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Ultrasound of the liver

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Content

Topographic Remarks

The liver is located intraperitonealy, and under the right (hemi-)diaphragm but can also extend across the midline reach to the left hemi-diaphragm and to the spleen in some cases. The liver is fixed to the diaphragm by the pars affixa and to the ventral abdominal wall by the ligamentum falciforme (falciform ligament) and its strong margin, the ligamentum teres hepatis. The minor omentum consists of the ligamentum hepatogastricum and of the ligamentum hepatoduodenale. The hepatoduodenal ligament carries three vessels – two containing blood (the portal vein and hepatic artery), and one carrying bile (common bile duct). The further courses of these three vessels is mainly parallel (Glisson`s triad).

The structures of the liver hilum (porta hepatis) are accompanied by a number of (in relation to the portal vein) ventrally and dorsally located lymph nodes which routinely can routinely be demonstrated by ultrasound (US). However,; lymphatic vessels are too small to be visualised on tiny, however, for ultrasoundd visibility. The liver has three main veins (hepatic veins) – left, middle and right one – which drain the liver blood to the retroperitoneally located inferior vena cava. The inferior vena cava is variably surrounded by liver parenchyma. The organs and structures surrounding the liver are the organs of the peritoneal cavity andbut also pleural and pericardial structures. Neighbourhood structures adjacent to the liver are numerous, including (clockwise) basal lung proportions separated by the muscular layers of the right diaphragma (and more or less extensively also of the left diaphragma too), heart, stomach, intestine (e.g., upper duodenal loop and right colonic flexure), abdominal aorta, inferior vena cava, right adrenal gland and right kidney.

Interposition of the colon between liver and the anterior abdominal wall can prevent the sonographic approach to the right liver lobe in case of Chilaiditi’s syndrome. In the case of complete or incomplete situs inversus the topographic relations are inverted.

Liver anatomy

Anatomic orientation

Liver anatomy is defined by ligaments and fissures as well as by the vascular architecture: branches of the hepatic artery, portal vein, and bile ducts in their parallel course define the centers of liver segment anatomy.

Liver segment anatomy

A simplified anatomy divides into the larger right lobe (including segment V, VI, VII, VIII), the left lobe with its medial (IVa,b) and lateral segments (II, III), and the caudate lobe (I).

Couinaud classification

Liver segment anatomy is explained by the widely accepted architecture described by Couinaud [(16;17)]. The Couinaud classification, modified by Bismuth (segment IVa, b), is based on 8 segments, each of which has its own arterial and portal venous vessel architecture (Glisson`s triad) indicating vascular inflow, outflow, and biliary drainage [(9;10)]. Because of this division into self-contained units, each can be resected (alone or in groups) without damaging those remaining as the vascular inflow, outflow and biliary drainage is preserved. Depending on the 3D volume orientation of the liver (longitudinal or oblique orientated) interpretation of Couinaud classification unfortunately finds some inconsistency in literature. While the portal vein plane has often been described as transverse, it may be oblique since the left branch runs superiorly and the right branch runs inferiorly. In addition to forming an oblique transverse plane between segments, the left and right portal veins branch superiorly and inferiorly to project into the centre of each segment.

Liver segment nomenclature

In a clockwise fashion starting with caudate lobe as segment I [video caudate lobe], left posterolateral segment is number II, left anterolateral segment III, left superomedial segment IVa, left inferomedial segment IVb, right anteroinferior segment V, right posteroinferior segment VI, right posterosuperior segment VII, and right anterosuperior segment VIII. After all, this looks more complicated than it is [see videos].

Right liver lobe

Anterior segments V and VI are separated from posterior segments VII and VIII on the plane of the right hepatic and portal veins. The anterior and posterior divisions are further subdivided by a plane defined by the right main branch of the portal vein.
Segments IVa (superior) and IVb (inferior) are situated to the left of the plane separating the right from the left liver lobe with segments V and VIII to the right and segment VIII being more superior and dorsal to segment V.
In the Couinaud classifications, the plane defined by the *middle hepatic vein* subdivides the liver into the true right and left lobes. A standard right or left lobectomy requires division along the plane of the middle hepatic vein. Segments IVa (superior) and IVb (inferior) lie to the left of the plane while segments V and VIII lie to the right with VIII being more superior to segment V. In Couinaud nomenclature, the plane defined by the right branch of the portal vein divides the anterior and posterior divisions of the right liver superiorly and inferiorly, thus dividing the right lobe into 4 segments (V-VIII) [(17)].

Left liver lobe

The *"umbilical level"* separates segments IVa,b from the lateral segments II and III. Remarkably, this level is the only plane with a vertical orientation not defined by a hepatic vein. It can be defined on the surface of the liver by its associated landmarks. It extends from the umbilical fissure anteriorly through the ligamentum venosum along the lateral aspect of the caudate lobe. Structures within the plane of the umbilical fissure include the falciform ligament, ligamentum venosum (remnant of the ductus venosus), and the ligamentum teres (remnant of the umbilical vein).
The left hepatic vein plane is somewhat controversial discussed. The left hepatic vein courses laterally to the umbilical fissure. Most investigators feel that the plane defined by the left hepatic vein is a true intersegmental boundary and is not the same as the plane of the umbilical fissure. Others have claimed that the true division between segments II and III is formed by the transverse plane of the left portal vein. We define virtually the plane of the left hepatic vein as the boundary between segments II and III. The medial segment of the left lobe can be divided into two segments by the plane of the portal vein (IVa and IVb).

Caudate lobe (segment I)

The most unique of the Couinaud segments is segment I which corresponds to the caudate lobe (sometimes called Spigel lobe). It is located on the posteriorly in surface of the liver adjacent to segment IV. Its medial and lateral boundaries are defined by the inferior vena cava

and ligamentum venosum respectively. The caudate lobe has a variable vessel anatomy that differs from the rest of the liver in that its portal inflow is deriveds both from the left and right branches of the portal vein, and it has its own short (and usually small) hepatic veins connecting directly to the inferior vena cava. Because of the variable and extensive crossing of vessels and its position relative to the liver hilum and inferior vena cava, segment I (if not absolutely necessary) is frequently not often resected.

Surgical resection

Surgical resections proceed along the vessels that define the peripheries of these segments. In general, this means resection lines parallel to the hepatic veins while preserving the hepatic arteries, portal veins, and bile ducts that provide vascular inflow and biliary drainage through the center of the segment. When a lesion occurs within the lateral segment of the left lobe, both Couinaud segments II and III are usually removed together based on the plane formed by the umbilical fissure (left lateral segmentectomy). Note that because the plane of the left hepatic vein is oblique, it forms a division between segments III anteriorly and segment II posteriorly.

Additional anatomical structures

Falciforme ligament runs between the ventral abdominal wall and and the liver, ending with its free caudal margin as ligamentum teres containing the obliterated umbilical vein. It is identified at the left lateral border of segment IVb (quadrate lobe), and it is usually mistaken to form the anatomical borderline between left and right liver lobe – which is not the case. This borderline follows a plane along the middle hepatic vein between the IVC and the longitudinal gallbladder axis. It is identifiable by ultrasound only in patients with one-sided biliary obstruction and a subsequently differing fluid content between right and left liver lobe in cholangiocellular carcinoma in Klatskin`s position.

The ventral border of segment I (caudate lobe) is delineated by the ligamentum venosum (Arantii, see fetal blood circulation) which runs caudally in direction to the hepatic artery which can be identified following this way.

Ultrasound Examination technique

Patient Preparation

It is recommended that a patient undergo a period of fasting prior to upper abdominal imaging to maximise the distension of the gall bladder and to reduce food residue and gas in the upper GI tract which may reduce image quality or precluded liver imaging. This is essential for full imaging of the liver and related biliary tree but may not be required in an acute situation such as trauma where imaging of the gall bladder is not immediately essential. A patient may take small amounts of still water by mouth prior to scan, particuarlry for taking any medications. There is some evidence that smoking can reduce image quality when scanning upper abdominal structures and it is good pratice to encourage a patient not to smoke for 6-8 hours prior to US scan. Smoking increases gas intake into upper GI tract and may reduce image quality. Also, some chemicals in tobacco are known to cause contraction of the smooth muscle of the GI tract and this can cause contraction of the gall bladder, even when fasting has occurred, and the gall bladder cannot be scanned.

Examination

The liver is a large, pyramidal shaped organ and liver sectional anatomy may be best described imaged and defined using by real time ultrasound imaging (see below in the subchapter “Liver segment anatomy” and examination technique videos). Conventional real time ultrasound, produces images of thin slices of the liver on the screen, and so it is essential that the operator scans the entire organ systematically/ritually, in at least two anatomical planes, to be entirely convinced that the entire volume of the liver tissue and structures has been imaged. The operator must then synthesise this 2 dimensional information in their brain to develop a 3 dimensional map of the individual patient`s liver anatomy and pathology. This requires good hand-eye-brain coordination.

For orientation, three levels of the central portion of the liver can be differentiated:

- Level of the cConfluences of the liver veins [Figure 1].
- Level of the Pars umbilicalis of the (left) portal vein branch [Figure 2].
- Level of the gall bladder [Figure 3].

Figure 1 Confluences of the liver veins. This "junction" level is the first one in ultrasound examination of the right liver lobe by subcostal scanning sections steeply "looking" upwards, preferably in deep inspiration [video]. VCI: inferior vena cava. LLV: Left liver vein. MLV: Middle liver vein. C: Confluens of the LLV and MLV. RLV: Right liver vein. The RLV often separately joins the inferior vena cava, whereas the LLV and MLV often reveal a common trunk ("C").

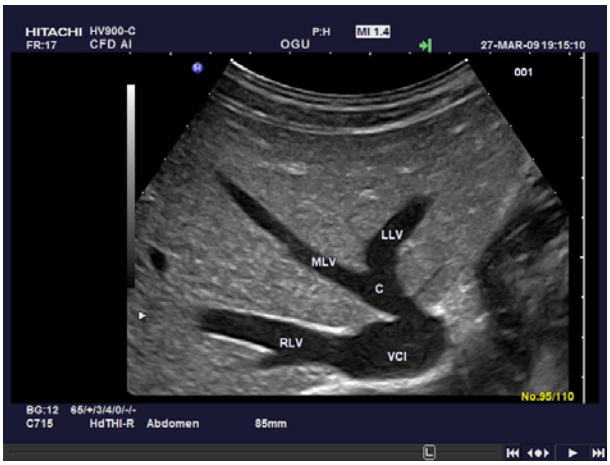


Figure 2 **"**Pars umbilicalis" of the portal vein – scanning planes display the left and right liver lobes in a more downwards orientated view into the right liver lobe as compared to the level of the confluens of the liver veins [video]. PA: Portal vein. PU: pars umbilicalis of the portal vein. VCI: Inferior vena cava.

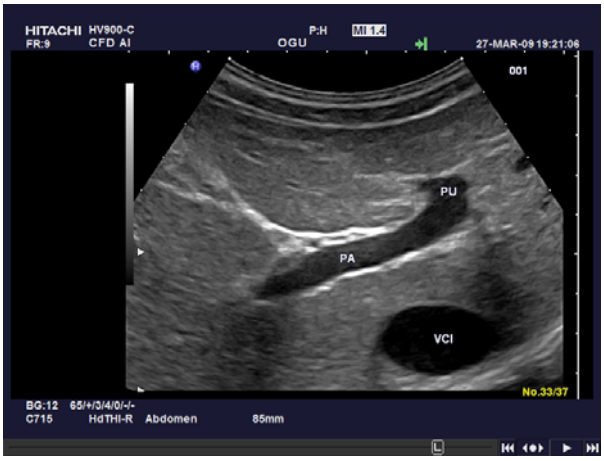
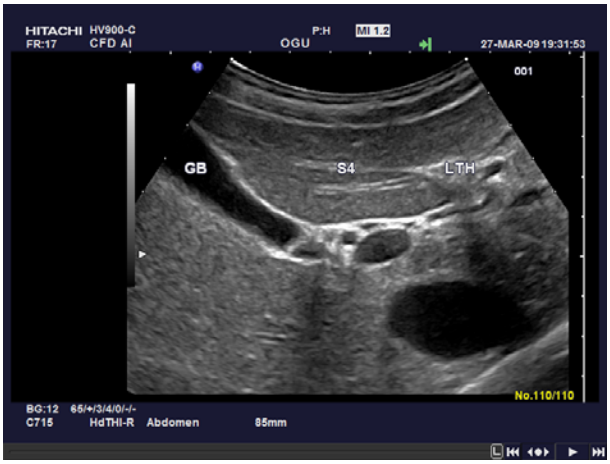


Figure 3 Gallbladder level as the most caudate scanning plane [video]. GB: Gallbladder. LTH: LLigamentum teres hepatis. S4: Segment IV of the liver (quadrate lobe).



Analysing the ultrasound examination, these levels mean the access for a number of (more or less) parallel scanning sections, which in there summary in the examiner`s brain form an real time three dimensional (“4D”) copy of the given patient`s individual anatomy and pathology. Standardised scanning in a ritualized sequence of probe- and patient positions and of scanning planes is mandatory to cover all segments and the complete liver surface [see videos].

The patient should be examined from sub- and intercostally in the decubitus position as well in modified slightly oblique positions with the right arm above the head and the right leg stretched during all respiration cycles to identify the best approach and to avoid artefacts caused by the thorax. Examination in the standing position is additionally helpful due to its weight, the liver moves caudally by gravity, and scanning from sub- or intercostal probe positions – according to the individual anatomy - avoides the interposed lung which is mainly true for the right posterolateral (superficial) parts of the liver using the intercostal approach. Other examination techniques have also been described but are not mentioned here in detail which might be additionally used.

A great number of variants of the normal has to be encountered – e.g. with respect to accessory lobules, vascular branching, shape and configuration.

The anatomy and examination technique are explained and visualised by videos.

Examination criteria

An acronym has shown to be didactically helpful [“SSOTM”]:

- S = size
- S = shape
- O = outline
- T = texture
- M = measurement

Size

The size of the liver has been measured by many methods, including 3D-reconstructions. Liver size measurement has no impact in daily routine because there is no reliable and reproducible ultrasound method established so far [Sienz M et al., submitted].

Shape

Normally described as pyramidal.

Outline

The normal liver surface should be smooth with no lumps protruding or indentations. The inferior liver border in the normal patient should have an acute angled edge. Liver surface border delineation and other ultrasound criteria: Other ultrasound criteria are described in the respective chapters.

Texture, echogenicity

The normal liver parenchyma is of medium homogenous echogenicity, usually slightly darker than the spleen and slightly brighter than the renal cortex independently of the age except in childhood [(32)]. It is essential when comparing the liver with the spleen and renal cortex that the comparison is done at the same depth. Liver surface and vessels borders are smooth and vascular architecture with its classic dichotomy in branching is percepted as an harmonic and detailed aspect. The image of the normal parenchyma varies very little among individuals.

Liver veins

The three liver veins are positioned in between the liver segments. Their course - additionally to the Glisson`s triad - is helpful in defining liver lobes and liver segments. Number and course of liver veins is somewhat variable [Figure 1].

Portal vein

Formed by the confluens of the splenic and superior mesenteric vein, the portal vein can be sonographically displayed using scans more or less perpendicular to the lower costal margin (orientation might be achieved referring from the right shoulder to the umbilicus), preferably in a left decubitus position and in variably deep inspiration. Intrahepatically, the portal vein bifurcates into a main left and right branch. The first (right) portal vein branch splits into an anterior and into a posterior branch, which itself leads to the segments V – VIII. The latter (left) main portal branch bifurcates into segments II and III and, additionally, into the left medial branches for segments I (caudate lobe), IVa and Ivb [Figure 2].

Hepatic artery

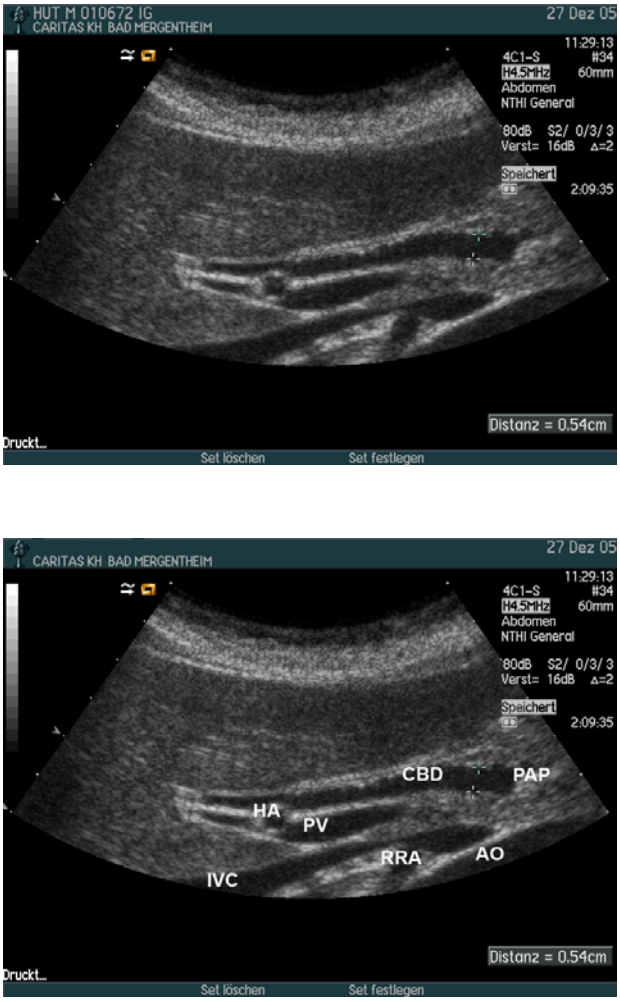
The common hepatic artery has its source from the celiac axis, branching into the gastroduodenal artery and into the proper hepatic artery (arteria hepatica propria). Anatomical variations are frequent (in up to 50 %), e.g. the origin of the left proper hepatic artery out of the left gastric artery as well as the variable arterial supply of the liver by superior mesenteric artery branches. The hepatic artery runs with the portal vein, the right main arterial branch frequently meandering around the portal vein sonographically displayed in short segments medially (or less often laterally) of the portal vein. The normal and pathological flow patterns are described below in the Doppler chapter.

Bile ducts

Bile ducts accompany the portal vein and hepatic artery branches from the liver hilum into the liver lobules, intrahepatically forming the ductus principalis dexter and the ductus principalis sinister, which join as common bile duct (CBD). The extrahepatic course of the CBD is cranially (pre-pancreatic) often ventral to the portal vein and caudally (intrapancreatic) more dorsolateral. The respective course of the hepatic artery is more variable [Figure 4].

Figure 4 Common bile duct (CBD). The CBD, and therefore, the liver hilum, is often best examined in a left lateral decubitus position using a subcostal approach in slight

inspiration [video]. In the typical view CBD (in between markers), portal vein (PV), hepatic artery (HA), inferior vena cava (IVC) and right renal artery (RRA) (and sometimes also the aorta [AO]) can be seen; the papilla region (PAP) is indicated.

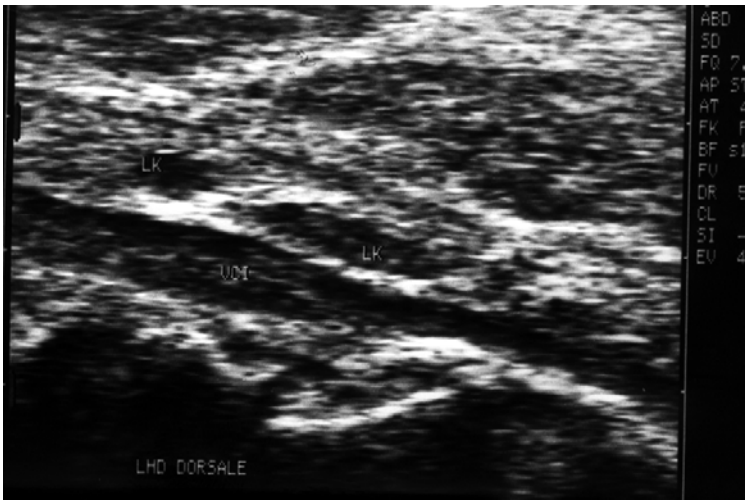


Perihepatic lymph nodes

Perihepatic lymph nodes in the hepatoduodenal ligament (LK) can be commonly found next to the cystic duct, so called cystic duct lymph node [Figure 5].

Figure 5 Perihepatic lymph nodes. Perihepatic lymph nodes in the hepatoduodenal ligament (LK) can be commonly found next to the cystic duct, so called cystic duct lymph node, as shown in the portmortem examination by ultrasound (a) and macroscopically (b). VCI: Vena cava inferior.

a



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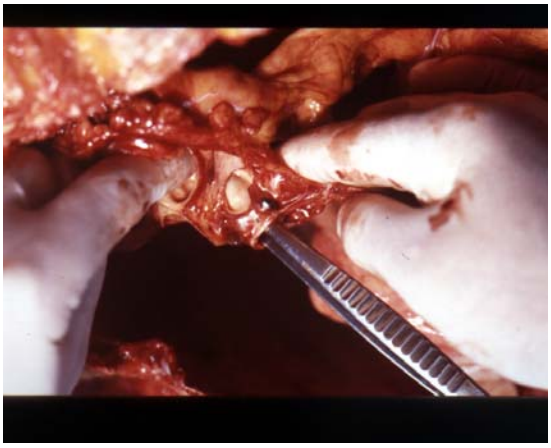


Liver pathology - diffuse liver disease

Criteria for analysing diffuse liver disease include evaluation of

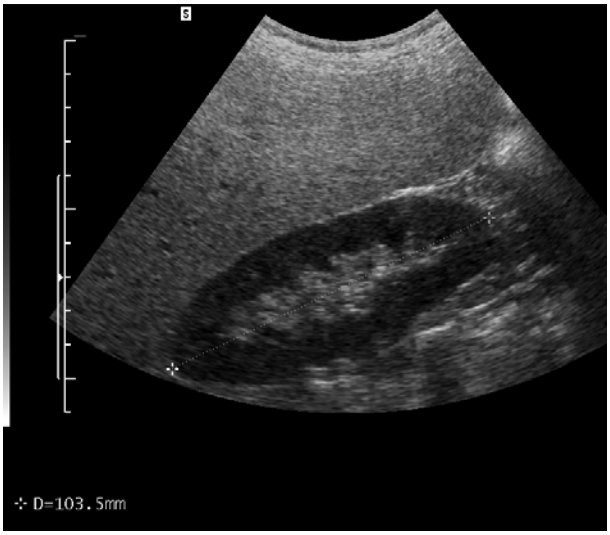
- liver parenchyma (echo texture, ultrasound attenuation, vascular architecture, etc.) as well as its surface (a high frequency transducer is helpful in detecting more details of the superficially located structures);
- liver hilum structures including perihepatic lymph nodes in the hepatoduodenal ligament, lymph nodes in inflammatory liver disease or neoplastic infiltration;
- analysis of hepatic vessel flow patterns using colour and pulsed wave Doppler imaging (CDI).

Ultrasound contrast agents (USCA) have improved the detection/exclusion rate of focal liver lesions; in diffuse liver disease, USCA potential is much lower (e.g., hepatic transit time).

