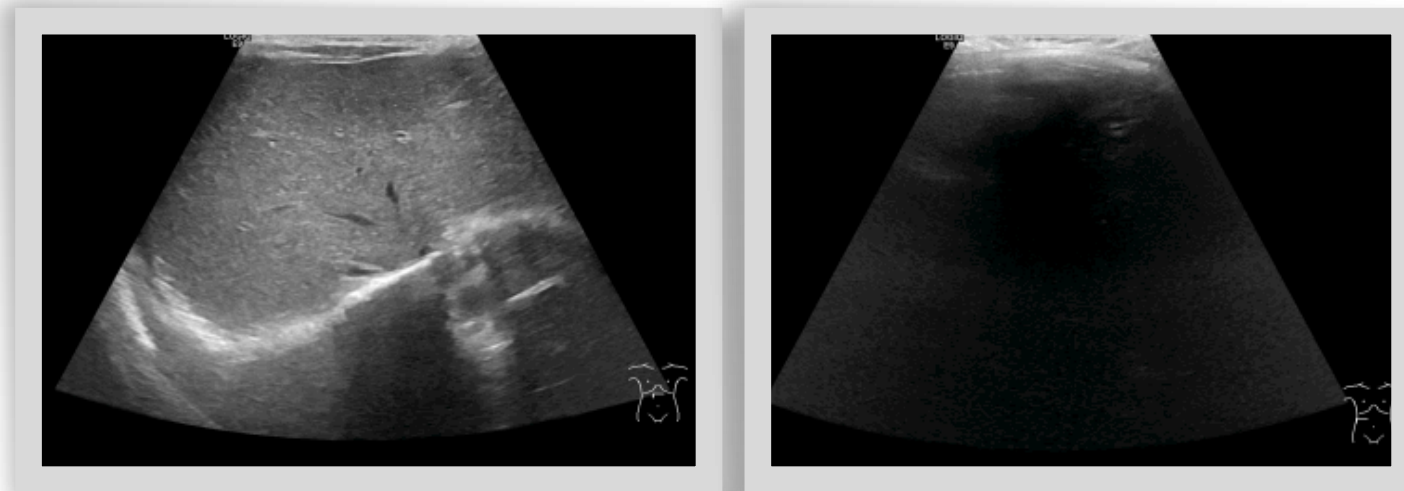
All	Cut-off	Sensitivity, %	Specificity, %
Chronic liver disease			
SSM	38.0 kPa	77	87
LSM	26.2 kPa	64	87
CPR	102.4	55	74
KVaPS	74.5	55	61
Portal vein thrombosis			
SSM	16.8 kPa	100	100
LSM	3.0 kPa	82	67



Lesion characterization

Nodular lesions

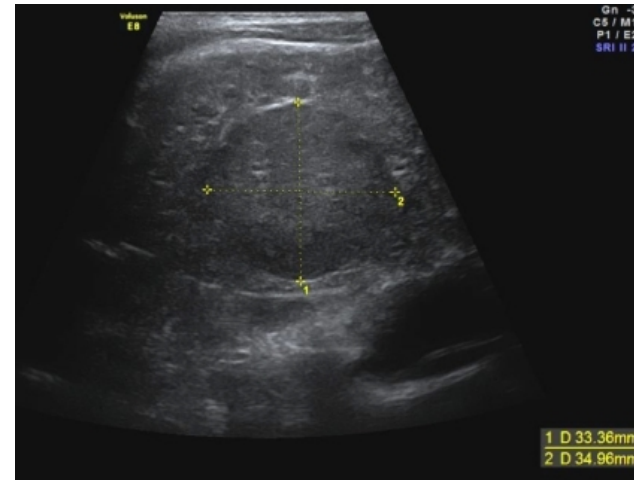
- Key feature of cirrhosis
- Regenerative nodules, dysplastic nodules, HCC
- In 25-40 % of children with HCC, etiology is linked to underlying cirrhosis
- High risk for HCC in children with
 - PFIC Type 2
 - Tyrosinemia Type 1 (untreated)
 - Glycogen-storage disease