Hepatic steatosis

Hepatic steatosis is the most common liver pathology. Sensitivity and specificity of the detection of hepatic steatosis by B-mode ultrasound examination may be very high in the hands of an expert investigator who consistently applies specific criteria in patients with significant fatty liver disease. In transabdominal ultrasound, hepatic steatosis is characterised by increased echogenicity, which is often compared to the spleen or kidney parenchyma at the same depth [(7;63)] [Figure 6]. Supporting findings may be ultrasound attenuation, which means a decrease in intensity as sound travels through a material, caused by absorption, scattering, and beam divergence. Attenuation decreases detail analysis of vascular architecture, and it may cause a loss of visibility deeper within the liver and impeded imaging of the diaphragm [(38)].

Figure 6 Hepatic steatosis (fatty liver). Sonographic signs of hepatic steatosis include hepatomegaly with rounded borders, increased echogenicity, ultrasound attenuation caused by absorption, scattering, and beam divergence and decreased detail display of intra-hepatic vascular architecture. There is exageration of the difference between the kidney parenchyma and liver echogenicity. Right kidney is shown between callipers (+).



In the majority of patients with hepatic steatosis, distinctive hypoechoic areas in the liver hilum can be demonstrated by ultrasound examination [Figure 7] [(7;28;38)]. It is believed that the presence of focal hypoechoeic areas (FHA) within the liver hilum (and elsewhere in the liver) corresponds to parenchymal islands with (close to) normal fat content (due to a locally different blood supply), that are surrounded and contrasted by bright echogenic parenchyma with fatty infiltration. Subcapsular FHA and FHA close to liver veins are other typical locations, the shape of these “pseudolesions” being polycyclic and non-round. FHA are relatively specific for hepatic steatosis and may be helpful to differentiate fatty from fibrotic liver disease.

Similar focal hypoechoeic areas were demonstrated in patients with liver steatosis due to systemic corticosteroid therapy, even though the more important focal lesions in this condition are hyperechoic [Figure 8]. Pathophysiologically areas of different fat content might be explained by a different arterial and portal venous blood supply in comparison to the surrounding liver parenchyma which is mainly portal venous and contains, therefore, a higher fat and insulin concentration in focal fatty infiltration [(32;38)].

Figure 7 Hepatic steatosis. Perhaps the most objective and therefore most important sign of of hepatic steatosis are circumscribed focal hypoechoic areas in the liver hilum examined in a left posterior oblique position. B-mode ultrasound demonstrates a focal liver lesion in between callipers(a). Colour Doppler imaging indicates a centrally located vessel of undetermined origin (b). CEUS showed the typical enhancement pattern. Typically a centrally located arterial vessel can be displayed [(32;38)] in the arterial phase (c, arrow) and a portal vein branch in the portal venous phase (d, arrow) and homogenous enhancement in the late phase [(38)].

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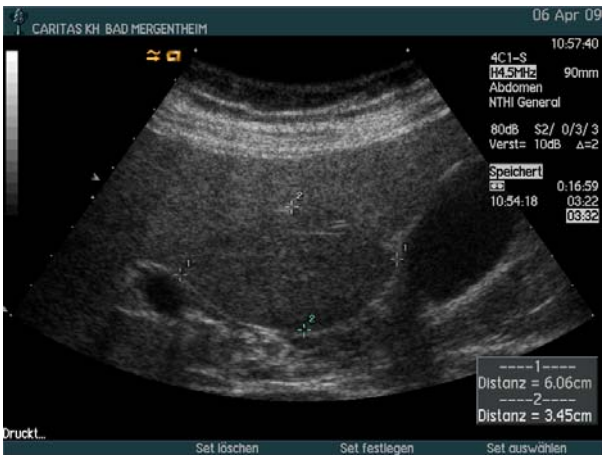

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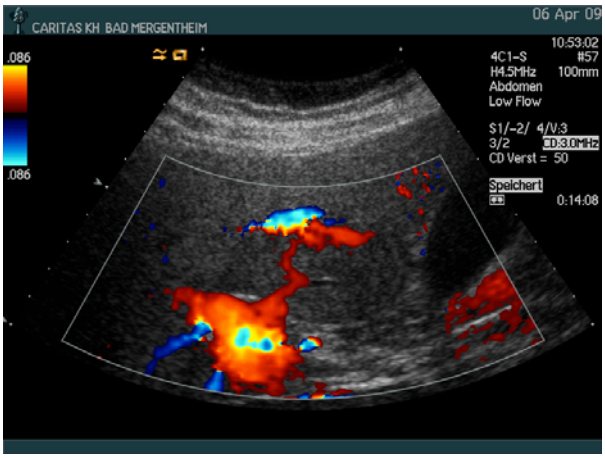
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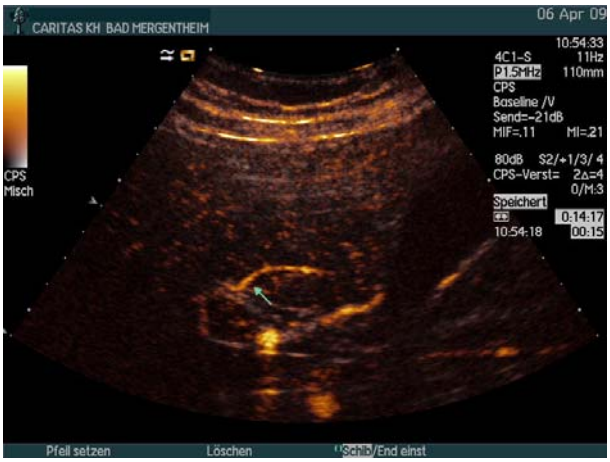
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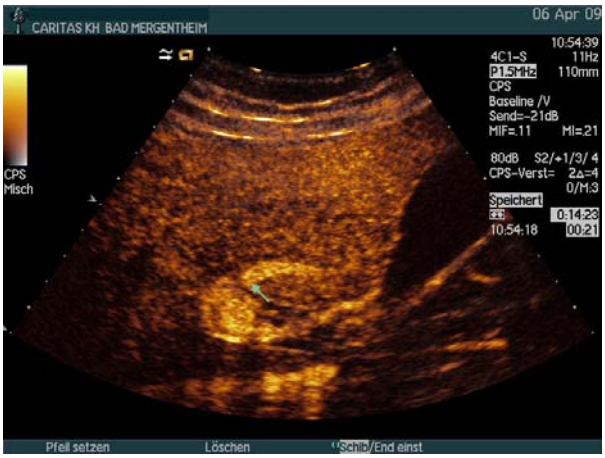
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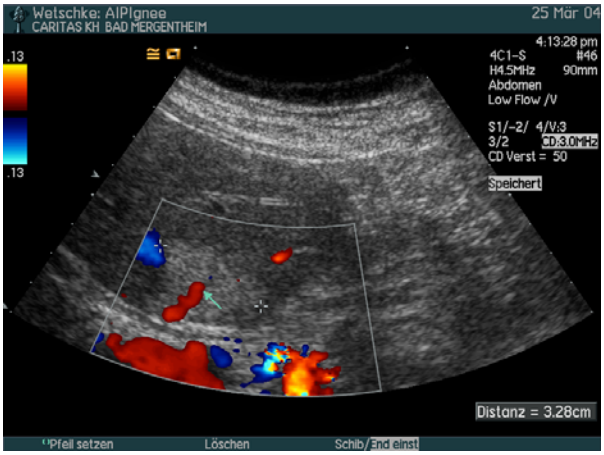
Figure 8 Hepatic steatosis indicated by focal hyperechoic ([(28)] areas in the liver hilum. They are characterised by centrally located (portal) vein branches identified by colour Doppler imaging (a), spectral analysis and CEUS (b). Such lesions are also typically found subcapsular next to the teres ligament [(28)].

a



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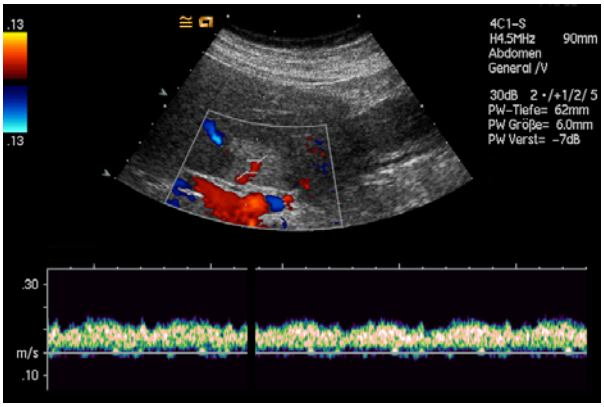

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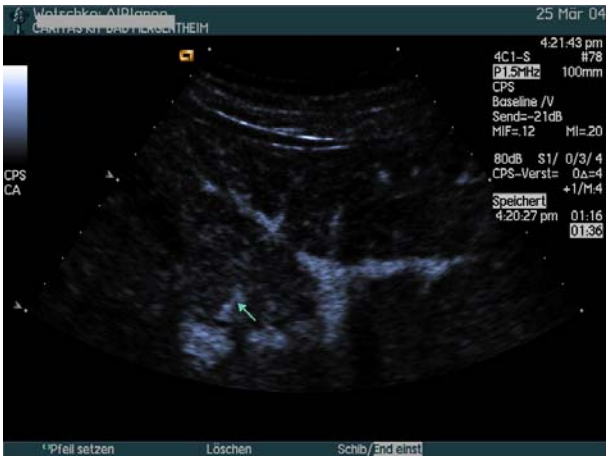

Liver cirrhosis

The accuracy of ultrasound in the correct diagnosis of “liver cirrhosis” in patients with complications (ascites, splenomegaly, collaterals) is high (> 90 %). In the initial stages and in micronodular cirrhosis, it may be overlooked in up to 30 % [(32)]. Sonographic signs of liver cirrhosis include inhomogenous echotexture and irregular-nodular liver surface delineation and a variety of other possible findings including destroyed vascular architecture also dependent on the etiology of diseases [Figure 9]. Dysproportional segment atrophy (and also hypertrophy) has been observed [Figure 10].

Figure 9 Liver cirrhosis. Typical signs of liver cirrhosis include inhomogenous echotexture and irregular liver surface delineation (a, arrow). In addition distinctive nodules are suggestive (b). Sometimes it might be difficult to identify the liver parenchyma, therefore the organ is indicated as well: Leber: liver.

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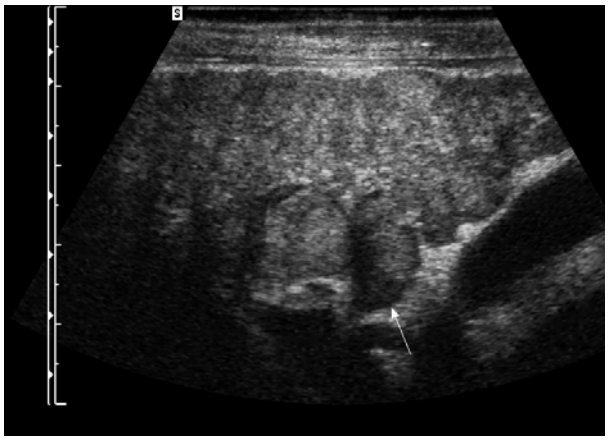

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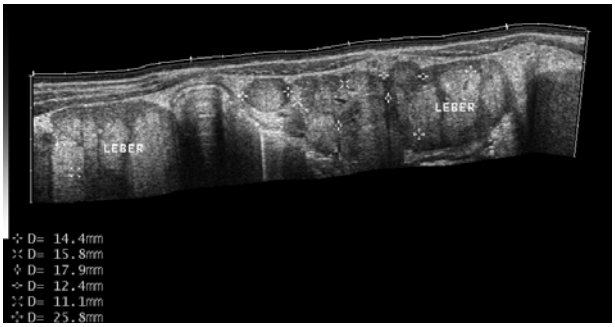
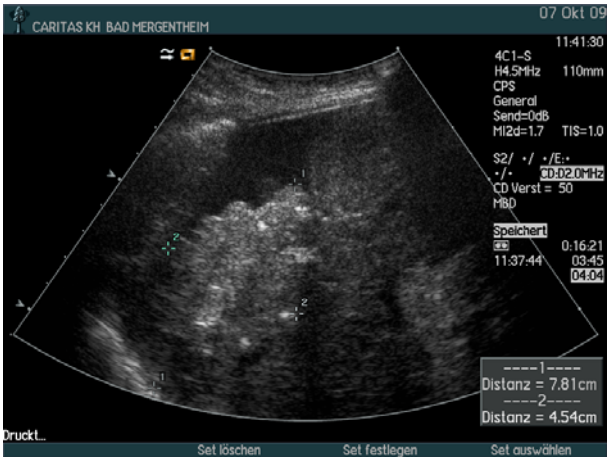


Nodular liver surface (especially using high frequency transducers) has an excellent positive predictive value close to 100 % for cirrhosis. A disproportional volume enlargement of the caudate lobe in relation to the right and left lobe may be indicative of liver cirrhosis but this sign is of limited value in daily clinical practice.

Coarse liver parenchyma and a disturbed or destroyed vascular architecture as a sign of portal hypertension - such as reversed portal flow and collateral vessels - are other signs of liver cirrhosis. In Doppler studies, a raise in the arterioportal peak velocity ratio (maximum velocity of the hepatic artery divided through the maximum velocity of the vena portae) of more than 3,5 is predictive for cirrhosis. The positive predictive value of the detection of signs of portal hypertension is excellent such as reversed portal flow and the detection of collateral vessels. The negative predictive value is worse. Overall, the accuracy is about 60 %. An enlarged portal vein diameter greater than 1.25 cm or a reduced portal vein flow velocity indicates cirrhosis with a sensitivity and specificity of about 80 %. All mentioned parameters, however, are of limited value.

Figure 10 Liver lobes and segments may behave different during the course of a disease, as shown in this patient with systemic sclerodermy with gradually shrinkeage of the right liver lobe (in between markers). The changes of the liver evolved gradually over the last ten years.

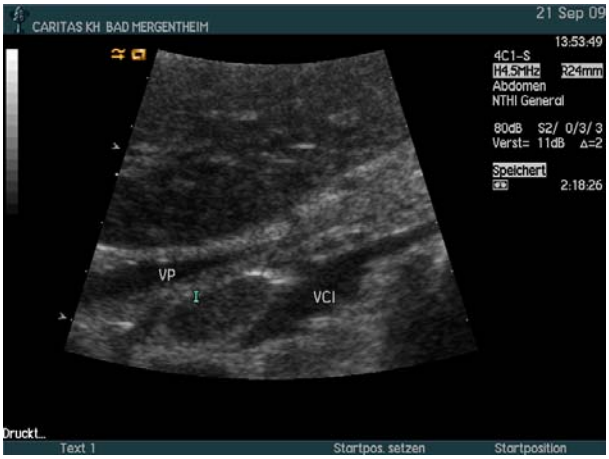


Detection of lymph nodes in the hepato-duodenal ligament (perihepatic lymphadenopathy)

Improvement of sonographic technology and techniques [(44)] and the knowledge of the well defined anatomical sites of perihepatic lymph nodes between the inferior cava and portal vein next to the right renal artery have lead to improved identification of enlarged, but also of normal sized lymph nodes in the liver hilum by ultrasound. Normal lymph node size is up to 17 (19) mm [(24;25;30;31;45)]. Two groups of lymph nodes can be detected regularly: dorsal in the hepato-duodenal ligament adjacent to the cystic duct (”cystic duct nodes”) and ventral in the hepato-duodenal ligament adjacent to the orifice of the foramen epiploicum next to the common hepatic artery [Figure 11]. The liver hilum should be examined in a slightly left lateral oblique position of the patient (15^{o} - 30^{o}) with the right arm elevated, thus improving the detection rate from 25 % to 75 % compared to the decubitus position.

Figure 11 Two groups of lymph nodes can be detected regularly in anatomic examinations: dorsal in the hepato-duodenal ligament adjacent to the common hepatic bile duct and cystic duct (”cystic duct nodes”, a and b [in between markers. VCI: inferior vena cava; VP: portal vein]) and ventral (c) in the hepato-duodenal ligament adjacent to the orifice of the foramen epiploicum next to the common hepatic artery (in between markers).

a



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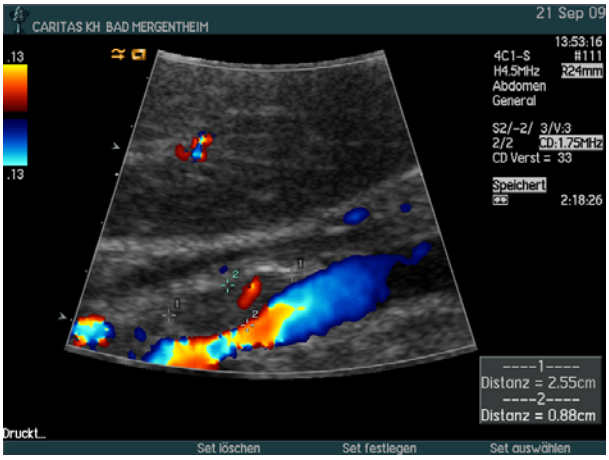

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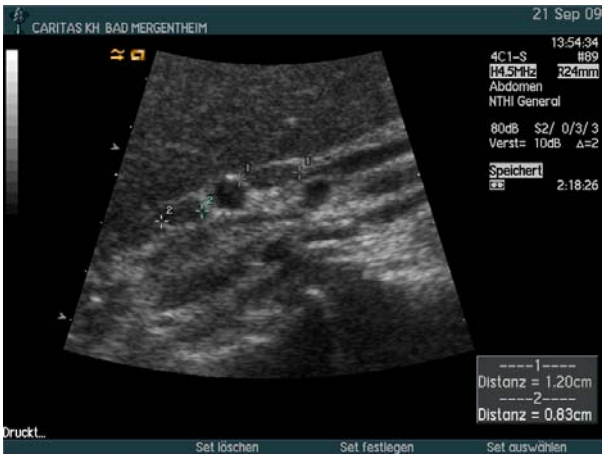


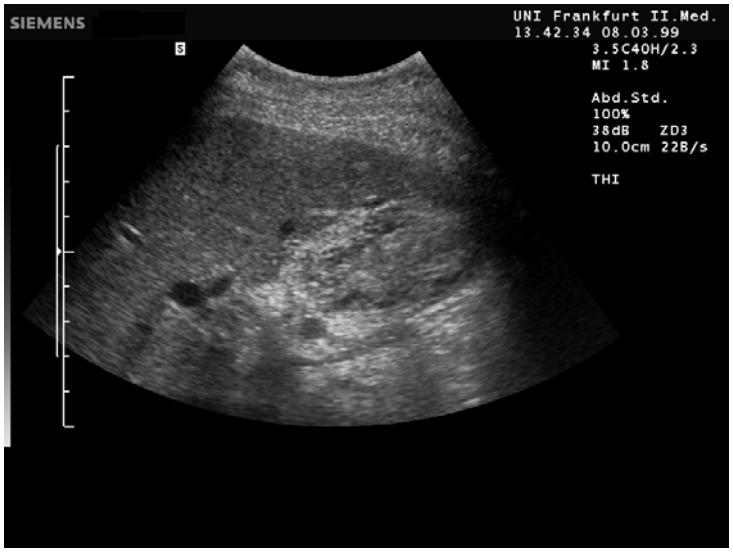
Acute viral hepatitis

There are no significant changes of liver echo-texture in acute viral hepatits. Enlarged perihepatic lymph nodes, however, are a fairly constant feature, which is also present in chronic hepatitis in conditions such asviral and autoimmune hepatitis including primary sclerosing cholangitis as well, but not in toxic inflammatory liver disease, or in hemochromatosis. In 40 patients with acute hepatitis, enlarged perihepatic lymph nodes could be identified by transabdominal ultrasound in all patients with adequate visualisation of the liver hilum (sensitivity of 100 %) which was helpful to differentiate between toxic and viral genesis [(12)]. In the same manner in chronic liver disease, perihepatic lymphadenopathy was present in 86 % of viral, in 90 % of autoimmune hepatitis, in 100 % of primary sclerosing cholangitis, in 97 % of primary biliary cirrhosis, but only in 6 % of hemochromatosis, in 1 % of fatty liver disease, and in 4 % of cholecystolithiasis.

Doppler techniques are used to exclude complications (e.g., portal vein thrombosis) and reveal an unspecific hyperdynamic state in hepatic vessels with a higher diastolic arterial blood flow when compared to healthy subjects. Portal venous blood flow is increased and, perhaps due to edema and narrowing of the hepatic veins, the flow pattern is often monophasic [(40)].

Gallbladder wall thickening [Figure 12] is a short-life sonographic phenomenon of the early phase of acute hepatitis in about half of patients which must not be confused with acute cholecystitis – there is no circumscript pain under US visualized palpation.

Figure 12 Gallbladder wall thickening. Gallbladder wall thickening (block arrow) in acute hepatitis is a short-life sonographic phenomenon of the early phase of acute hepatitis in about half of patients which might be confused with acute cholecystitis.



Chronic viral hepatitis C

In patients with chronic viral hepatitis C infection, hepatic steatosis is a frequent histological finding, occurring in more than 50 % of cases. The reason for this remains poorly understood. Even when the most common causes of steatosis are carefully excluded, a significant proportion of patients with chronic HCV infection show signs of liver steatosis.

Perihepatic lymphadenopathy

Lymph nodes are detectable within the hepato-duodenal ligament in almost all patients with chronic viral hepatitis C. The total perihepatic lymph node volume changes according to the antiviral response and leads to progressive normalisation of the perihepatic lymph node volume in sustained virological responders. The decrease in the perihepatic lymph node volume is associated with an improvement in liver histology. Mediastinal lymphadenopathy has also been described in patients with chronic virushepatitis C using mediastinal ultrasound whereas other abdominal lymph node locations are not sinigificantly altered in patients with chronic virus hepatitis C infection.

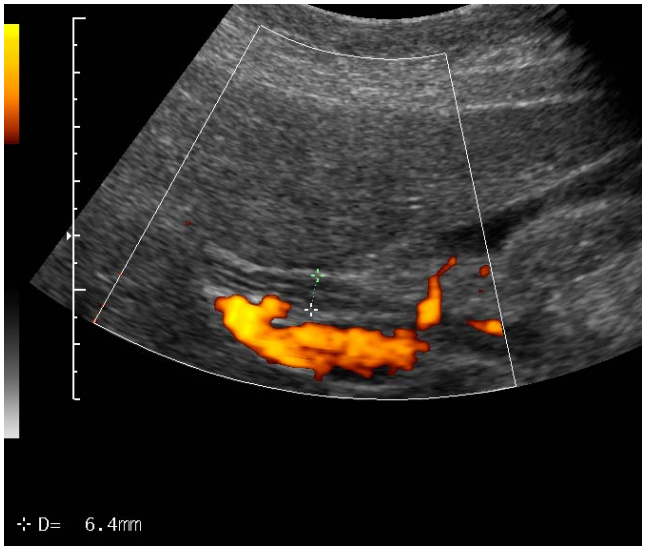
Primary biliary cirrhosis (PBC)

The echo texture of the liver parenchyma in patients with PBC in stages I and II is often unremarkable. In stage IV typical signs of liver cirrhosis are detectable. The liver parenchyma of patients with stage III PBC show advanced sono-morphological modifications like inhomogenous parenchyma but no indicative signs of liver cirrhosis. The extent of perihepatic lymphadenopathy reflects progression of the disease with larger lymph node size in more advanced stages [(25)].

Primary sclerosing cholangitis (PSC)

Neither the clinical symptoms nor the biochemical evidence of cholestasis are specific for PSC and lack sensitivity, particularly in the early course of the disease. Ultrasound is useful in the detection and follow up of extra-hepatic bile duct lesions, but it has to be noted that alterations of the intra-hepatic duct system cannot be displayed under all circumstances. Asymmetric mural thickening is a typical ultrasound finding in advanced PSC [Figure 13]. But, it is important to mention that symmetric mural thickening by itself is a rather unspecific marker for cholangitis. Enlarged hilum lymph nodes are detectable in almost all patients with PSC [(39)].

Figure 13 Primary sclerosing cholangitis. *Asymmetric* mural thickening of the common bile duct (in between markers) is a sensitive sign of PSC.



Other liver diseases

Patients with autoimmune hepatitis (AIH) generally show perihepatic lymphadenopathy with lymph nodes sized > 19 mm. There are no other typical ultrasound features of the liver texture or of the hepatobiliary tract in patients with AIH.

Changes of the liver parenchyma and echotexture in patients with sarcoidosis are unspecific but sometimes circumscribed (isoechoic) sarcoid infiltrations can be observed mimicking malignancies even with contrast enhanced techniques. Perihepatic lymphadenopathy in these patients is sometimes impressive with lymph node sizes up to 60 mm. Perihepatic lymphadenopathy is indicative of hepatic involvement. In patients with advanced disease, signs of liver cirrhosis and portal hypertension are common with respective flow changes of the hepatic vessels. Similarly to PBC, the flow pattern in the portal and hepatic veins is increased in contrast to other forms of liver cirrhosis.

In none of recently published literature, there have been no cystic fibrosis patients reported with enlarged perihepatic lymph nodes(except e.g. in patients with common bile duct stones and cholangitis). There were no typical sonographic findings of the liver echo texture. A micro-gallbladder as typical sign of CF was found in 18 of 72 (25 %), whereas a micro-gallbladder did not appear in the control group [(19)].

In patients with alcoholic steatohepatitis (ASH) and non-alcoholic steatohepatitis (NASH) attenuation of the ultrasound beam makes it more difficult to examine the liver hilum. Adequate visualisation is possible in only 80 % of patients. In a series of 60 patients no enlarged perihepatic lymph nodes could be found.

Sonographic features in patients with frequently encountered toxic liver disease are unspecific. In a up to now unpublished series of 100 patients, no enlarged perihepatic lymph nodes could be found.

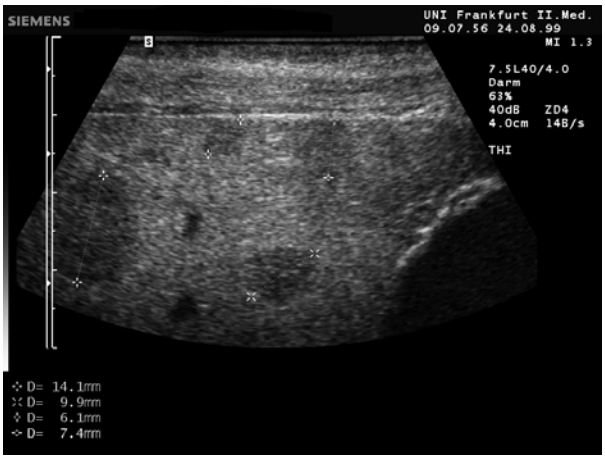
Changes of the liver parenchyma in patients with HIV infection are dependent on the kind of opportunistic infections or neoplastic infiltration. Many causes have to be considered [e.g., bacillary angiomatosis]. In a consecutive series 82 of 100 patients (by whom?) with AIDS showed enlarged perihepatic lymph nodes. Coinfection with the hepatitis B and C virus and mycobacteriosis are common. We found no significant correlation with viremia. Hepatobiliary infections as a cause of perihepatic lymphadenopathy have also to be considered, e.g. cytomegaly virus infection.

Enlarged perihepatic lymph nodes have been found in almost all patients with end-stage liver disease.

Wilson's disease is a rare, autosomal-recessive inherited disorder of copper metabolism resulting in accumulation of copper in the liver and many other organs. Liver disease varies depending on the severity of the disease at time of diagnosis. Histopathological findings include (focal) fatty changes, signs of acute (including hepatic necrosis) or chronic hepatitis, and fibrosis and cirrhosis. Liver imaging findings reflect a wide range of physiopathological processes of the disease and also demonstrate the associated findings of cirrhosis in cases with advanced disease.

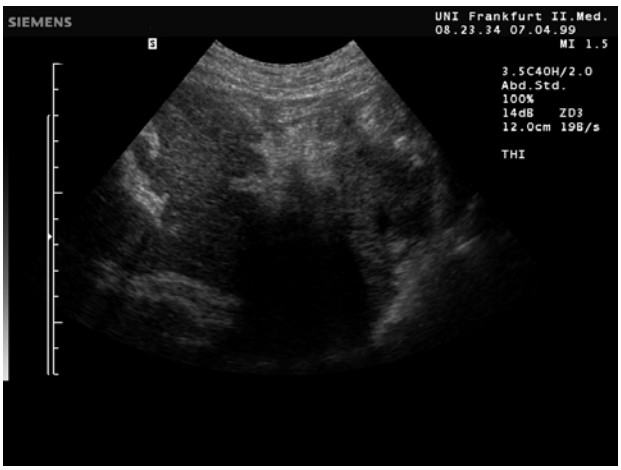
Ultrasound findings in end-stage Wilson’s disease resemble liver cirrhosis caused by other aetiologies. In earlier stages multiple intrahepatic, mainly small (< 20 mm) hypoechoic nodules could be observed in 8/10 consecutive patients with Wilson’s disease. In these lesions biopsy and histologal examination revealed prominent copper accumulation in comparison to the surrounding liver parenchyma [Figure 14] and in two patients additionally dysplastic nodules.

Figure 14 Wilson disease. The parenchymal echo pattern is typically of increased echogenicity with abundant roundish or oval foci of decreased echogenicity (between callipers) resembling metastatic liver disease. Biopsy and histology revealed prominent copper accumulation.



There are many liver diseases with specific and unspecific ultrasound changes which are not described here in the context of more common diseases in the western world only. There are, however, examples in other areas of the globe with stiking ultrasound features as e.g. patients with hepatobiliary schistosomiasis and portal hypertension showing typical fibrotic strands as sequelae of fibrous portal venous obliteration [Figure 15].

Figure 15 Schistosomiasis. Schistosomiasis show hyperechoic typical fibrotic strands as sequelae of fibrous portal venous obliteration.



Doppler ultrasound techniques in the evaluation of liver disease

Anatomy, blood supply of hepatic vessels

Two vascular systems with completely different haemodynamics and one outflow system characterize hepatic perfusion:

- Arterial inflow (high pressure, low flow resistance) [Figures 16 & 17]
- Portal-venous inflow (low pressure, low flow resistance) [Figure 18]
- Venous outflow (low pressure and low flow resistance) [Figure 19]

Vascular hepatopathies occur with abnormal vascular courses, aneurysms, stenoses and occlusions of these vessels.

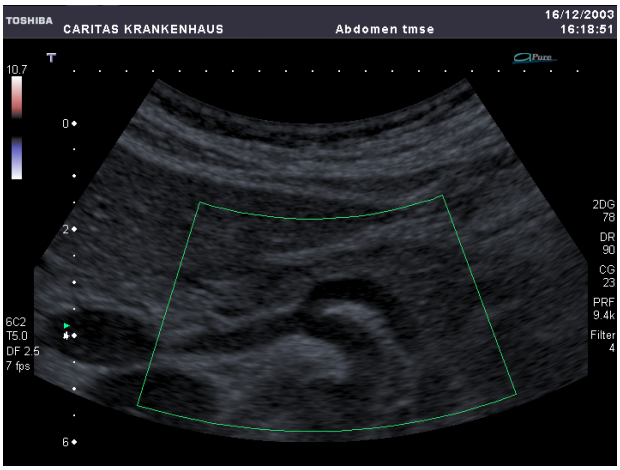
Arterial flow

Arterial liver perfusion disorders are rare, both in the sense of hypo- and hyperperfusion. A diminuished arterial lood flow may be caused by congenital malformations as well as by acquired embolic, thrombotic, inflammatory, vascular-tumourous, vasculitic or arteriosclerotic-degenerative changes, or in (acute) myocardial forward failure and shock [(15;40;43;49;50;52)]. Hyperperfusion is observed even less frequently and is caused by arteriovenous shunts which are of congenital (e.g., Osler`s disease), traumatic or septic-embolic origin, as examples.

- Hypoplasia and aplasia of the common hepatic artery and/or its branches with atrophy of related liver segments,
- Aneurysms of the common hepatic artery and its branches.
- Atypical vascular courses (e.g. with impression of the hepatic choledochal duct).
- Arteriovenous and arterioportovenous shunts (e.g., occurrence of M. Osler).
- Abnormal hepatic vascular malformations occur more frequently in connection with vascular changes in other organs (heart, lungs, brain, and kidneys) which tend to determine the clinical course and prognosis to a greater extent.

Figure 16 Extrahepatic hepatic arterial vessels. The coeliac trunk (B-mode [a], colour Doppler imaging [b]) is the arterial blood supply for the liver and the perihepatic structures. The liver hilum, is often best examined in a left lateral decubitus position [video 5].

a



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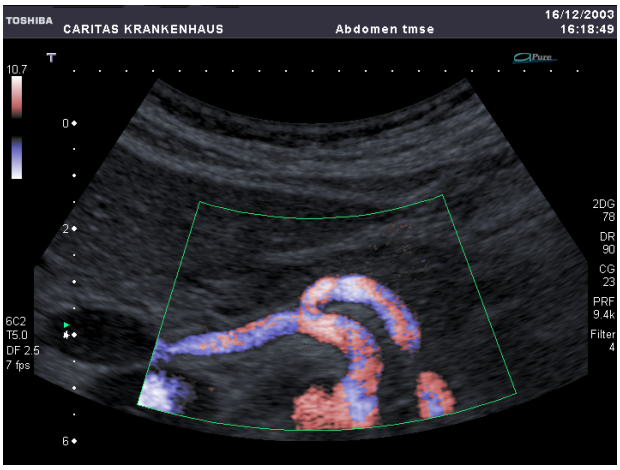


Portal venous system

Signs of portal hypertension (splenomegaly, ascites and collateral vessels) with continued liver function impairement are supected or proven by ultrasound including thrombosis [(3;34-36;40;47-51;53-55;57;58;60-62)]. Its most important disorder is *portal vein thrombosis*.

Venous outflow

With disorders of the venous outflow, first a (substantial) restriction of the liver function occurs and second, signs of high portal vein pressure are detected. *Right-ventricular heart failure* is the most frequent venous outflow disorder. The increase in post hepatic resistance reduces the portal hepatic perfusion and may lead to a pendular or retrograde flow in the portal vein, especially in cases with an additional intrahepatic increase in resistance.

Colour Doppler imaging (CDI) for analysis of hepatic vessel flow pattern – an introduction

CDI is accurate and well established in evaluating portal hypertension, portal vein thrombosis due to different causes, Budd Chiari-syndrome and other forms of veno-occlusive diseases. CDI is routinely used to evaluate patients prior to liver transplantation to determine portal vein patency, signs of portal hypertension, and hepatic artery patency postoperatively. CDI is also important to monitor flow direction and patency of spontaneous and artificial porto-systemic shunts, e.g. TIPSS. Patients after liver transplantation are monitored by analysing the hepatic artery profile. Stenosis and rejection are indicated by changes in the resistance flow pattern (e.g. pulsus parvus et tardus).

Chronic heart failure reveals tetra-phasic flow in the right liver vein and highly undulating flow patterns in the portal vein, reversing during intensified therapy. Analysis of the flow pattern in the liver veins is helpful to characterise diffuse parenchymal liver disease [(4-6)].

Vascular (Doppler) indices

Vascular indices, e.g., Doppler perfusion index (DPI), hepatic transit time and various ratios analysing different vessels have been used for liver tumour detection and characterisation but are currently only used in experimental settings.

The portal vein congestive index (PVCI) is defined as ratio of cross sectional area of the extra-hepatic portal vein to time averaged mean velocity of blood flow in the portal vein. The PVCI is elevated in liver cirrhosis at an early stage with a constant portal vein blood flow (cross sectional area multiplied by the time averaged mean velocity) which can be reached by an increased portal vein pressure with consecutive dilatation of the latter vessel. The method – more difficult in its wording than in its application after some training – has, however, not been able to reach general acceptance.

The Doppler perfusion index (DPI) is the ratio of hepatic arterial blood flow (normal below 20 %) to the total liver blood flow (hepatic arterial and portal venous blood flow). DPI is reported to be elevated in the presence of intra-hepatic tumours as well as in patients with liver cirrhosis, and was used to screen patients with suspected metastases. The promising data could not be reproduced.

Examination of the hepatic artery in patients with diffuse liver disease

Examination technique

There are only limited data analysing hepatic arterial vessels in diffuse hepatic disease as compared to portal venous studies. The reasons are obvious: anatomic variations of the coeliac trunk are common in up to 50 % do not allow standard examination techniques. Due to many variants in the hepatic arterial supply absolute parameters like blood flow velocities and blood flow volumes are problematic whereas the resistance and pulsatility indices represent the parenchymal influence distal to the measurement point. These indices can therefore represent hepatic parenchymal influence with a certain degree of confidence. The interobserver variability analysing the hepatic arterial blood flow at the measurement point mentioned above for the resistance and pulsatility index is below 12 % and much higher for

the velocities (peak systolic, end diastolic, time averaged mean velocity), and for blood flow volume (about 30 %) [(21;40)].

Hepatic blood flow depends on food intake, posture, activity and can be also influenced by drugs.

Figure 17 Hepatic artery in its typical topographic neighbourhood to the common bile duct and portal vein [video 4]. A low resistance flow pattern is typical with a significant diastolic flow [(40)].

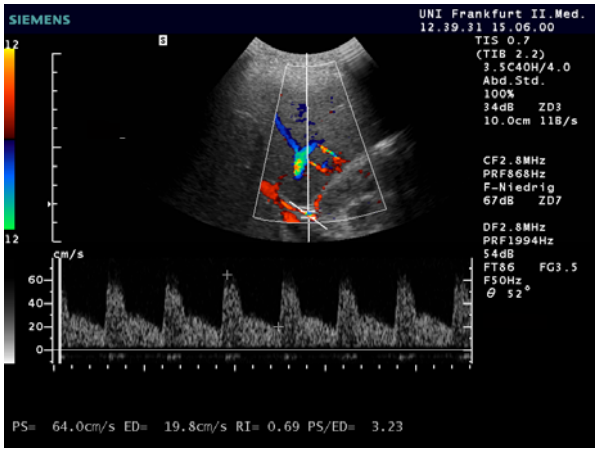


Table 1 Table of normal flow parameters analysed in 47 healthy probands.

Vessel	TC	AMS	AHC	AHP
PSV [cm/s]	137 ± 45 [53 – 260]	145 ± 42 [47 – 228]	102 ± 46 [31 – 202]	58 ± 34 [23 – 193]
EDV [cm/s]	39 ± 15 [17 – 90]	18 ± 9 [5 – 40]	27 ± 11 [10 – 56]	20 ± 12 [8 – 60]
RI	0,7 ± 0,06 [0,59 – 0,88]	0,87 ± 0,05 [0,74 – 0,96]	0,71 ± 0,09 [0,5 – 0,83]	0,65 ± 0,07 [0,52 – 0,78]
PI	1,86 ± 0,9 [1,03 – 4,77]	3,74 ± 1,39 [1,77 – 7,75]	1,68 ± 0,59 [0,72 – 2,93]	1,16 ± 0,25 [0,73 – 1,75]
TAV_{max} [cm/s]	59 ± 21 [22 – 115]	37 ± 15 [15,6 – 73]	45 ± 20 [15 – 108]	34 ± 20 [13 – 102]
TAV_{mean} [cm/s]	33 ± 12 [10 – 70]	22 ± 9 [9 – 40,66]	25 ± 13 [10 – 72]	20 ± 12 [9 – 68]
D [mm]	6 ± 1 [4,2 – 8,8]	6 ± 1 [4 – 10]	4 ± 1 [3 – 7]	3 ± 1 [2 – 6]
BF [ml/min]	630 ± 250 [184 – 1239]	395 ± 206 [159 – 1061]	250 ± 220 [88 – 1163]	105 ± 89 [24 – 503]
Angle [°]	26 ± 19 [1 – 60]	42 ± 16 [7 – 63]	59 ± 14 [22 – 81]	42 ± 19 [7 – 73]

TC = celiac trunk; AMS = mesenteric superior artery; AHC = common hepatic artery; AHP = proper hepatic artery; PSV = peak systolic velocity; EDV = end diastolic velocity; RI = resistance index; PI = pulsatility index; TAV_{max} = time averaged maximum velocity; TAV_{mean} = time averaged mean velocity; D = diameter; BF = blood flow volume;

Examination of the portal vein in patients with diffuse liver disease

Examination technique

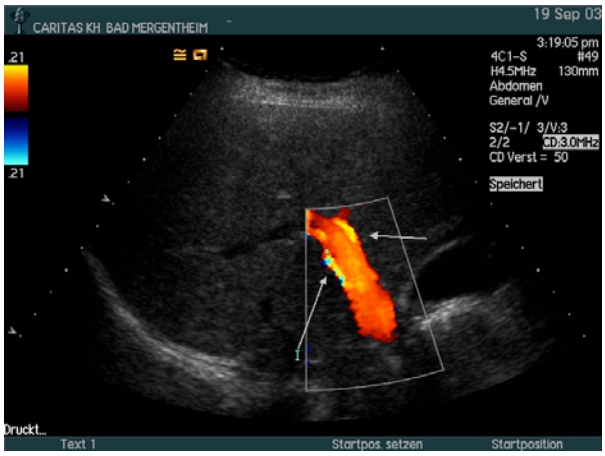
Portal vein diameter and flow pattern is measured via an intercostal approach at an angle close to zero degree, just before the portal vein splits into the right and left branches. Biphasic Fast Fourier Transformation (FFT) Doppler spectrum of the portal vein should be documented during a 5 - 8 seconds suspended respiration at a mid respiration level, avoiding respiratory and thoracic pressure influences. The sample gate is adjusted to the inner diameter of the vessel and Fast Fourier transformation spectral analysis is recorded. The maximum (V_{max}) and minimum (V_{min}) velocity [cm/seconds] of an undulational circle are set automatically or manually. The differences of V_{max} and V_{min} are calculated as a parameter of biphasic oscillations as well as the portal vein resistance index ($(V_{max} - V_{min})/V_{max}$) in analogy to the resistance index of arterial vessels. The reproducibility of the method was also investigated by repeated sonographic examinations of the portal vein flow in ten healthy subjects over seven consecutive days. The mean coefficient of variation for intra-individual assessment of the flow velocity (V_{max} and V_{min}) was 12 % and 10 % respectively [(23)].

Normal and pathological portal venous blood flow

Normal portal venous blood flow is slightly undulating [normal values 12 – 24 cm/sec examined by the intercostal approach with a mean resistance index of 0.36]. Different pathological flow patterns of the portal venous system have been described [(21;23)].

Figure 18 Portal vein. The portal vein (arrows) is scanned transcostally shown by colour Doppler imaging (a) and continous duplex scanning (b) with a normal flow pattern range of 12 – 24 cm/sec [(23)].

a



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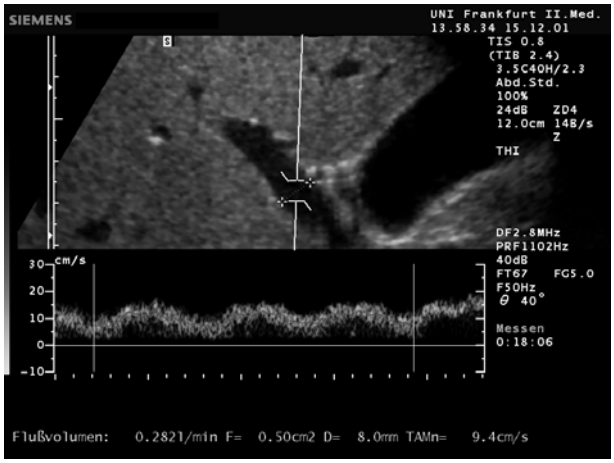
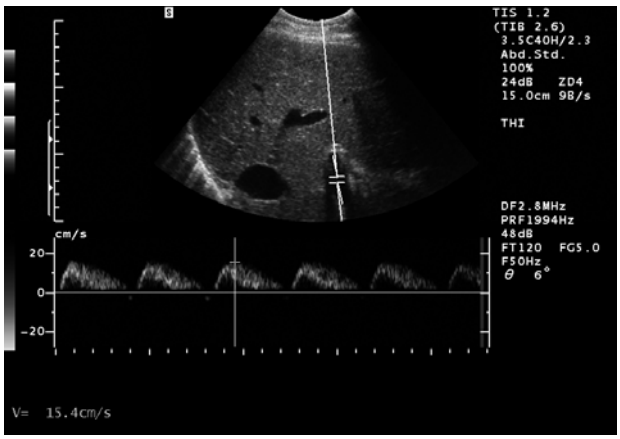


Portal hypertension

Colour Doppler ultrasound examination is recommended in patients with suspected portal hypertension since CDI is helpful in the detection of the presence and direction of blood flow in the portal venous system [(48)]. Hepato-fugal flow in the portal vein is found in about 10 % patients with liver cirrhosis [(40)]. Prevalence does not differ in relation to the aetiology of liver cirrhosis but is stage dependent and could be more often found in Child B and C cirrhosis than in Child A cirrhosis. The clinical significance of this Doppler phenomenon is still unclear, especially with its relation to (repeat) variceal bleeding.

Increased pulsatile flow (high resistance index) in the portal vein has predominantly been found in patients with severe right heart failure, demonstrating right atrial pressure negatively correlated with portal vein pulsatility ratio [Figure 19] [(35;48;50)]. In patients with steatosis the flow is flattened which is demonstrated in a low resistance index.

Figure 19 Increased pulsatility in the portal vein. Increased pulsatile flow in the portal vein has predominantly been found in patients with severe right heart failure, demonstrating right atrial pressure negatively correlated with portal vein pulsatility ratio.