Nodular lesions

Conventional US

- Used for screening and follow-up
- Children at risk every 6-12 months (plus AFP)
- High sensitivity for detection of nodules in experienced hands
- No safe differentiation of reg. nodules from HCC
- CEUS for suspicious lesions (max. 2 nodules)

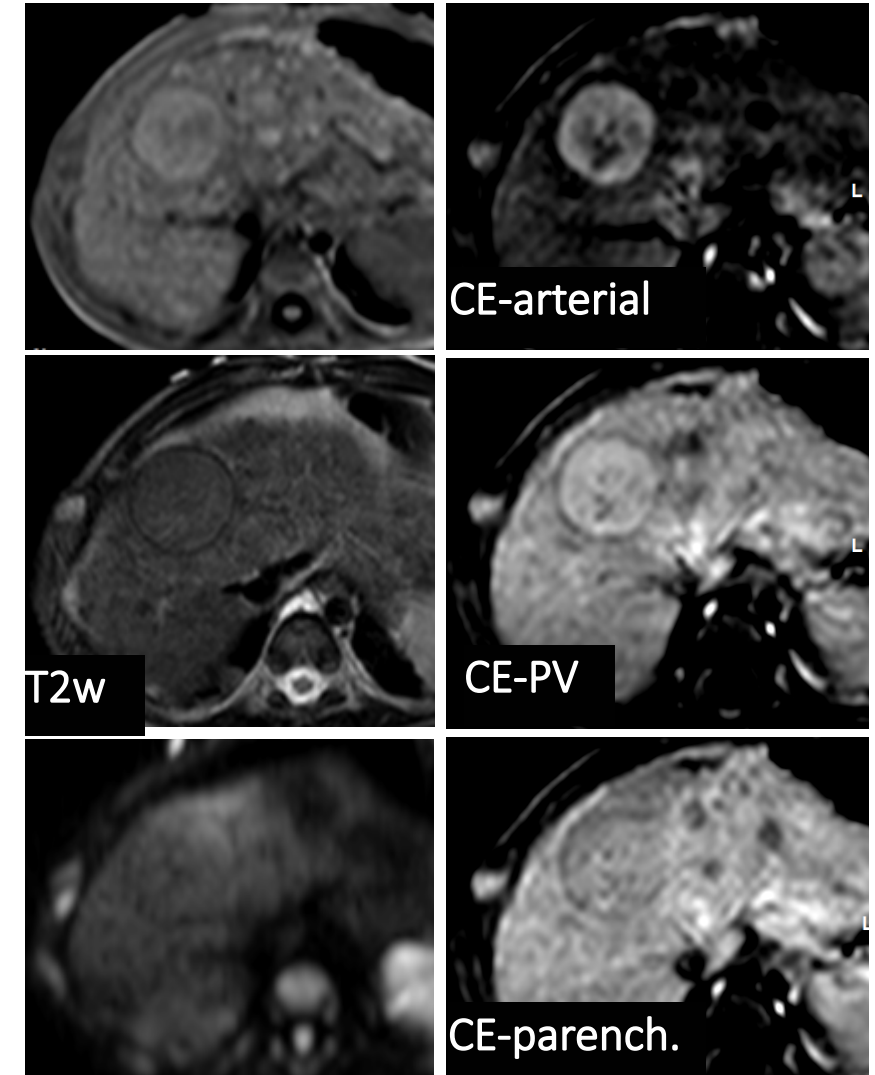


Nodular lesions

MRI

- If > 2 lesions or high index of suspicion
- Specific hepatocyte phase can identify additional lesions and contributes to risk stratification
- Consensus guidelines strongly recommend use of HBA
 - GdEOB-DTPA, Eovist/Primovist
 - Gd-BOPTA, MultiHance

(may be off-label in several countries)



	US	MRI	CT
Non-invasiveness	✓ ✓	✓✓	
Repeatability (screening, monitoring)	✓ ✓	✓✓	
Multiparametric imaging	✓ ✓	✓✓	✓
- Lesion detection	✓	✓	✓✓
- Tissue characterization	✓	✓	✓
- Vascular anatomy and flow	✓	✓	✓ ✓

Role of imaging in the diagnostic pathway –

US, CT, MRI?