No portal venous blood flow

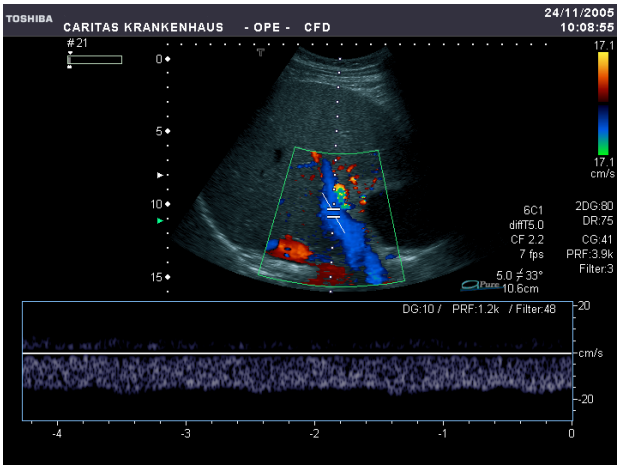
Very slow portal vein velocities of less than 2 cm/sec are difficult to detect because this Doppler signal is lower than the threshold of the ultrasound equipment and additional respiratory modulation of the patients. A stagnant or portal venous "0" flow is mainly seen in patients with advanced liver cirrhosis. In patients with stagnant portal vein flow the use of ultrasound contrast enhancing agents might be helpful in the exclusion of portal vein (appositional) thrombosis [(41)].

Retrograde portal venous blood flow

Reversed portal venous blood flow can be observed when intra-hepatic resistance is greater than the resistance of porto-systemic collaterals [Figure 20]. An association has been found between portal venous flow patterns (e.g., abnormal flow direction) and the presence of mainly spontaneous porto-systemic shunts but also oesophageal varices and ascites. The increase of intrahepatic resistance might be explained by structural abnormalities, e.g., hepatocyte enlargement, Disse space collagenisation and hepatic vein sclerosis. Retrograde portal venous flow has been observed mainly in patients with portal hypertension. Respiration dependent hepato-fugal portal flow is a rare finding associated with periodic portal hypertension in patients with right heart insufficiency and/or liver disease. Its clinical significance is unclear.

Pericardial effusion, constrictive pericarditis, pericardial tumours and right atrial tumour and possible other causes leading to an increased right atrial pressure are responsible for a pressure-related hepatic venous out-flow block with subsequent trans-sinusoidal hepato-portal shunting, similar to the mechanical outflow block that causes reversed pulsatile flow in liver cirrhosis. Severe pulmonary hypertension may be responsible for a second important pathophysiological mechanism. Portal vein–hepatic vein shunts and portocaval (portosystemic) shunts may also cause pulsatile portal flow.

Figure 20 Retrograde portal venous blood flow as a typical sign of severe portal hypertension.



Portal vein thrombosis

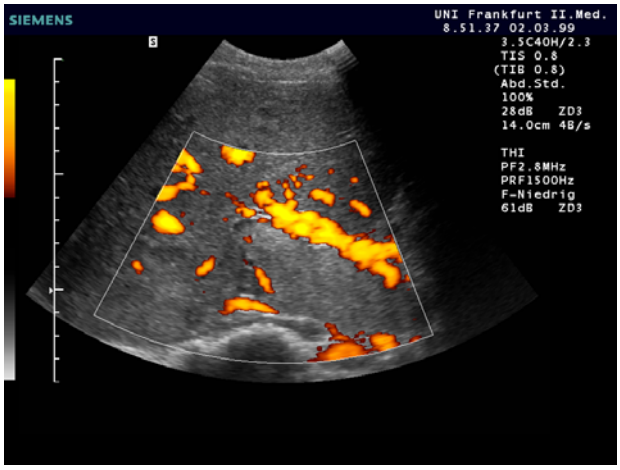
Portal vein occlusion with an increase in pre-hepatic portal vein pressure may have different causes – coagulation defects with thrombocystosis, an increase in fibrogen concentration due to inflammation and similar conditions have to be encountered.

Periportal venous collaterals as cavernous transformation may at least partially compensate the portovenous hepatic inflow. Moreover, reduced portovenous blood supply may be compensated by an increased arterial perfusion so that the liver function usually appears only slightly impaired. Portosystemic collaterals, however, lead to a reduced “first-pass” effect, deteriorating e.g. encephalopathy. This is especially important when portal vein thrombosis is caused by cirrhosis with reduction of flow, since because of this, encephalopathy may become manifest and the liver-dependent medication metabolism may be disturbed.

Colour-coded duplex sonography is the method of choice and has a high degree of sensitivity (> 90 %) in detecting segmentally localized or complete portal venous thrombosis [Figure 21].

Figure 21 Portal vein thrombosis. Echorich and total portal vein thrombosis intrahepatically (a) and also extrahepatically (b). Circumscript portal vein thrombosis is shown in B-mode and using contrast enhanced ultrasound (c,d).

a



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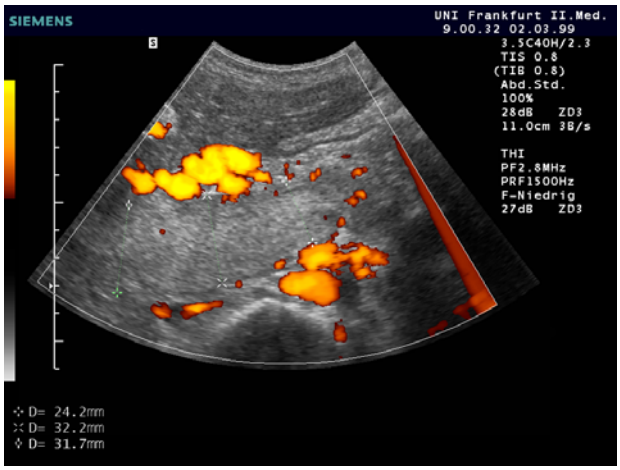

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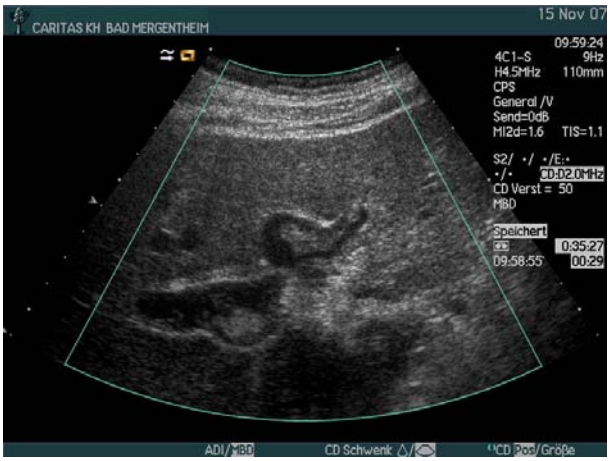

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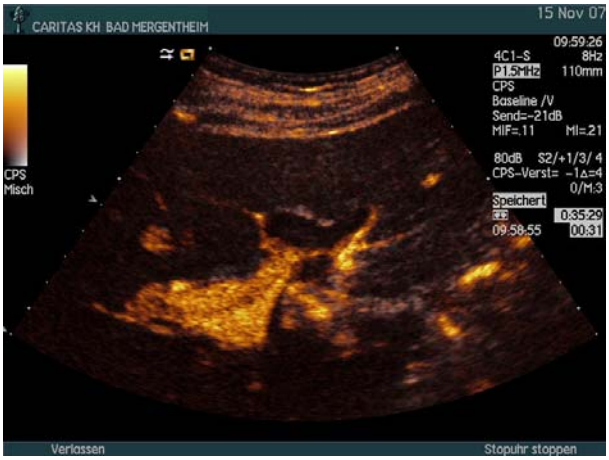

Contrast enhanced computed tomography is an alternative in the diagnosis of portal vein thrombosis, especially with obese patients. Magnetic resonance tomography and splenic portography are unnecessary.

Before operations or interventions it may be desirable to perform angiography of the visceral vessels. Ultrasound is specific for exclusion of infiltration of hepatic vessels (e.g. portal vein and hepatic veins). Portal vein thrombosis is a common sign of tumour angiogenesis, especially in extensive tumour stages. To differentiate between benign and malignant portal and hepatic vein thrombosis it is useful to use colour Doppler imaging or contrast enhanced techniques. Using colour Doppler imaging malignant infiltration can be assumed, if pulsatile flow is derived from inside of the thrombus. If this is not conclusive, contrast enhanced ultrasound is more sensitive in showing arterial enhancement of the thrombus.

Examination of the hepatic veins in patients with diffuse liver disease

The normal flow pattern in the right hepatic vein is triphasic [(23)] [Figure 22]. The FFT-Doppler ultrasound spectrum of the right hepatic vein next to the inferior vena cava reflects mainly cardiovascular and respiratory changes in pressure and flow pattern. In contrast, the FFT-Doppler ultrasound spectrum of the right hepatic vein 6 - 8 cm distal to the confluence of the hepatic veins reflects histological changes of the liver parenchyma and can be classified into a triphasic waveform with a short reversed flow, a biphasic waveform with no reversed flow, but fluttering of more than 10 % of the mean phasic amplitude, or a monophasic flat waveform with fluttering of less than 10 % of the mean phasic amplitude. In patients with heart insufficiency the flow can be tetraphasic which means that there is a significant amount of hepatopetal flow showing a pendular flow (forward and backward). The maximum, medium, and minimum (reversed flow) velocity [cm/seconds] could be additionally recorded. Because of changes in the vessel diameter up to 2 mm per cycle during systole and diastole and different directions of the normal triphasic hepatic vein flow, it is not useful to calculate the blood flow [ml/minute] in the hepatic veins [(23)].

Examination technique

The right hepatic vein is identified via the right intercostal approach, displayed longitudinally by a counterclockwise turn, and the sample gate is positioned 6-8 cm distal to the confluence of hepatic veins and adjusted according to the inner diameter of the vessel (typically 3 – 7 mm). Fast Fourier Transformation (FFT) spectral analysis is recorded for at least 5 sec. The Doppler ultrasound spectrum can be recorded within a short breathing pause of 5 to 8 seconds without relevant intra-abdominal or intra-thoracic pressure related artefacts. To avoid artefacts due to different respiratory positions and different abdominal and intrathoracic pressures, the evaluation of the right hepatic vein via the tenth or eleventh intercostal space 6 - 8cm distal to the confluence of the hepatic veins offers a standardised procedure and provided reproducible results with an acceptable insonation angle in all patients and healthy subjects [(23)].

Which liver vein should be examined?

The close anatomical relationship between the left liver lobe and the heart frequently leads to Doppler signal artefacts in any signal obtained from the left hepatic vein. Because of these artefacts, which are mainly due to heart movements, the left hepatic vein cannot always be reliably evaluated. Adequate sonographic visualisation of the middle hepatic vein and evaluation of the FFT-spectrum is best accomplished during slight inspiration and via the

subcostal route. In 35/135 patients however, evaluation of the middle hepatic vein was only possible during deep inspiration with respiration related artefacts of the Doppler ultrasound spectrum with an initial monophasic waveform changing to a bi- and triphasic waveform during the examination. The most reproducible Doppler ultrasound spectrum can be obtained from the right hepatic vein via the right intercostal approach [(23)].

The reproducibility of the method was investigated by repeated sonographic examinations of the flow pattern in the right hepatic vein in ten healthy subjects over seven consecutive days. The mean coefficient of variation for intra-individual assessment of flow velocity was 13 % for the hepato-fugal flow and 19 % for the reversed flow. The flow pattern in the ten subjects investigated was always triphasic. The reproducibility for the middle hepatic vein was less favourable with a mean coefficient of variation for intra-individual assessment of the flow velocity of 25 % for the hepato-fugal flow and of 76 % for the reversed flow [(23)].

Clinical application

It was previously shown that a non-triphasic hepatic vein flow (HVF) is mainly associated with the degree of fat deposition within the liver and less related to inflammatory parameters and the extent of liver fibrosis. Recently a large scale study on patients with chronic HCV infection confirmed that hepatic steatosis can be excluded by normal liver hemodynamics, however, some operative characteristics (specificity and positive predictive values) were rated insufficient. Non-triphasic HVF and FHA within the liver hilum are both parameters that can be easily measured and quantified by ultrasound. The recorded values are reproducible and less dependent on the investigators interpretation than conventional grey scale imaging.

In general more than 90 % of healthy probands have a triphasic flow pattern, whereas only 60 – 70 % of patients with a hepatopathy show a non-triphasic pattern. So, for non triphasic flow and the diagnosis “liver disease” the positive predictive value is high but the negative predictive value is low.

Figure 22 Hepatic vein blood profile. The normal hepatic flow profile is triphasic (a,b) in the right liver vein (RLV); the portal vein is also indicated. Monophasic flow deformation is mainly due to hepatic fat infiltration, as shown in this patients with steatohepatitis (c) [(23)].

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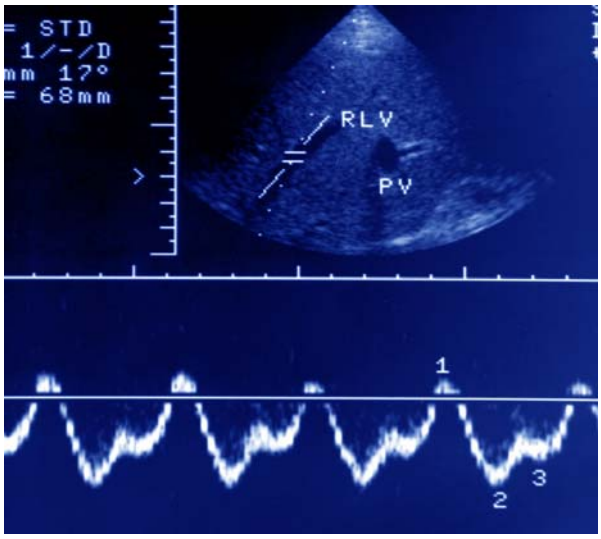
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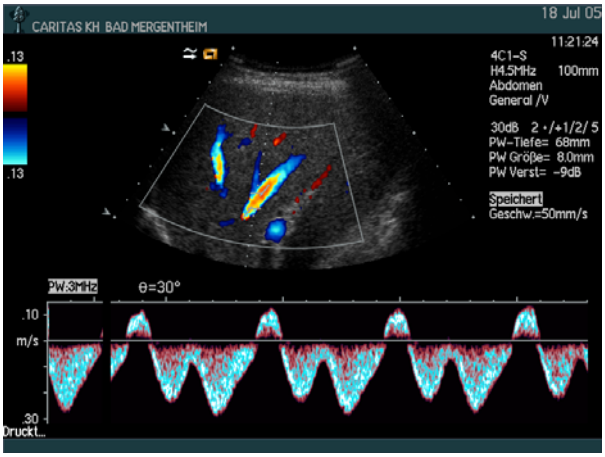
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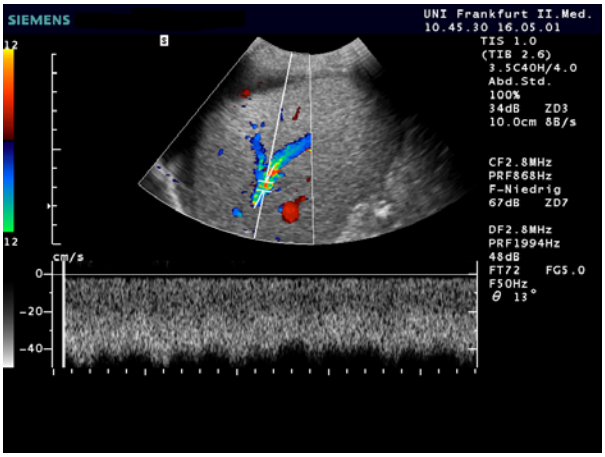
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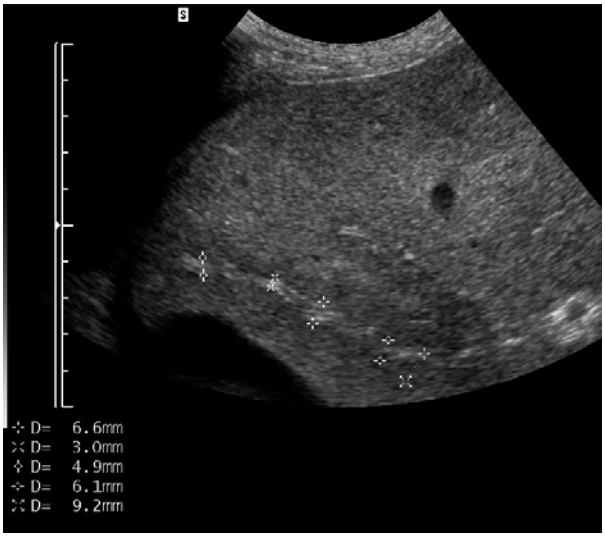
Hepatic venous outflow obstruction (Budd Chiari-syndrome, BCS)

Budd-Chiari syndrome is a rare cause of liver disease with or without signs of portal hypertension. About one third of patients present with acute disease with sonographically detectable thrombosis. About two thirds have chronic presentation sonographically with occluded hepatic veins and intrahepatic collaterals [Figure 23].

Figure 23 Budd Chiari syndrome. About one third of patients present with acute disease with sonographically detectable thrombosis. About two thirds have chronic presentation songraphically with occluded hepatic veins (a, in between markers), retrograde portal venous outflow (b), and intrahepatic collaterals with or without extrahepatic shunts. PV: portal vein.

a



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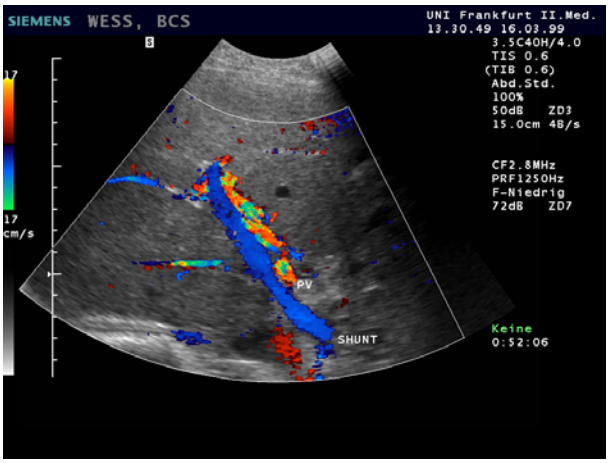


The hepatic vein might in this stage be occluded appearing as fibrous strand or spontaneously partially or completely recanalised dependening on the etiology. Colour Doppler imaging is helpful in the diagnosis of BCS. Doppler ultrasound accurately detected the site of the block in 31 of 39 patients (79%). In patients with newly diagnosed Budd-Chiari syndrome hepatocellular carcinoma has to be ruled out by contrast enhanced ultrasound or other imaging methods.

Veno-occlusive disease (VOD)

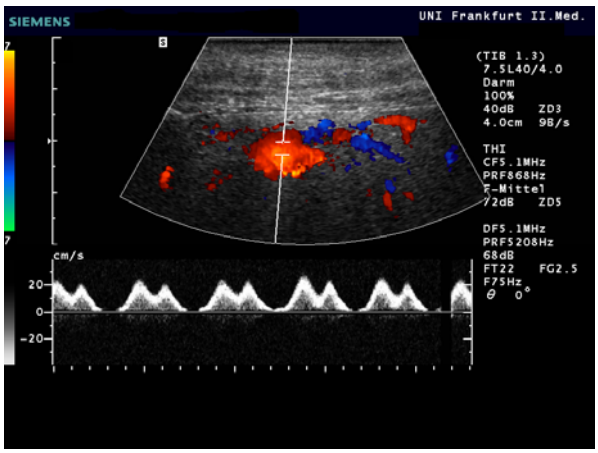
Duplex sonography of the portal vein system and the hepatic veins may show typical changes, although displaying only a relatively low sensitivity and specificity. Sonographic signs of VOD are ascites, thickening of the gall bladder wall, increase of the resistance index in the hepatic artery (RI) as well as retrograde flow in the portal vein and changes in the portal vein flow profile. Colour Doppler imaging in the diagnosis of 12 patients with veno-occlusive disease after bone marrow (stem cell) transplantation reveals low (< 10 cm/sec) or reversed portal venous flow, high resistance arterial flow pattern (resistance index > 0,85) and flattened monophasic flow pattern in the right liver vein of less than 8 cm/sec. Published data is sparse in patients with veno-occlusive disease.

Osler`s disease

Liver involvement (in 30 % – 70 % of the cases) can lead to a specific form of liver cirrhosis, due to sclerosis formed around the multiple vascular malformations which can be easily detectable by ultrasound [(13;42)]. Doppler ultrasound helps to identify the nature of shunts (arterio-portal, arterio-systemic, arterio-porto-systemic) [Figure 24].

Especially in the supply area of the superior mesenteric artery dense networks of vessels (oval cystic lesions using conventional B-mode ultrasound) with corresponding malformations are found representing shunts.

Figure 24 Osler disease showing intrahepatic arterio-porto-venous shunts with typical Doppler spectrum for shunts.



The cirrhosis as well as the amount of (multiple) portosystemic shunts caused by vascular malformations contributes to the development of encephalopathy. The liver cirrhosis caused by the basic illness flow pattern must be distinguished from the effects of the often multiple transfusions (post transfusion hepatitis).

In the case of an arterio-venous shunt formation in the liver with systemic effects (which frequently occur at a later age), *the selective arterial embolisation* of the supplying vessels has proven successful. Due to the general state of health of the patient, surgery (ligature of the supplying vessel, partial resection of the liver) is not always possible.

Transjugular intrahepatic portosystemic shunts (TIPSS)

A high percentage of patients with transjugular intrahepatic portosystemic shunts (TIPSS) have post procedural shunt complications, including thrombosis of the stent, stenosis of the stent, or stenosis of the hepatic vein draining the stent. Doppler ultrasound is an excellent non-invasive screening technique for the detection of complications of TIPSS. Complications of TIPSS can be detected by using different criteria: no flow for thrombosis, a temporal change in peak stent velocity greater than 50 cm/sec for stent and/or hepatic vein stenosis, and reversed flow in the hepatic vein draining the stent and, rarely, stent stenosis. In 45 patients use of a change (increase or decrease) in peak stent velocity greater than 50 cm/sec from the post-TIPSS baseline sonogram as the diagnostic criterion for the detection of shunt stenoses resulted in a 93 % sensitivity and 77 % specificity. A more detailed description can be found elsewhere in the European Course Book.

Liver pathology - detection and characterisation of focal liver lesions (FLL)

The definition of a focal liver lesion (FLL) is differences in echogenicity between a circumscribed area and the surrounding liver tissue. Differences in ultrasound echogenicity usually, although not necessarily, show more or less pronounced differences in X-ray attenuation and in magnetic resonance (MR) as well. Consequently, most FLL are visualized by all three sectional imaging modalities, whereas some few are shown by one or two of these modalities only.

FLL are detected and characterised sonographically by echogenicity differences from the surrounding liver tissue as well as by the detection of hyper- or hypovascularisation (colour Doppler ultrasound).

Conventional B-scan ultrasound makes it possible to detect unequivocally the frequently occurring typical liver cysts and calcifications.

Detection and characterisation of liver tumours on the other hand, still represents a challenge to all imaging modalities despite all the advances in imaging techniques (ultrasound, CT and MRI scanning).

More recently, contrast enhanced utrasonography can provide important additional information on FLL perfusion kinetics and vascularisation pattern. Circumscribed lesions of liver-foreign tissue (e.g. metastases) can be detected by the absence of uptake of contrast media (e.g. SonoVue® and Levovist®. Albunex® and Optison® are not used in Europe any more).

Such lesions appear in the post vascular late-phase image as storage defects, though this late-phase effect is neither absolutely specific nor absolutely sensitive. As a result of their doubled blood supply via the portal vein and the hepatic artery, focal lesions in the liver often exhibit no general hyper- or hypo perfusion but, depending on the flow phase and the histology, present a complex temporal and spatial picture of increased and reduced contrast. Certain lesions can give a characteristic vascular picture (e.g. the wheel-spoke phenomenon) or a distinctive perfusion pattern (e.g. halo contrasting or iris diaphragm phenomenon), allowing the lesions to be characterised, but the contrast patterns do not always take this typical form. Similar arterial, parenchymatous, and venous characteristics are exhibited by the spleen and by lymph nodes.

The technique of contrast enhanced ultrasound (CEUS) is described in the technical chapter. The use of contrast agents in the liver is possible for different purposes [(14;18)]:

- detection of liver tumours;

- characterisation of liver tumours (benign versus malignant);
- monitoring of local ablative treatment;
- imaging hepatic vessels;
- describing diffuse liver disease by demonstrating intrahepatic microscopic shunts by measuring the hepatic transit time (time interval between appearance in the hepatic artery to the liver veins);
- Analysing time intensity curves.

Liver tumour detection

CEUS increases the detection rate of metastases as compared to conventional B-scan ultrasound which has been demonstrated also by multicenter trials. Comparative studies have shown that the detection rate is of the same accuracy as the detection rate for contrast enhanced CT and MRI scans.
CEUS allows the same detection rate for benign FLL as compared to their occurrence in normal liver parenchyma (10 % of all livers) which is of importance when it comes to a differential diagnosis.

Differentiation of benign and malignant lesions

Characterisation of a liver lesion begins once an abnormality is found. An imaging procedure that is used to detect liver masses should also enable the examiner to differentiate between benign and malignant lesions. Contrast enhanced ultrasound in the portal venous and late phase after injection of Levovist® and SonoVue® considerably improves the characterisation of liver tumours compared with conventional B-mode ultrasound, leading to differentiation of benign and malignant liver lesions in most patients - if cysts and calcifications are excluded by conventional B-mode ultrasound. CEUS facilitates the clinical decision as to whether a sonographically detected liver lesion will need further investigation or not. From this point of view, this new technique might help to reduce unnecessary or invasive examinations in certain cases, such as invasive liver biopsy, CT-scan and MRI. Only few false positive findings have been observed so far, mainly due to abscesses or necrosis, old fibrous focal nodular hyperplasia with predominantly scar tissue, sarcoidosis lesions, and inflammatory pseudo-tumours of the liver [(20)].

Focal liver lesion (liver tumour) characterisation

Liver cyst

Liver cysts are a frequent finding [Figure 25 - 27]. They are readily diagnosed using conventional B-mode ultrasound. Liver cysts are characterised, as other cysts by - typically round, anechoic, smoothly delineated structures with refraction shadows at the edges, strong posterior wall echo and postcystic enhancement due to the intensity difference between the beam intensity deep to the cyst and in the cysts displaying all sonographic sign are defined as typical [Figure 25] whereas cysts with not all sonographic signs of typical cysts are defined as being atypical [Figure 26]. Very early echinococcosis might be confused with atypical liver cysts. Cystadenoma are another differential diagnosis [Figure 27].

Figure 25 Typical liver cyst. Exophytic liver cyst next to the spleen. Typical liver cysts display all morphological criteria (echo-free, round-oval, well-defined borders with lateral shadowing and transducer distal (posterior) echo enhancement) whereas atypical liver cysts do not.

a

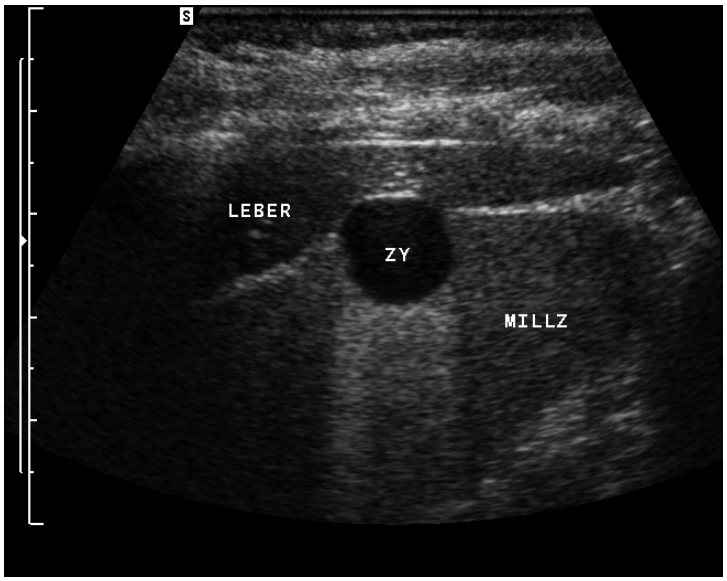
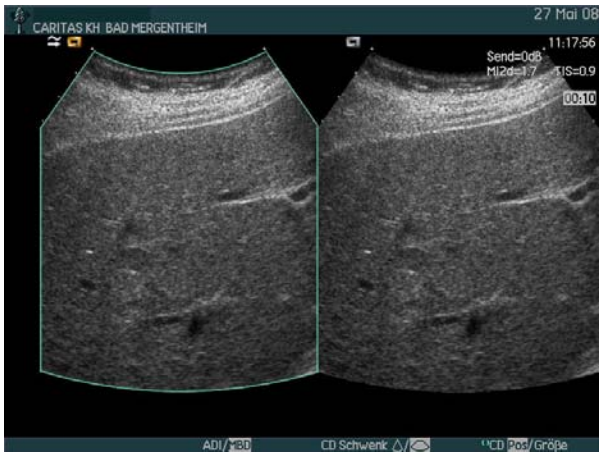


Figure 26 Atypical liver cyst. Atypical liver cysts do not display all morphological criteria of typical liver cysts (echo-free, round-oval, thin walled, well-defined borders with lateral refraction shadowing and postcystic echo enhancement). Due to the small diameter and other artifacts (slice thickness artefact) the cyst is not echofree (a), but contrast enhanced

ultrasound (CEUS) proves the cyst (b). In another example the cyst like structure is a hepatic vessel which might be sometimes difficult to recognise using conventional B-mode (c,d).

a



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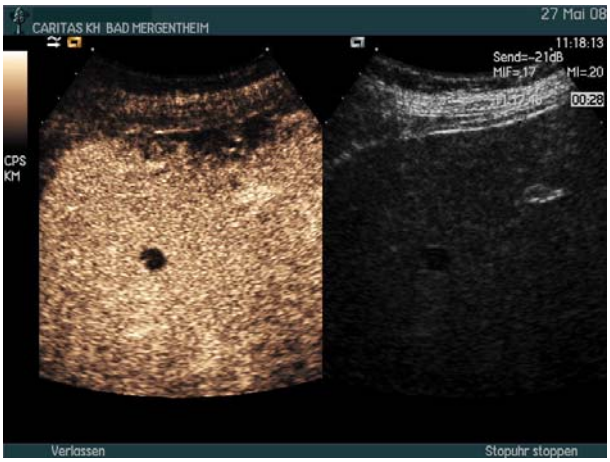

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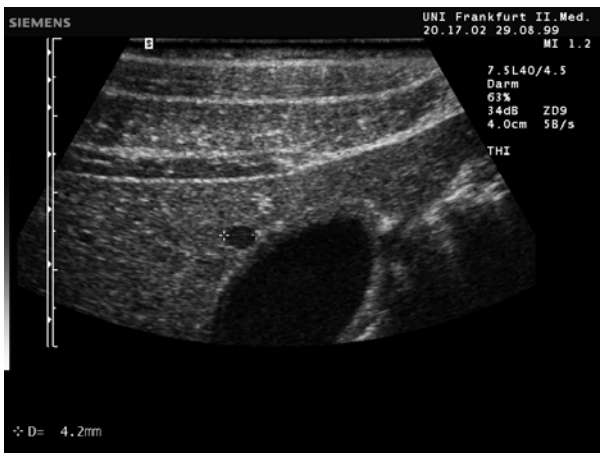

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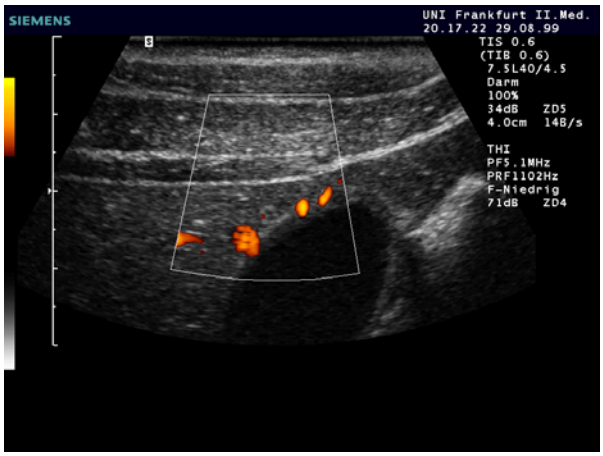
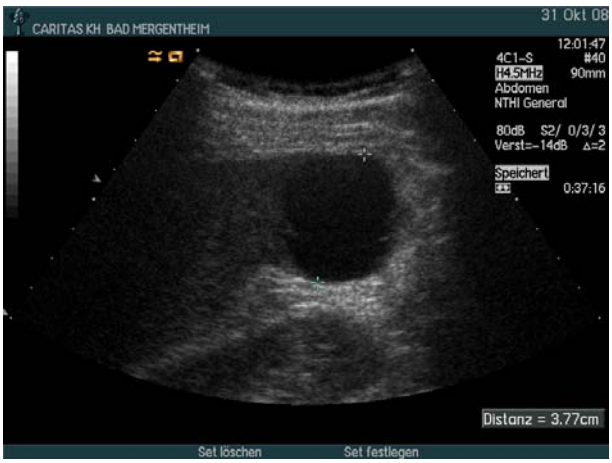


Blood vessels mimicking a simple cyst have to be excluded by colour Doppler imaging ruling out arterio-portal venous malformations [Figure 26]. Using CEUS, cysts show no contrast enhancement at all. As small cysts may be confused with metastases in CEUS, conventional B-mode ultrasound has to precede CEUS.

Cystadenoma are rare neoplastic differential diagnoses of atypical cysts.

Figure 27 Cystadenoma. Cystadenoma are rare neoplastic differential diagnoses of atypical cysts. Contrast enhancing nodules are indicative for this diagnosis.

a



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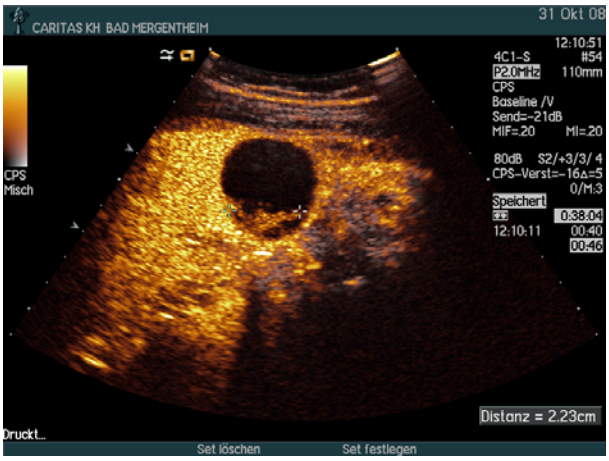


Echinococcosis, *Echinococcus cysticus*

Gharbi et al (1981), first introduced the widely used and most cited classification of hydatic disease which has been modified many times. Gharbi type I cysts consist of pure fluid; Gharbi type II have a fluid collection with a split wall; Gharbi type III cysts contain daughter cysts (with or without degenerated solid material); Gharbi type IV have a heterogeneous echo pattern; and Gharbi type V have a calcified wall. It is of importance that lesions may show different stages of hydatid evolution [(1;2)].

US and CEUS is helpful in recognising echinococcosis in all stages. Most useful is the combination of morphological criteria and the biological behaviour (fertile cysts with viable protoscoleces [Gharbi type I, II], transitional phase [Gharbi type III] and inactive cysts which have lost their fertility [Gharbi type IV, V]). Characteristics on ultrasound that are suggestive of an inactive lesion include a collapsing, flattened elliptical cyst (corresponds to low pressure within the cyst), detachment of the germinal layer from the cyst wall ("water lily sign"), coarse echoes within the cyst, and calcification of the cyst wall.

The use of a combined classification including imaging criteria and biological evidence of viable parasites will enable clinicians to perform the correct clinical procedures for the different cyst types [(27)].

Type I The most common type I lesion (50 – 80 %) represents an anechoic smooth, round pure fluid collection without hydatid sand and septa. containing usually fertile cysts with viable protoscoleces, which can be difficult to distinguish from a benign cyst. The roundish lesion with well defined borders is most importantly characterised by an irregular localised thickened wall (initial stage of splitting the wall) which should be carefully sought by high

frequency and therefore high resolution probes (7 – 15 MHz) and contrast enhanced ultrasound which delineates the nodular appearance very early in the course of the disease.

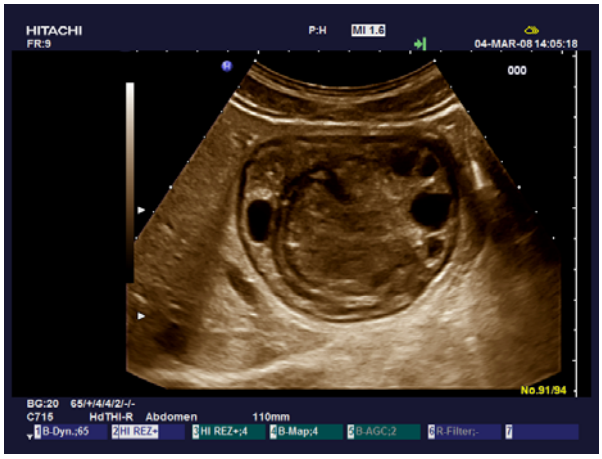
Type II: Splitting of the wall (infoldings of the inner cyst wall resulting in floating membrane, so-called water lily sign) is typically for type II fluid filled lesions also containing fertile cysts and seems to be the most important and pathognomonic sign of echinococcosis. It is of interest that splitting of the wall to the outer margin (“outfoldings”) implies the typical fine nodular appearance of contrast enhancement. When the liver cyst contains membranes and “sand”, mixed echoes will appear that can be confused with a neoplasm or abscess. The term "hydatid sand," reflects a complex image which consists predominantly of parts of protoscolices (hooklets and scolexes). This finding of mobile “sand” may be overt and visible turning patient's position, e.g. into the standing position.

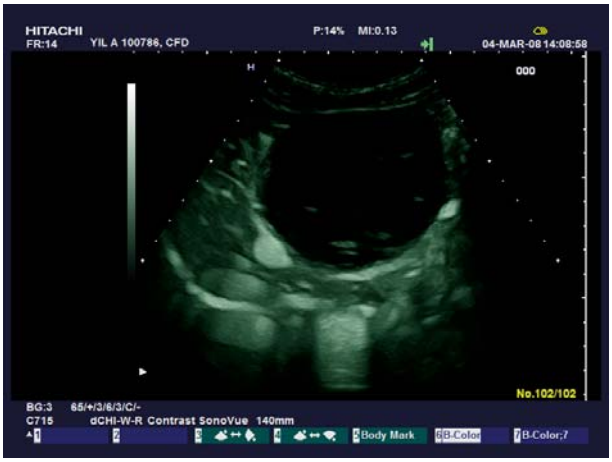
Type III: When daughter cysts are present, characteristic internal septation results. Type III is characterised by septa resulting in a honeycomb appearance with infolding membranes. This stage has been described as transitional where the integrity of the cyst has been compromised either by the host or by medical treatment. The “cyst in the cyst sign” by separation of the hydatid membrane from the wall, “hydatid sand” in combination with fine nodular appearance of contrast enhancement are pathognomonic of echinococcosis. Neoplasia can be ruled out by exclusion of contrast enhancement within the lesion. In the very early stages of echinococcosis without calcifications ultrasound can depict the specific intralesional morphology in detail much earlier than any other imaging modality [Figure 28].

Type IV: Type IV lesions are characterised by a heterogenous echo pattern. The echogenicity of the lesion might be more hypoechoic but can also be hyperechoic due to regressive changes. This stage is more unspecific compared to the pathognomonic II and III stages.

Type V: The type V pattern reflects a solid heterogeneous mass which is difficult to differentiate from tumours. An identifiable thickened hyperechoic calcified wall suggests echinococcal cyst. Cysts with a calcified rim may have typically an "eggshell" appearance. Type IV and V lesions represent inactive cysts with degeneration which have lost their fertility. Calcification, which usually requires five to ten years to develop, occurs most commonly with hepatic cysts. Calcifications in pulmonary or bone cysts are more rarely encountered. Total calcification of the cyst wall suggests that the cyst is nonviable.

Figure 28 Echinococcosis. Echinococcosis stage in this patient is characterised by multiloculated cysts in a honeycomb appearance with infolding membranes. Calcifications are difficult to recognise.

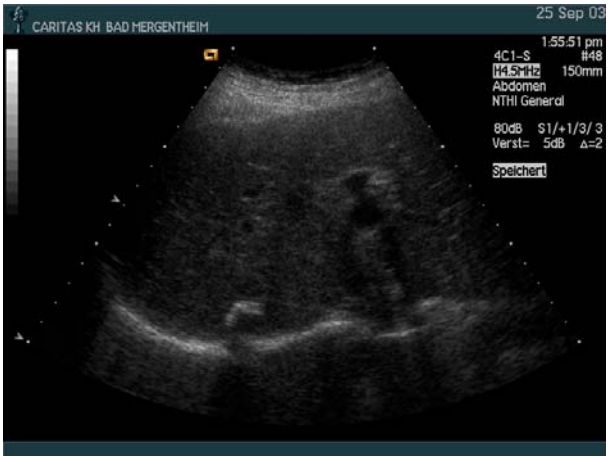


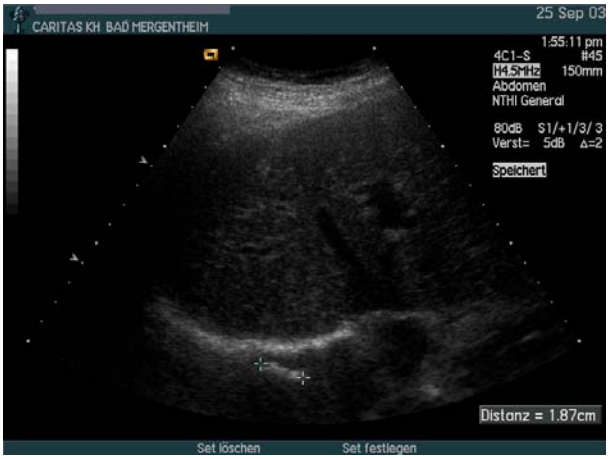


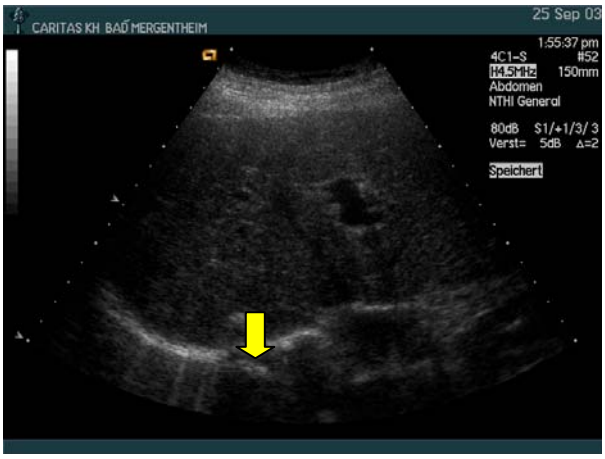
Calcification

Calcifcations are characterised as echo-rich structures normally showing acoustic shadowing distally due to reflection/attenuation of the ultrasound. [Figure 29].

Figure 29 Calcifications. Calcifications within the liver. Mirror artefact due to the acoustic impedance characteristics of the lower lung surface is also shown. Disctinct changes of the transducer position shows different kind mirror artefacts.







Liver cyst

Haemangioma

Hepatic haemangiomas are known to be the most common benign liver tumours, with an incidence in autopsy and imaging studies of up to 7 % [Figure 30-32]. Up to 10 % of patients with haemangiomas cannot be reliably diagnosed using imaging methods; in those patients only ultrasound guided liver biopsy and examination of the specimen is decisive for final diagnosis which is mainly true in the patient with malignant underlying disease. One retrospective study of percutaneous biopsies of 38 patients (1 cm to 13.5 cm, with a mean of 3 cm) with suspected hemangioma using 20 gauge needles reported that it is safe and effective for establishing the diagnosis of hemangioma.

Conventional B-mode ultrasound

Most haemangiomas demonstrate typical sono-morphological features in conventional B-mode, characterised as: less than 3 cm in diameter, lobulated with a well defined outline, located adjacent to liver vessels, demonstrating an echo-rich texture and sometimes posterior acoustic enhancement due to blood filled capillaries [Table 2].

Table 2 Typical hemangioma, diagnostic criteria

B-mode Criteria
Less than 3 cm in diameter
Echo-rich structure
Homogeneous inside
Round or slightly oval shape
Smooth outline
Absence of any halo sign
Possible detection of feeding and draining vessel
Absence of any signs of invasive growth
Posterior acoustic enhancement

Colour Doppler imaging

Although haemangiomas are highly vascularised masses, from the histo-pathological perspective, they consist essentially of a large number of capillary-sized vessels and so, even with the use of high-end ultrasound systems, conventional colour Doppler ultrasound often detects little or no blood flow inside the haemangioma due to the fact that the blood flow velocity in the capillary haemangioma is too slow. The supplying and draining vessels ("feedings vessels") may be visualised (depending on the ultrasound systems performance) at the edge of the lesion.

Contrast enhanced ultrasound

Contrast enhanced ultrasound has markedly improved the correct diagnosis of haemangioma which is possible in about 95 % of patients. CEUS demonstrates typical haemangioma imaging characteristics, i.e. peripheral nodular contrast enhancement and iris-diaphragm sign in a high percentage of patients with undetermined lesion. Difficult differential diagnosis includes shunt haemangioma (synonymous high-flow haemangioma, 5 - 10 %) which might be confused with focal nodular hyperplasia when small, hepatocellular adenoma or hepatocellular carcinoma. A thrombosed haemangioma might be confused with a metastasis by demonstrating contrast sparing in the arterial and portal venous phase.