Modalities

US

- Primary imaging tool
- Baselayer for screening & monitoring
- Specific, multiparametric imaging tool

	US	MRI	CT
<i>Non-invasiveness</i>	✓ ✓	✓✓	
Repeatability (screening, monitoring)	✓ ✓	✓✓	
Multiparametric imaging	✓ ✓	✓✓	✓
- Lesion detection	✓	✓	✓✓
- Tissue characterization	✓	✓	✓
- Vascular anatomy and flow	✓	✓	✓ ✓

Modalities

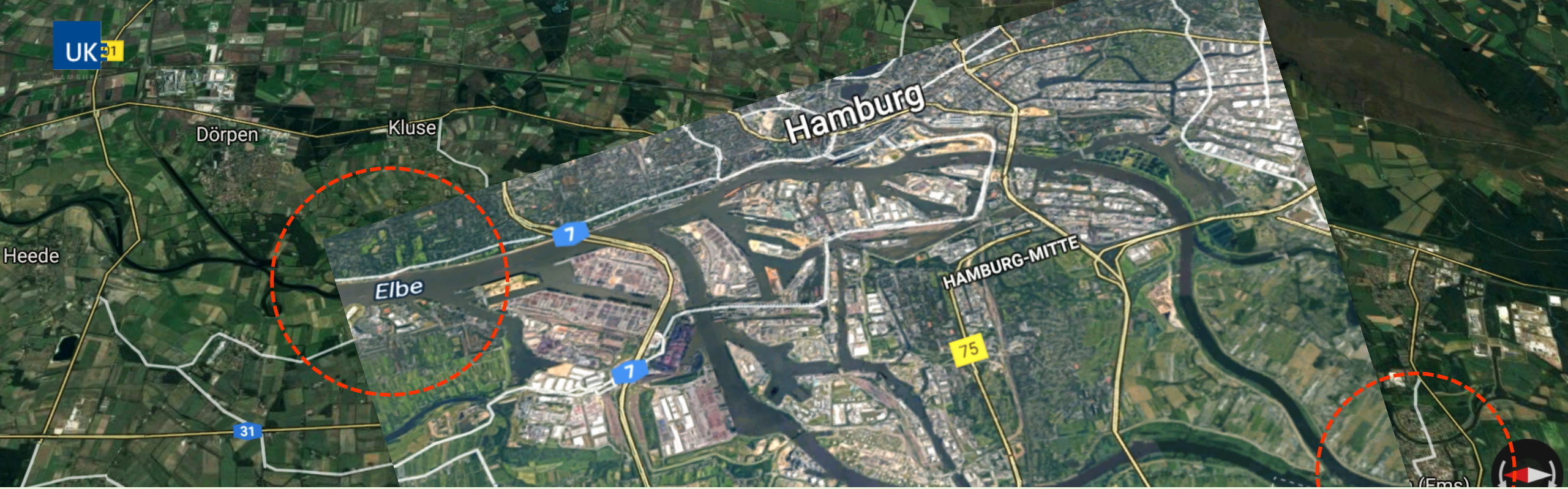
US

- Primary imaging tool
- Baselayer for screening & monitoring
- Specific, multiparametric imaging tool

MRI and CT

- Used second-line
- Lesion and tissue characterization (MRI)
- High-resolution vascular anatomy (CT)
- Functional tool to assess complex hemodynamics (MRI)

	US	MRI	CT
<i>Non-invasiveness</i>	✓ ✓	✓✓	
Repeatability (screening, monitoring)	✓ ✓	✓✓	
Multiparametric imaging	✓ ✓	✓✓	✓
- Lesion detection	✓	✓	✓✓
- Tissue characterization	✓	✓	✓
- Vascular anatomy and flow	✓	✓	✓ ✓



Thank you for your participation!