Arterioportal shunts

Arterioportal shunts associated with a hepatic tumour have been reported primarily in patients with malignant tumours, especially in advanced hepatocellular carcinoma with portal vein invasion. However, arterioportal shunts have been observed in hepatic hemangiomas not only using CEUS but also on multiphase helical CT and MRI. One possible explanation for rapidly enhancing small haemangiomas is a hyperdynamic status with large arterial inflow, rapid tumoural enhancement, and consequently, large and rapid outflow, which seems to result in early opacification of the draining portal vein via shunts. Shunt haemangiomas are typically surrounded by focal hypoechoic areas representing less fat content in comparison with the surrounding liver parenchyma [(26;46)]. The metabolic changes are explained by a mainly arterial blood supply of the hypoechoic areas whereas blood supply of the surrounding liver parenchyma is mainly by portal venous vessels containing more lipids and this might be due to a higher concentration of insulin [Figure 32].

Figure 30 Haemangioma. The typical contrast-enhanced ultrasound findings are peripheral nodular contrast-enhancement and centripetal fill in with the exception of thrombosed areas and calcifications (iris diaphragm phenomenon) (between callipers) [case of the month, EFSUMB.org].

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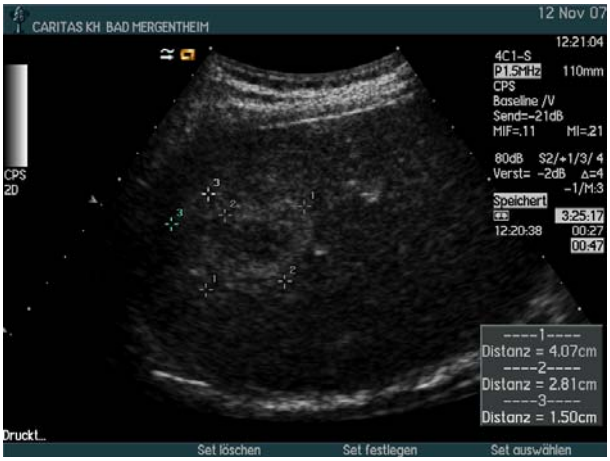

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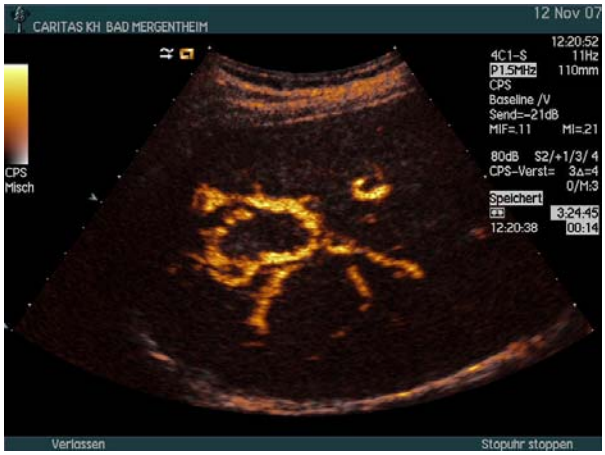

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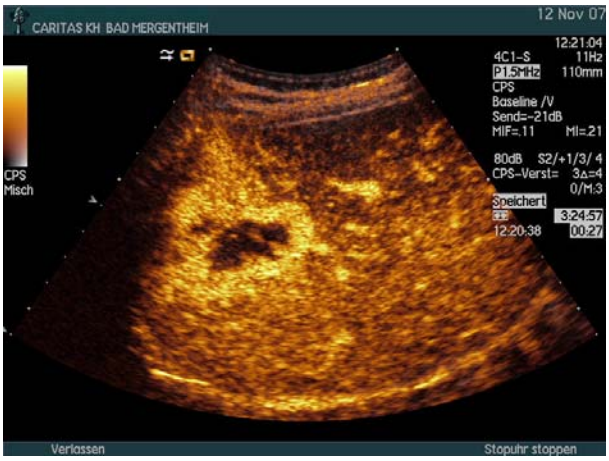

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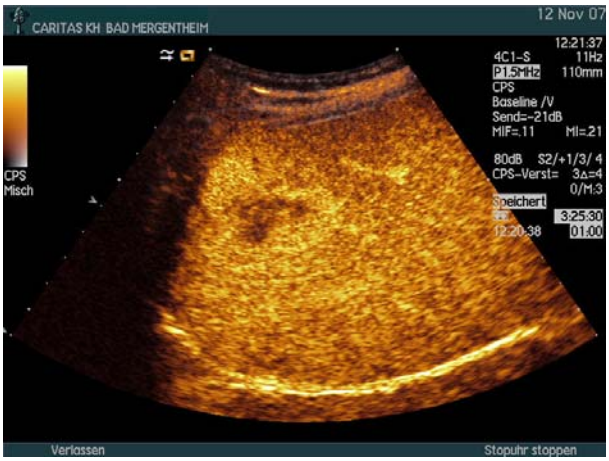
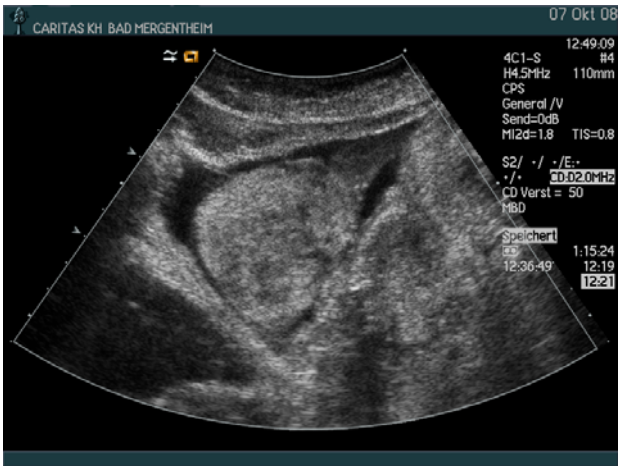


Figure 31 Haemangioma. The typical B-mode appearance is echorich (a) also seen in liver cirrhosis. Contrast-enhanced ultrasound findings are peripheral nodular contrast-enhancement and centripetal fill in with the exception of thrombosed areas and calcifications (iris diaphragm phenomenon).

a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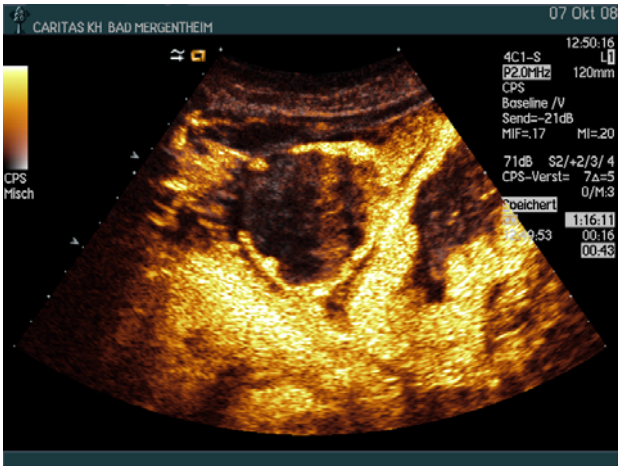
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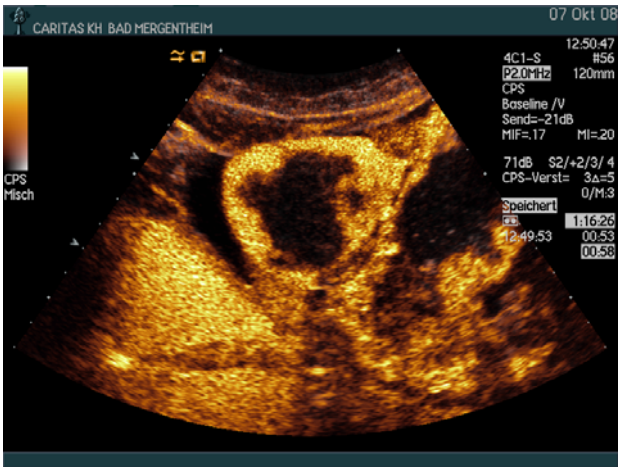
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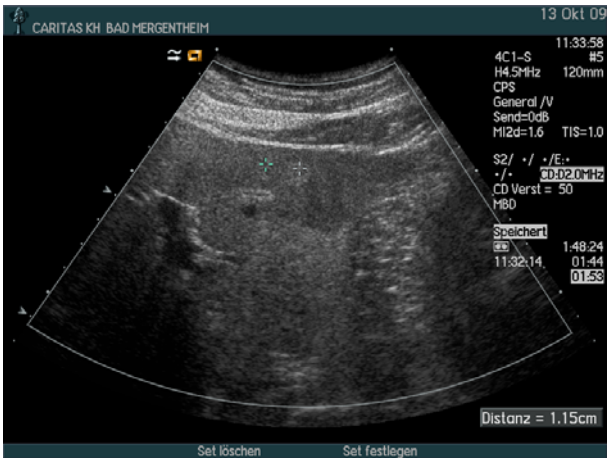
Figure 32 Shunt haemangioma. Focal hypoechoic and hyperechoic lesions subcapsular with inhomogenous echogenicity (a). Colour and Power Doppler imaging were not helpful. The real lesion is shunt-haemangioma (in between callipers) with arterio-portal venous shunts (shunt haemangioma) leading to regional inhomogenous fat content. The typical contrast-enhanced ultrasound finding is centripetal fill-in within seconds and bright appearance in the portal venous phase (b,c). The lesions are often missed by computed tomography and magnetic resonance imaging due to the small size (typically less than 15 mm) and differences in the arterial enhancement pattern in comparison to the surrounding parenchyma for only 1 - 2 seconds. Final diagnosis is made by histology in patients with malignant underlying disease [(26;46)].

a



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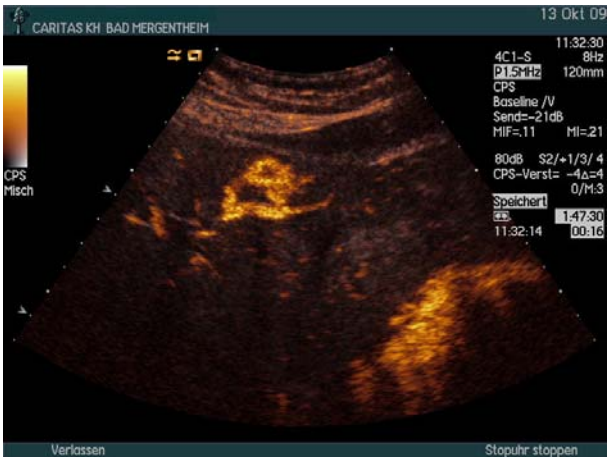

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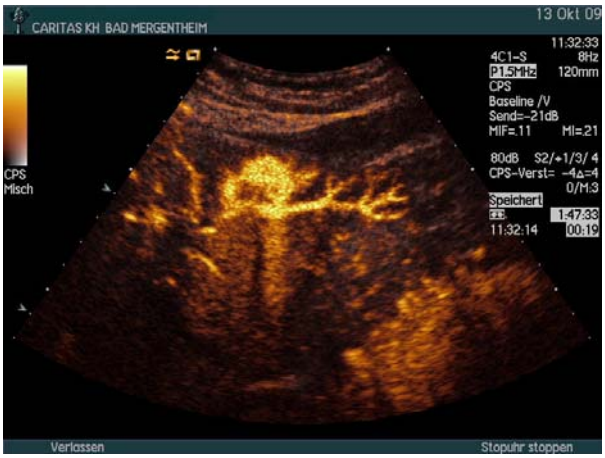


Focal nodular hyperplasia (FNH)

Focal nodular hyperplasia (FNH) and the important differential diagnosis of hepatocellular adenoma (HCA) are two benign, mostly incidentally discovered hepatic neoplasia, which occur predominantly in young and middle-aged women. Differentiation is essential because of different therapeutic approaches: HCA is an indication for surgery because of the risk of haemorrhage and potential malignant transformation; in contrast, FNH can be managed conservatively. However, until recently the non-invasive differentiation of especially atypical FNH from HCA and other benign or malignant neoplasia has remained challenging, with no satisfactory tests apart from histological examination of a liver biopsy sample. Histological features of FNH are controversially discussed in the literature. Congenital absence of portal veins has been reported in few patients, mainly children.

Helical CT and MR imaging do provide some useful information in the diagnosis of FNH, especially when the lesion depicts typical features, such as a central scar and uniform hypervascularity. Typical features are only reported in about 50 %. In a series of 305 FNH studied macroscopically, a central scar could be found only in about 50 %.

Conventional B-mode ultrasound

FNH is typically an isoechoic tumour of variable size, with a central scar and calcifications (50 – 80 %).

Colour Doppler imaging

Typically, colour Doppler imaging reveals a (arterially) hypervascularised tumour (> 90 %) with characteristic (para-) central arterial blood supply. In many patients, increased blood

flow compared with the surrounding liver tissue can be detected even in colour Doppler mode, causing a so-called wheel-spoke phenomenon. This hyperperfusion that can be recognised in native imaging is by no means obligatory and is reported only in about 50 - 70 % of patients. It could also be shown that inter-observer reliability in recognising the wheel-spoke appearance is very low.

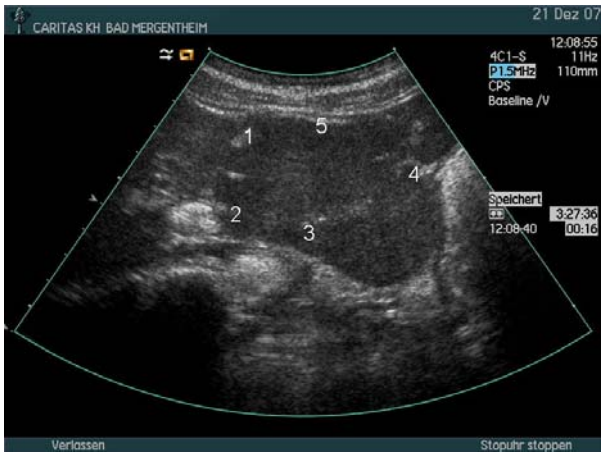
Contrast enhanced ultrasound

The examination of the hepatic arterial and portal venous / sinusoidal phase by contrast enhanced phase inversion ultrasound allows for reliable differentiation between FNH and HCA. This important finding could be explained by the lack of portal veins in contrast to FNH which presents (atypical) portal veins in many but not all patients.

In a contrast enhanced examination, FNH typically appears as a hyperperfused tumour-like lesion relative to the surrounding liver tissue in the early arterial phase. This hyperperfusion is easily visible during continuous scanning, comparing the contrast enhancement of the lesion with the surrounding hepatic arteries. Depending on the patient's cardiac output, some 8 to 20 seconds after injection of the echo-signal enhancer into the cubital vein there is a rapid take-up of the substance with demonstration of the arterial vascular pattern and enhancement from the centre outwards. During the portal venous phase FNH is isoechogenic with the portal vein, and, therefore, slightly hyperperfused in comparison to the surrounding liver parenchyma [(20;29)] [Figure 33].

Figure 33 FNH using B-mode often appears as isoechoic in comparison to the surrounding liver parenchyma and can not be differentiated from malignant tumours like hepatocellular carcinoma (a). FNH in the arterial phase appears typically as a hypervascular and hyperperfused structure relative to the surrounding liver tissue demonstrating the typical central artery in up to 70 % whereas in larger FNH more than one supplying artery can be displayed (b and c, indicated by numbers). During the portal venous phase FNH is slightly hyperechoic in comparison to the surrounding liver parenchyma in more than 90 % of lesions. The typical central scar (in between markers) can be found in up to 70 % of patients with FNH which has been proven in autopsy studies.

a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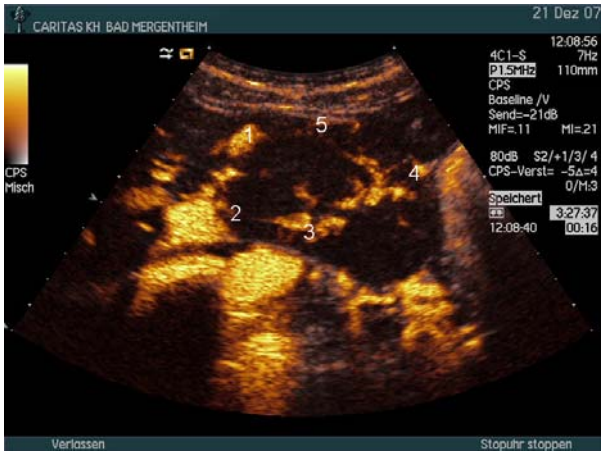
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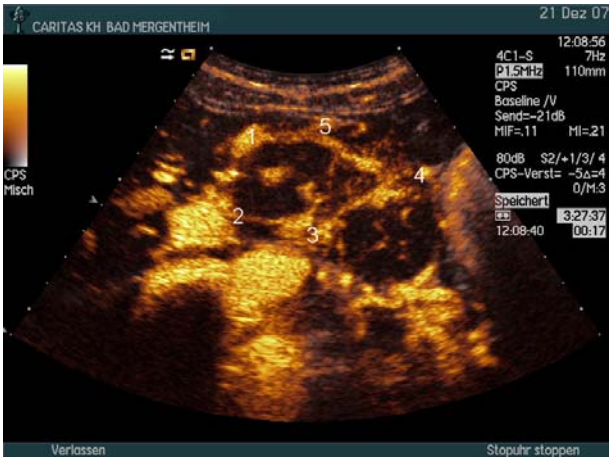
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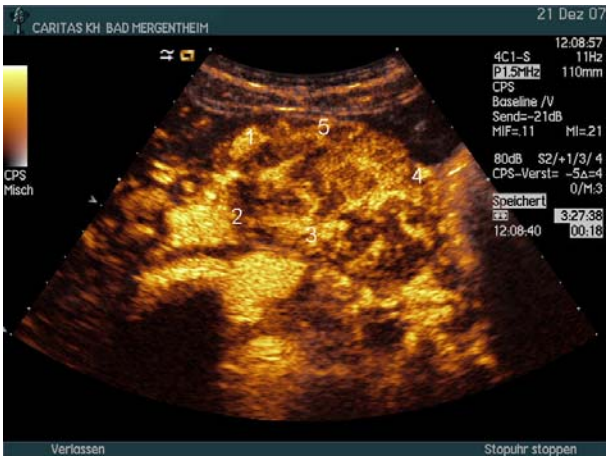
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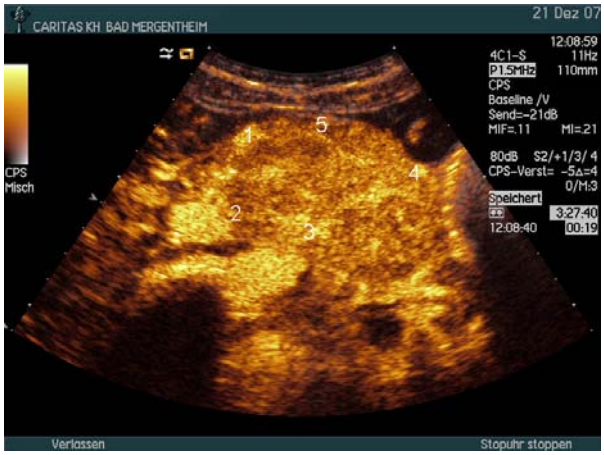
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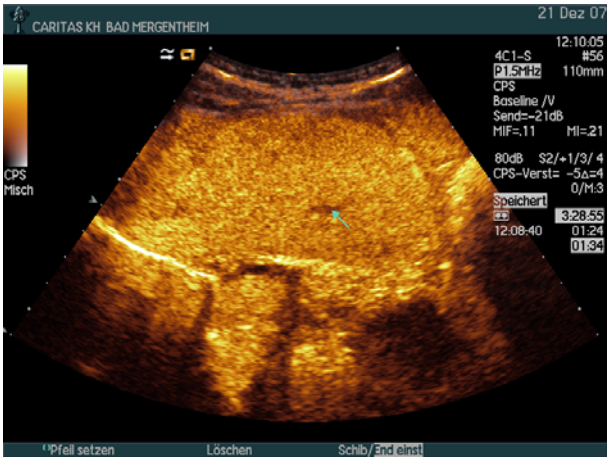
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Hepatocellular adenoma (HCA)

Conventional B-mode ultrasound

In B-mode ultrasound of an otherwise normal liver, a hepatocellular adenoma is usually isoechogenic with the surrounding liver tissue. Because of this lack of echogenicity, an adenoma can be very difficult to differentiate from the surrounding liver tissue. In a fatty liver, adenomas may be poorly echogenic, whereas in patients with storage diseases (e.g. glycogenosis or Niemann-Pick disease) adenomas may even give stronger echoes (hyperechoic) [(37)]. A rounded contour or a vascular impression may indicate a tumour poorly discernable from liver parenchyma. There are no other typical criteria in B-mode ultrasound.

Colour Doppler imaging

Hepatocellular adenoma exhibit (predominantly marginal) arterial hypervascularity which can be shown by colour Doppler imaging and contrast enhanced ultrasound. However, this vascular pattern can also be encountered in hepatocellular carcinomas and hyperperfused metastases, and is therefore not pathognomonic. Calcifications and other regressive changes are observed depending on the size of the lesion.

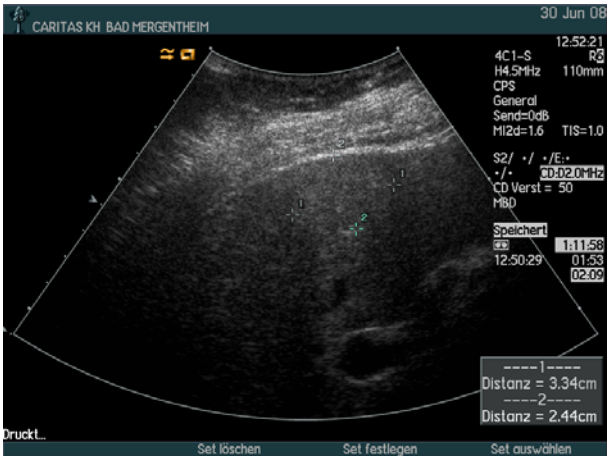
Contrast enhanced ultrasound

Histologically no portal veins (and in addition, no bile ducts) are present in adenomas, therefore, CEUS demonstrate only homogeneous enhancement during hepatic arterial phase (8 to 25 seconds after the injection) but no portal venous enhancement [Figure 34] resulting in slightly hypoenhancing (hypoechoic) appearance in comparison to the surrounding liver parenchyma since some overlap of the arterial and capillary phase (continuing over minutes) might be observed [(29)].

Figure 34 Hepatocellular adenoma. B-mode and contrast enhanced ultrasound (CEUS) of a patient with hepatocellular adenoma. B-mode ultrasound showed an unspecific slightly hyperechoic focal liver lesion (a). CEUS revealed only arterial phase enhancement after administration of SonoVue® (b,c). At the end of the arterial phase (< 30 seconds after administration of SonoVue®) a hypoechoic liver tumour was detected by CEUS (d) which

is the typical enhancement pattern of HCA in comparison to FNH which showed in 96 % of 300 patients with FNH more portal venous enhancement than the surrounding liver parenchyma.

a



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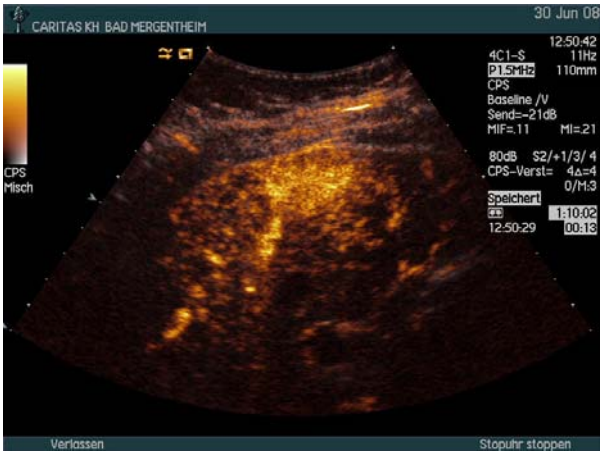

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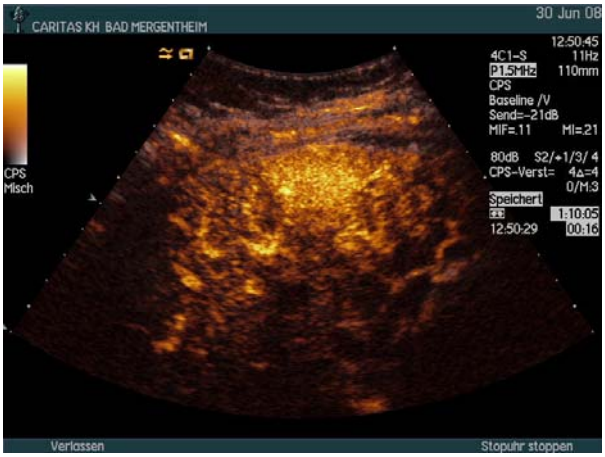

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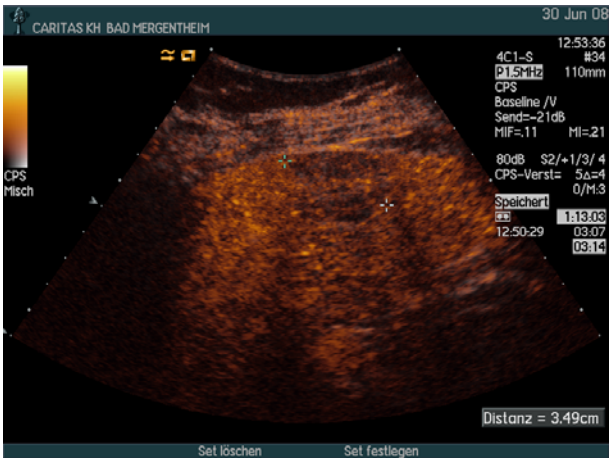


Differential diagnosis

Hepatic adenomas are frequently seen in patients with glycogen storage diseases (GSD 1), but their pathogenesis is not understood. Glucagon/insulin imbalance, cellular glycogen overload, and proto-oncogene activation have been suggested as possible mechanisms.

Focal fatty lesion (regional focal fatty infiltration)

Fatty infiltration was generally considered to be a diffuse process involving the entire liver. Since Brawer and Scott identified focal hepatic fatty infiltration at autopsy and in imaging studies in 1980, focal hepatic fatty infiltration has been widely discussed. Bright focal areas in the liver hilum occur in > 40 % of inflammatory bowel disease patients during medication with corticosteroids. The histological nature of these corticosteroid derived lesions is not yet clear. Different amounts or types (large, small vacuoles) of fat deposition are likely, because a change of appearance over time can be observed. Changes in arterio-portal venous perfusion have been suggested. Hemangiomas may mimic such lesions, but not all bright lesions in the liver are hemangiomas. It is well known that the vascular supply of the hilar region in liver segment IV differs from the perfusion of liver tissue adjacent to the gallbladder. This could give a possible explanation for different reactions of liver parenchyma to fatty infiltration. In patients with focal fatty lesions we observed depending on the quality of the equipment used centrally located arterial blood supply and direct venous drainage into the liver hilum [Figure 32].

Conventional B-mode ultrasound

Fatty infiltration may affect the liver diffusely or focally, but it does usually not cause any mass effect or displace vessels. Sonographically, hepatic fatty infiltration appears as segmental or lobular areas of brighter echogenicity, in contrast to the echogenicity of the normal liver parenchyma. A central, peri-hilar location in segment IV or V is typical-other locations are rarely involved.

An oval shaped hypoechoic lesion in the liver hilum is always related to fatty liver and could represent normal liver tissue surrounded by diffuse fatty infiltration of the liver. A hypoechoic lesion in the liver hilum without signs of expansion seem to be a relevant sign of fatty liver and should not be confused with mass lesions. The typical relationship to fatty liver, the typical location and shape are helpful in differential diagnosis [(38)].

Colour Doppler imaging

In colour Doppler ultrasound, both focal fatty degeneration and its focal absence appear normal; neither hyper- nor hypoperfusion is apparent, since the liver tissue is normal. Typically, central feeding and draining vessels [Figure 7] may be detected in a high percentage of patients demonstrating the pathogenetic mechanism of different vascularisation of the liver hilum.

Contrast enhanced ultrasound

Contrast enhanced ultrasound is helpful to rule out malignant infiltration. In the arterial and venous phase the supplying and draining vessels of the liver hilum can be imaged. In the enhanced echo signal sequence, different fatty degeneration regions are imaged like normal liver tissue in the portal venous phase. Therefore, in the portal venous phase these lesions are indistinguishable from the background. Enhancement in the arterial phase might be slightly delayed in comparison to the surrounding liver parenchyma.

Hepatocellular carcinoma (HCC)

Conventional B-mode ultrasound

There are no typical criteria in B-mode ultrasound in small hepatocellular carcinoma < 30 mm. Echogenicity of the lesion depends on its size and on the surrounding liver tissue (cirrhotic versus non-cirrhotic) [Figure 35-36]. HCC in an otherwise normal liver parenchyma is usually iso- or slightly hypoechoic compared to the surrounding liver tissue. Hepatocellular

carcinoma can be very difficult to identify in patients with liver cirrhosis and tumours morphology might be iso- hypo- or hyperechoic. Dysplastic nodules are sometimes difficult to differentiate [Figure 37].

Colour Doppler imaging

HCC are in most cases (80 – 90 %) distinctly hypervascularised using conventional colour Doppler imaging [Figure 35] and are mainly peripherally located. In such cases, confusion is possible with other hyperperfused liver tumours which, however, are rarely observed in a cirrhotic liver. From the differential diagnostic point of view it is then necessary to consider metastases of hyperperfused tumours, e.g. a hypernephroma, breast carcinoma, lung cancer, or more typically carcinoids. Metastases of primary extrahepatic tumours are however rare in a cirrhotic liver.

Contrast enhanced ultrasound

HCC typically exhibit hyperperfusion of the tumour compared with the surrounding liver tissue at a time when in the surrounding liver no contrast effect is as yet discernible. In the HCC a chaotic vascular pattern is typically observed, as a sign of neovascularisation of the tumour. Regenerative nodules may also exhibit additional arterial enrichment; by analysis of the portal venous phase it may be possible to differentiate these (isoenhancing) nodules from hepatocellular carcinomas (weakly contrasting).

Sonographic recognition of hepatocellular carcinomas in liver cirrhosis can be difficult if the echo texture is very inhomogeneous. One possible approach is to examine the liver in the early arterial phase after the injection of a signal enhancer, with low mechanical index (< 0.4). The use of Levovist® (a technique with high mechanical index (MI 1.2-1.6, 20 dB, scan rate 10-15 per second)) analysing the late phase (> 3 min) has been found to be helpful in improving the detection in some patients.

CEUS has proven to be effective in the differential diagnosis of cirrhotic nodules (regenerative nodule, hyperplastic nodule).

Figure 35 Hepatocellular carcinoma. Hypoechoic (more common) hepatocellular carcinoma with typically peripheral located hypervascularity using colour Doppler imaing.

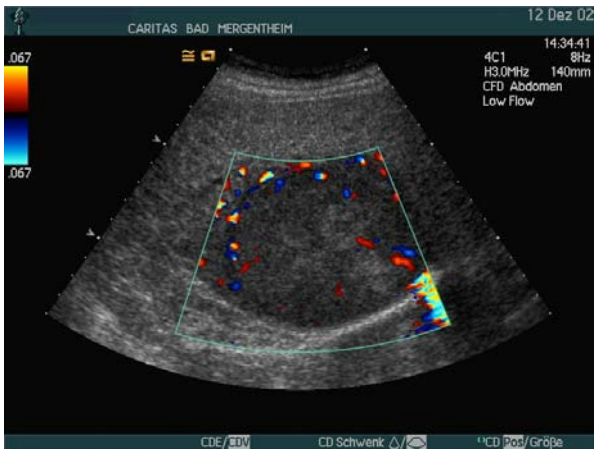
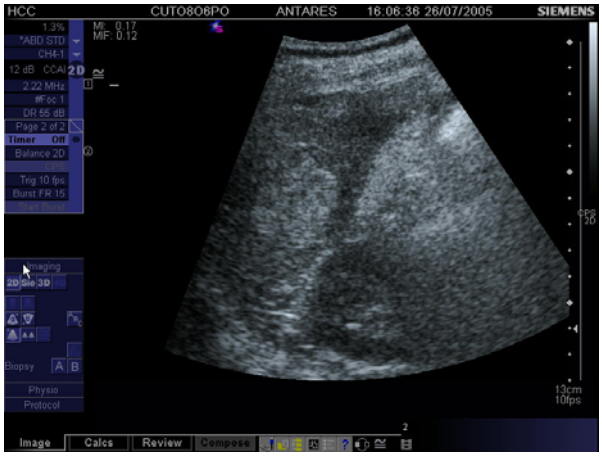


Figure 36 Hepatocellular carcinoma. Hyperechoic hepatocellular carcinoma with arterial enhancement. A satellite is shown as well not easy to recognise using B-mode.

a



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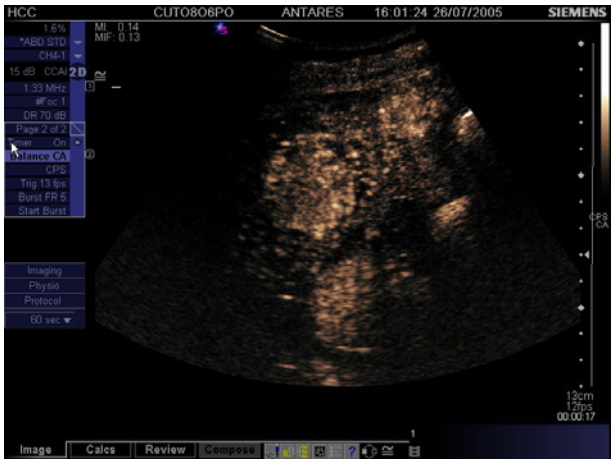
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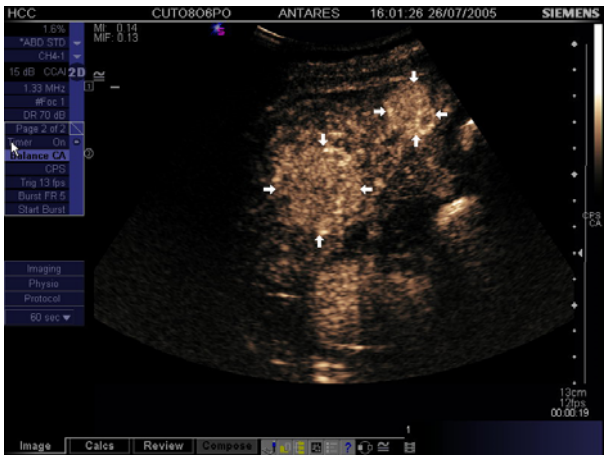
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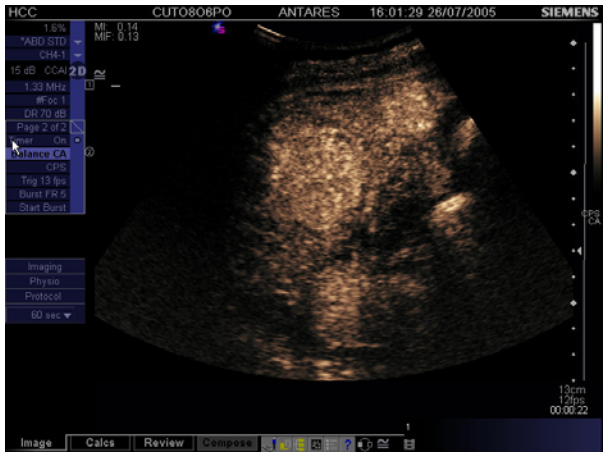
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Figure 37 Regenerative nodule. Regenerative nodule (histological proven and surveilled over 3 years) protruding into the gall bladder lumen mimicking hepatocellular carcinoma.

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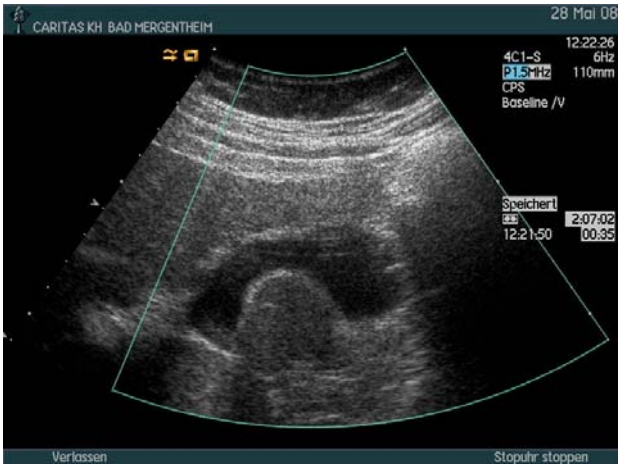

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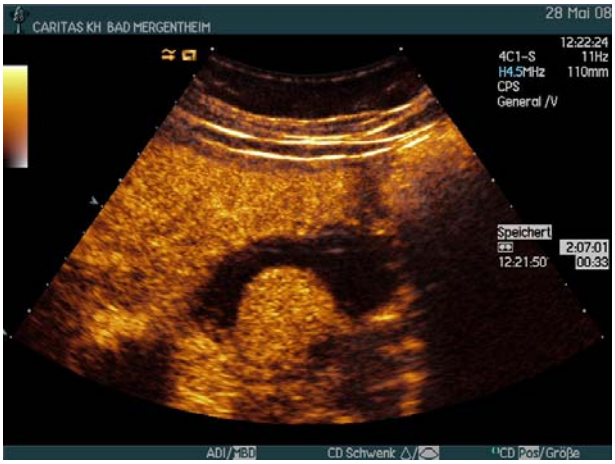

Cholangiocellular carcinoma (CCC)

Conventional B-mode ultrasound

Cholangiocellular carcinomas can occur along the bile duct in the liver hilum as so-called Klatskin tumours (hilar CCC, more common) [Figure 38], but they may also appear as primary solid tumours in the liver (peripheral CCC). For the peripheral type there are no typical sonographic characteristics, and the diagnosis is usually made incidentally, within the framework of a biopsy of a mass found in the liver. Ultrasonographic examination shows a solid mass which can have any echogenicity and exhibits signs of a malignant growth. The

liver metastases of a peripheral CCC are often situated like satellites around the primary focus.

Colour Doppler imaging

The majority of circumscribed cholangiocellular carcinomas are slightly hyperperfused in the native colour Doppler but colour Doppler imaging findings vary widely.

Contrast enhanced ultrasound

In the arterial phase the perfusion picture is variable, but mainly hyperperfused; in the late portal venous phase CCC are contrasted as punched-out defects. This behaviour is not always easy to demonstrate in the case of the Klatskin tumours, which often exhibit an appreciable pericholangitic component. As far as differential diagnoses are concerned, in the case of the hilar type of CCC inflammatory bile duct alterations should be considered, for example cholangitis. Stratification of the bile ducts is then, however, preserved, and may actually be accentuated in the sonographic image.[(13)] For the detection of cholangiocellular carcinomas the examination technique in the liver specific late phase has also proved to be diagnostically useful in patients giving normal CT, MRI, and MRCP results, but so far there have been no conclusive studies on differential diagnosis of primary sclerosing cholangitis and cholangiocellular carcinomas.

Figure 38 Cholangiocellular carcinoma (CCC). Cholangiocellular carcinomas (between callipers) can occur along the bile duct as so-called Klatskin tumours (hilar CCC, more common), but they may also appear as primary solid tumours in the liver (peripheral CCC [(11)]). The different morphological pattern of CCC are abundant].

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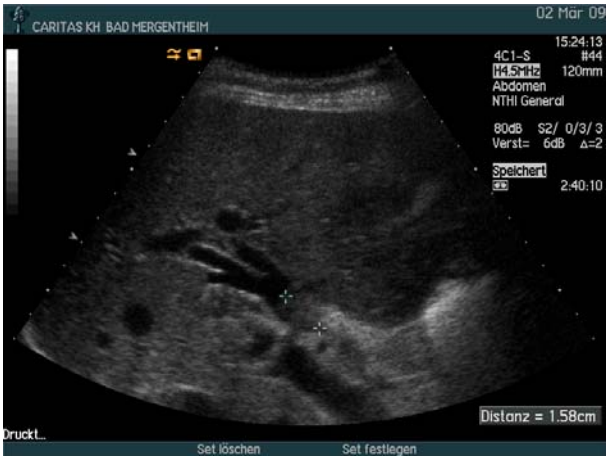

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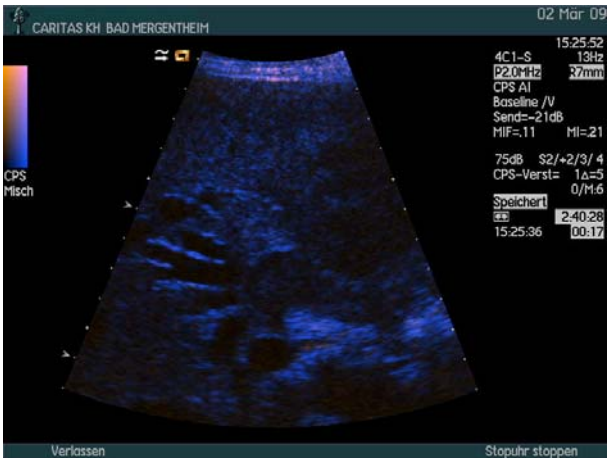
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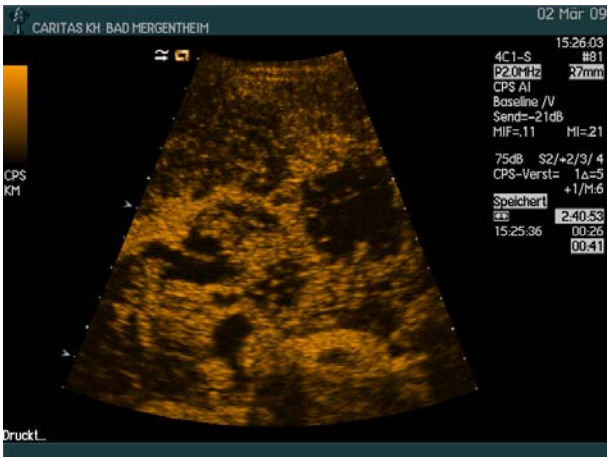
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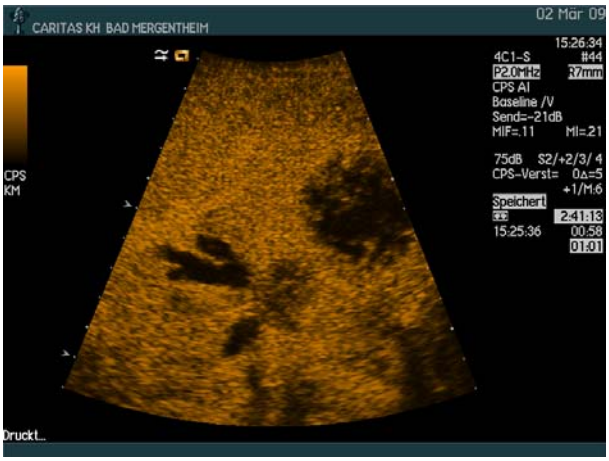
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Other tumours of extrahepatic bile ducts

Other tumours of extrahepatic bile ducts are sometimes mistaken as focal liver lesions. Cholangiocellular carcinoma represent only 10 % of the incidence of carcinoma and are much more common in the gallbladder than extrahepatic biliary tree. Other forms of benign tumours are rare, e.g., carcinoid of the extrahepatic bile ducts. Cholangiocarcinoma in the Klatskin position (liver hilum) arise at the confluence of right and left hepatic ducts at the liver hilum. They are slow growing. Features to report also from a surgical point of view are degree of obstruction, bile duct wall thickness (as a sign of infection), stones, tumour location and size, depth of invasion, tumour extension to adjacent structures and regional lymph nodes. Details are described in the hepatobiliary chapter.

Metastases

The liver is the parenchymatous organ in which metastases of extrahepatic tumours are encountered most often. The special features of portal vein circulation favour haematogenic metastasisation in the liver.

Conventional B-mode ultrasound

Size of the metastases can be anywhere between only microscopically detectable (cellular) infiltration and giant masses measuring more than 20 cm, and the echogenicity varies widely. Intraoperative ultrasound (IOUS) might be helpful in certain cases during surgery.

Colour Doppler imaging

Metastases are as a rule poorly vascularised analysing large definable vessels and their essential characteristic is a predominantly arterial blood supply (with little or no portal venous blood supply). Like the echogenicity (most often hypoechoic), the vascularisation depends on the size, the biological behaviour, and nature of the primary tumour. Irregular vascularisation is often observed, with broken-off vessels and peripherally situated arterio(porto-)venous shunt formation. The metastases of neuroendocrine tumours (and also e.g. metastases of renal cell carcinomas) may be more richly vascularised than other metastases. However, no conclusions are possible about the primary tumour on the basis of the echotexture and vascularisation pattern observed.

Contrast enhanced ultrasound in metastatic disease

Contrast enhanced ultrasound has markedly improved the detection rate of liver metastases. Liver metastases can be reliably diagnosed as hypoenhancing lesions during the liver specific portal venous sinusoidal phase. False negative findings are rarely encountered whereas false positive findings have to be ruled out by puncture and histological examination, e.g. abscess, necrosis, fibrous tissue and others [(22;59)].

Metastases may be contrasted already in the arterial phase, even though early arterial enhancement (in less than 15 seconds) is not typical and often the only observation is a degree of signal enhancement with a marginal emphasis (“halo sign”, “rim sign”). Contrasting of the vessels proceeds from the periphery towards the centre, and the vascular pattern is irregular. In poorly vascularised metastases contrast enhanced colour Doppler ultrasound also often reveals only small blood vessels situated at the edges (or within the lesion), and in many patients vascularisation cannot be imaged at all. In the portal venous phase metastases are contrasted increasingly as signal “black spots” against the background of uniformly enhanced normal liver tissue [Figure 39]. Contrast enhanced intraoperative ultrasound might be helpful in certain cases to detect lesions during surgery.

Figure 39 Metastases have a wide variety of B-mode appearances and can be confused with any kind of liver lesion (a). Colour Doppler imaging is helpful in only few patients. Hypervascular metastases reveal the typical peripheral rim sign using CEUS in the arterial phase (b-f) which can also be encountered sometimes in hepatocellular adenoma and hepatocellular carcinoma, and is, therefore, not pathognomonic. Metastases typically exhibit a sharp contrast to normal liver tissue in the liver specific portal venous (sinusoidal) phase (g).

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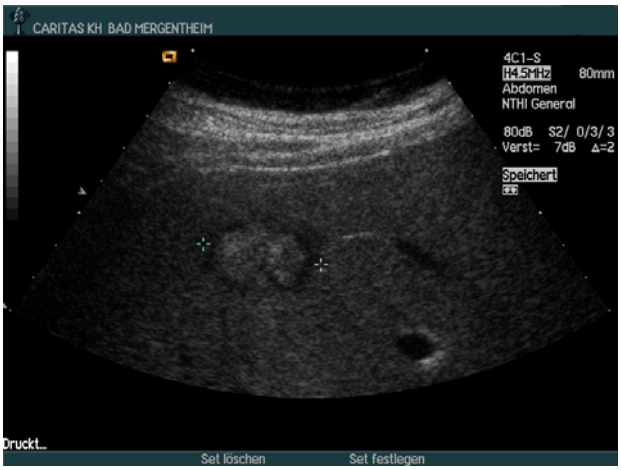
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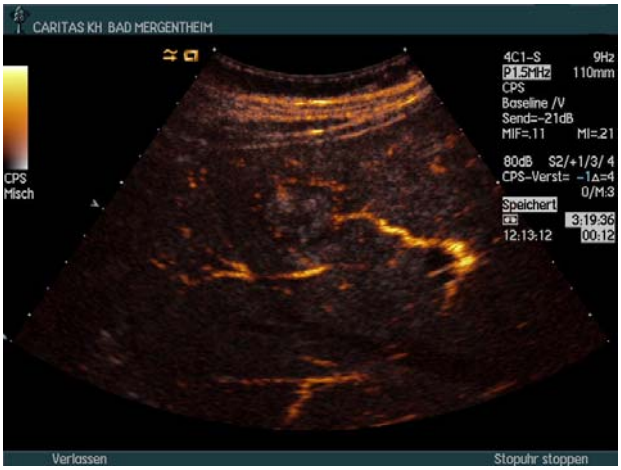
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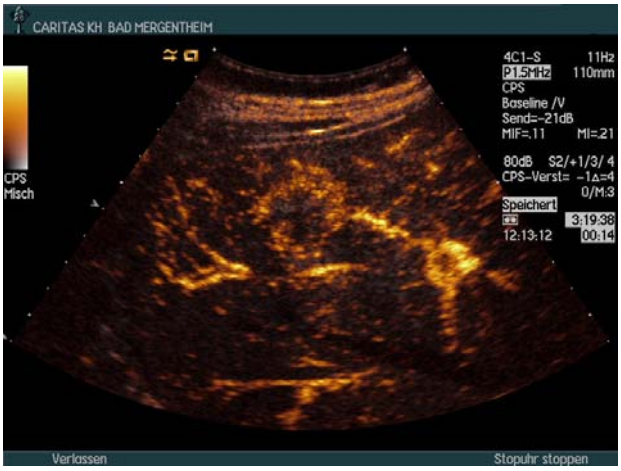
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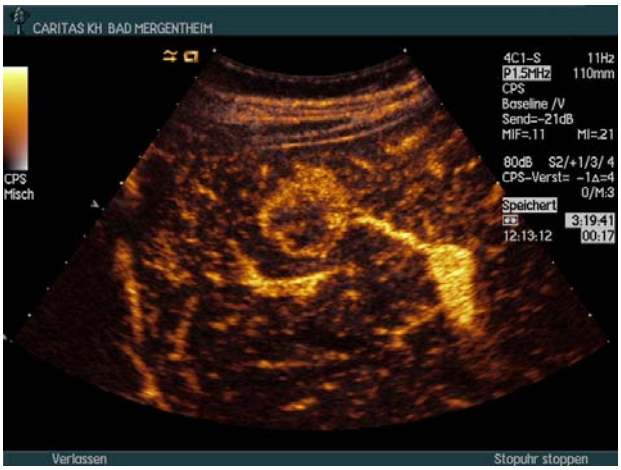
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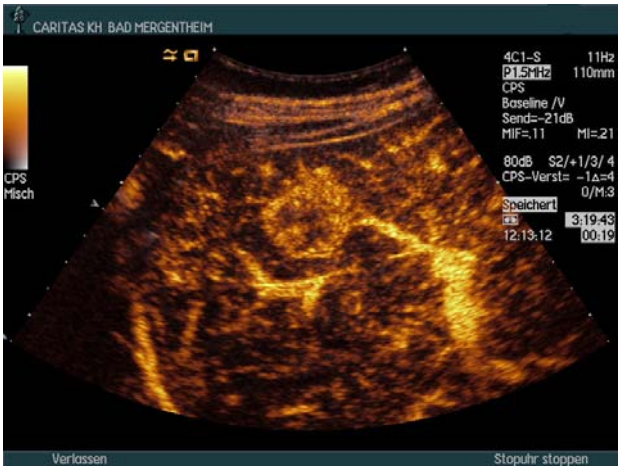
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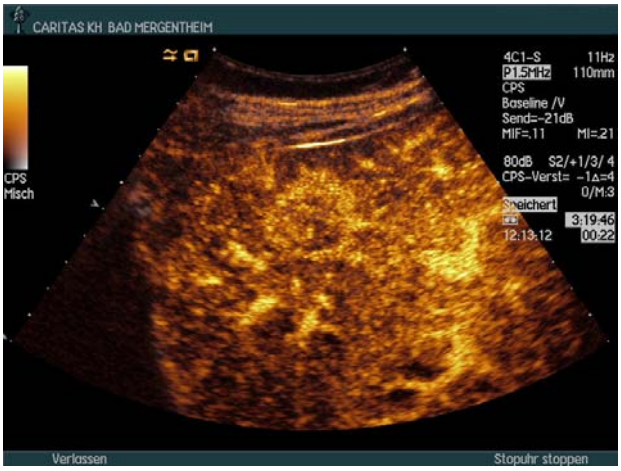
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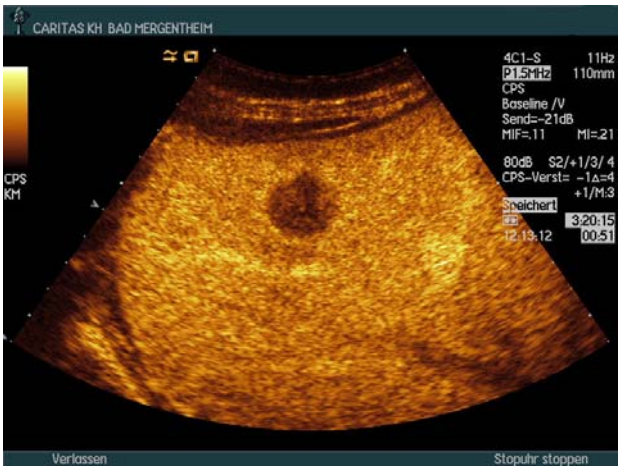

Unlike the portal venous “black spot” effect of metastases, as a rule large haemangiomas show a decrease in the unenhanced signal area (the iris diaphragm phenomenon). Any differential diagnosis must take into account complications of the underlying disease, and complications of therapy (e.g. neutropenia with bacterial and/or mycotic abscesses).

Benign liver lesions are found with the same frequency (5 – 20 %) in patients with metastases as in a healthy population (for example liver cysts, calcifications, hemangiomas, FNH, adenomas).

Neuro-endocrine metastases (NET)

Metastases of neuro-endocrine tumours are often small and hyperechoic and therefore mimic haemangioma and sometimes metastases of other origins (e.g., gastrointestinal). With increasing size of neuro-endocrine metastases, a combined echo rich and centrally echo poor texture is observed as a typical sonomorphological characteristic, due to frequent central necrosis, intra-tumoural hemorrhage, necrosis, fibrous tissue or calcifications. Therefore, visual diagnosis by B-mode ultrasound may be possible in about 50 % of the cases. Neuro-endocrine metastases are often hypervascularised, with a strong arterial and capillary blood supply similar to shunt hemangioma, small hepatocellular adenoma or hypervascular tumours of other origin [(46)].

Lymphoma

Conventional B-mode ultrasound

Unlike the often diffuse infiltration of the liver by extranodal Hodgkin's, and in particular non-Hodgkin's lymphomas (about 50 %), circumscribed alterations can be detected relatively rarely by ultrasound (in less than 10 – 20 % of the cases).

Circumscribed lymphomas can infiltrate the liver in small or large nodules or over an extended area, and also depending on their rate of growth, are often very hypoechoic compared to the surrounding liver tissue. In individual cases they may in fact give no echoes at all. Characteristically, amplification of the echo distally is then observed. Depending on the regressive changes taking place (e.g. an inward flow of blood or necroses), on the other hand, echo-rich lymphomas are also not uncommon.

In our experience, lymphoma infiltrations of the liver are accompanied by sonographically detectable (often only moderate, however) enlargement of the perihepatic lymph nodes (the normal lymph node size is up to 17 mm [median value plus two standard deviations] and 19 mm [maximum]) [Figure 40]. From a differential diagnosis perspective, inflammatory liver conditions should be considered (e.g. viral hepatitis B or C, PBC, PSC, other), and also lymph node metastases.

Colour Doppler imaging

The vascularisation of circumscribed lymphomas is often, though not always, more sparse than in healthy liver tissue. Broken-off vessels shunts are typically observed, which in the Doppler wave spectral analysis can lead to the disappearance of the diastolic flow component.

Contrast enhanced ultrasound

In contrast to the variable arterial perfusion, characteristically lymphomas reveal reduced contrast enhancement in the portal venous phase in comparison with surrounding liver tissue, due to the relative absence of portal veins in the lymphoma region.

By differentiation in the liver specific late phase, inflammatory lymph nodes can be distinguished from lymph nodes with malignant infiltration, since the latter exhibit (at least in the early stage) sharply demarcated malignant infiltrated areas; however, this hypothesis still needs to be checked in prospective studies.

The conditions that should be considered as differential diagnoses are complications of the underlying lymphoma (e.g. extramedullary haematopoiesis, more frequent subcapsular

haematomas in the presence of coagulation disturbances) and complications of therapy (e.g. neutropenia with bacterial and/or mycotic abscesses), but also haemophagocytosis syndrome.

Figure 40 Lymphoma. Correct diagnosis of hepatic lymphoma infiltration might be improved analysing also the perihepatic lymph nodes. Generalised lymphoma often shows intrahepatic mass lesion (a) and perihepatic lymphadenopathy (b).

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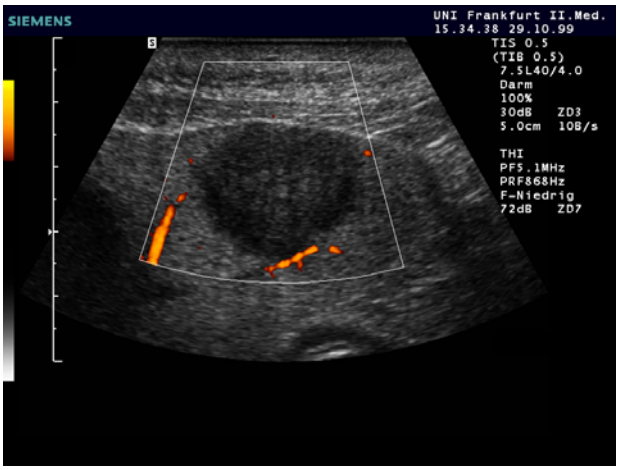

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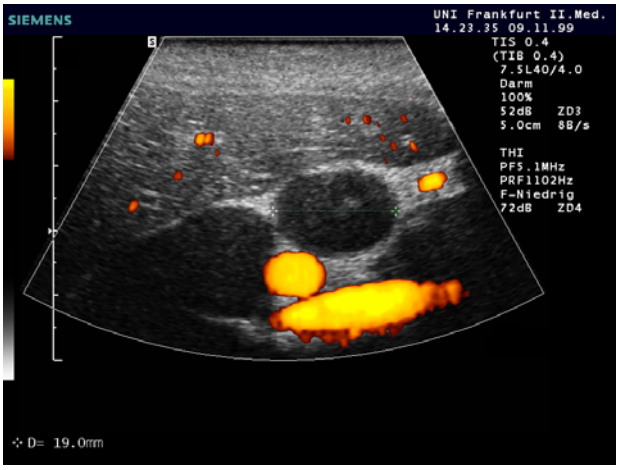

Abscess

The patient's medical history and sometimes also physical examination (febrile temperature, signs of sepsis) are most helpful in differentiation from necrotic metastases [(20;56)].

Phlegmonous inflammation and abscesses demonstrate variable and sometimes confusing B-mode images changing over time. The initial phlegmonous inflammation is often isoechoic in comparison to the surrounding liver parenchyma and is sometimes difficult to recognise. In older (chronic) abscesses hypervascularitiy of the nodule border might be confused with pseudotumour of the liver, even histologically. Small disseminate candida abscesses might be confused with lymphoma or circumscribed hemophagocytosis syndrome (especially in the young). Puncture and drainage (if necessary) are the diagnostic and therapeutic interventions. Abscesses up to 5 cm might be drained by one procedure whereas larger abscesses need to be treated over a number of days.

The initial phlegmonous inflammation is often hypervascular in comparison to the surrounding liver parenchyma but difficult to recognise. In older (chronic) abscesses hypervascularitiy of the nodule border is typical [Figure 41].

In typical cases CEUS shows sharply delineated hypervascularity demonstrating the pseudocapsule and no gas bubbles inside the lesion.

Figure 41 Liver abscess. Typical liver abscesses demonstrating gas inside the lesion (a, arrow). In CEUS, there will be no central signal at all but a pronounced hyperperfusion at the abscess border (b-c). The underlying cause in this patient – choledocholithiasis - is detectable as well (not shown).

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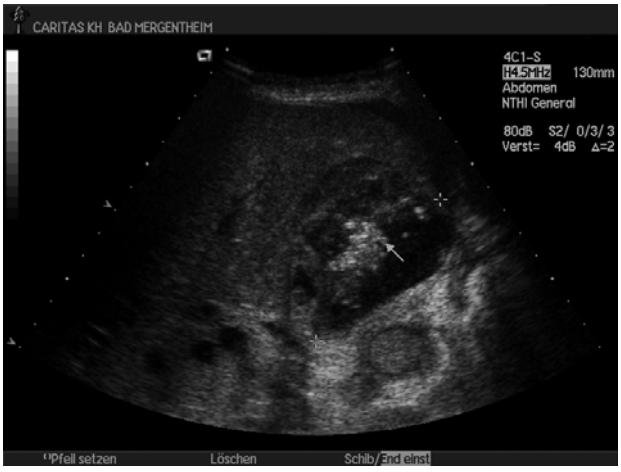

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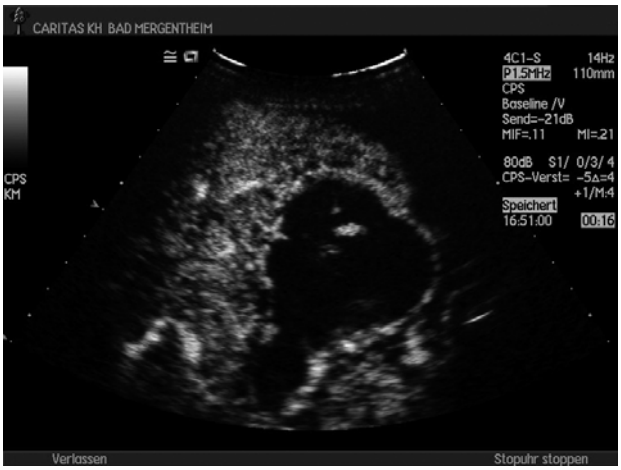

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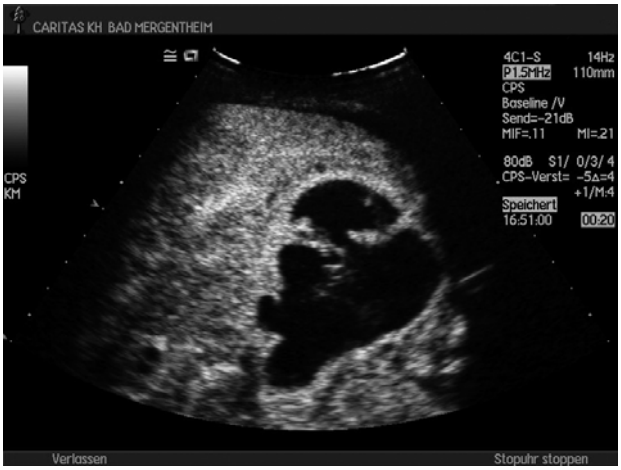
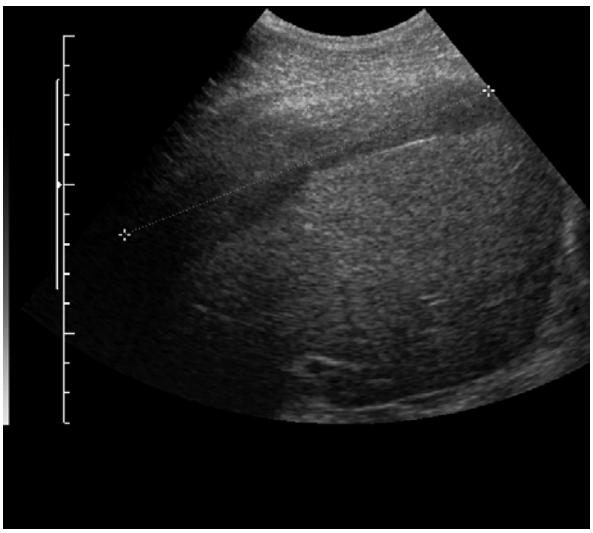


Haematoma

Haematoma can be clinically diagnosed in most cases. Spontaneously evolving and painful haematoma is typical for amyloidosis of the liver [Figure 42].

Figure 42 Spontaneously evolving and painful haematoma (“blut”) is typical for amyloidosis of the liver [(8)].



B-mode image appearances depends on the stage of haematoma. The very early haematoma is hyperechoic, later stages are iso- or mostly hypoechoic. Therefore, change in morphology is typical for haematoma. Colour Doppler imaging demonstrates no flow pattern as no vascularity. CEUS is helpful in defining circumscribed versus diffuse infiltrating haematoma. CEUS might be helpful in clinically uncertain cases with similar results as those shown for computed tomography [Figure 43].

Figure 43 Perihepatic Haematoma. Perihepatic hematoma using B-mode is stage dependent hypoechoic (a). CEUS demonstrated early vessel invasion (b).

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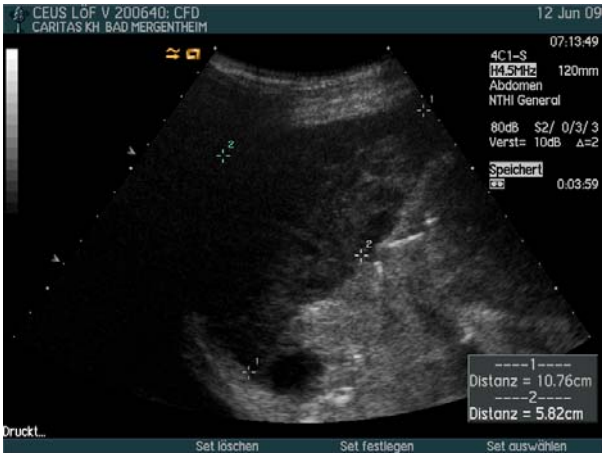

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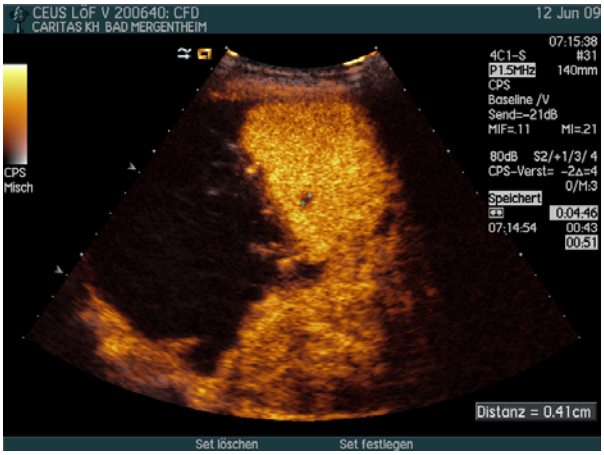

Rare focal liver lesions and other entities

Nodular regenerative hyperplasia (NRH)

Nodular regenerative hyperplasia of the liver (NRH) is a rare pathological finding, typically associated with haematological or autoimmune disease. The main clinical symptom is portal hypertension without underlying liver cirrhosis. NRHL itself consists of multiple hepatic nodules resulting from peri-portal hepatocyte regeneration with surrounding atrophy. Typically, fibrous septa between the nodules are missing. Ultrasound typically shows multiple (unspecific) hepatic nodules, which are suggestive of multi-locular hepatocellular carcinoma or metastatic disease of the liver. Signs of portal hypertension and the rarer Budd-Chiari-syndrome should be carefully sought. CEUS is helpful in defining circumscribed versus diffuse infiltrating nodular regenerative hyperplasia [(33)]. Histological assessment of the liver is necessary for diagnosis, because the nodular appearance of the hepatic surface may otherwise be difficult to differentiate from cirrhosis or from hepatic metastases.

Inflammatory Pseudotumour

Inflammatory pseudotumour is a rare disease that can present with fever, abdominal pain, vomiting and weight loss indicating and sonographically mimicking malignancy or abscess. The definite diagnosis is often only achieved by surgery. Contrast enhanced ultrasound may reveal hypoechoic contrast enhancement falsely indicating malignant disease [(56)].

Clinical importance of liver ultrasound in daily routine

Ultrasound is the first and most important imaging method in suspected liver disease – which holds true both in the sense of proving (e.g., metastatic disease) and excluding pathology.It is the single best tool in the evaluation of focal liver lesions, unbeaten by any other imaging modality, due to realtime, dynamic nature, high resolution and good safety record. It is invaluable in the differential diagnosis of jaundice, in describing liver cirrhosis complications, and in any form of ultrasound guided intervention. In summary ultrasound is an indispensable tool in clinical hepatology.

Ultrasound of the liver:

- is the first and most important imaging method in suspected liver disease;
- is first line indication in:
    - evaluation of elevated liver functions tests and cholestasis indicating enzymes;
    - differential diagnosis of icterus (diagnosis / exclusion of cholestasis);
    - monitoring of complications of liver cirrhosis (ascites, portal hypertension, HCC);
    - tumour detection / exclusion / follow up;
- Contrast enhanced ultrasound is helpful especially for tumour detection and characterisation; it prevents unnecessary further imaging.

Liver sonography is essential for guidance of liver/biliary tree interventions such as biopsy.
Sonography is the most important imaging method in oncological follow up.
The use of sonography is limited in:

- the exact measurement of the size of the liver (which is of limited value in the clinical routine);
- the diagnosis of early cirrhotic stages and in the differential diagnosis of diffuse parenchymal diseases.

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