White Paper

Liver Total Approach

esaote

“Real technological developments have been integrated with elastosonography techniques and fusion imaging for use during liver ultrasound examination”

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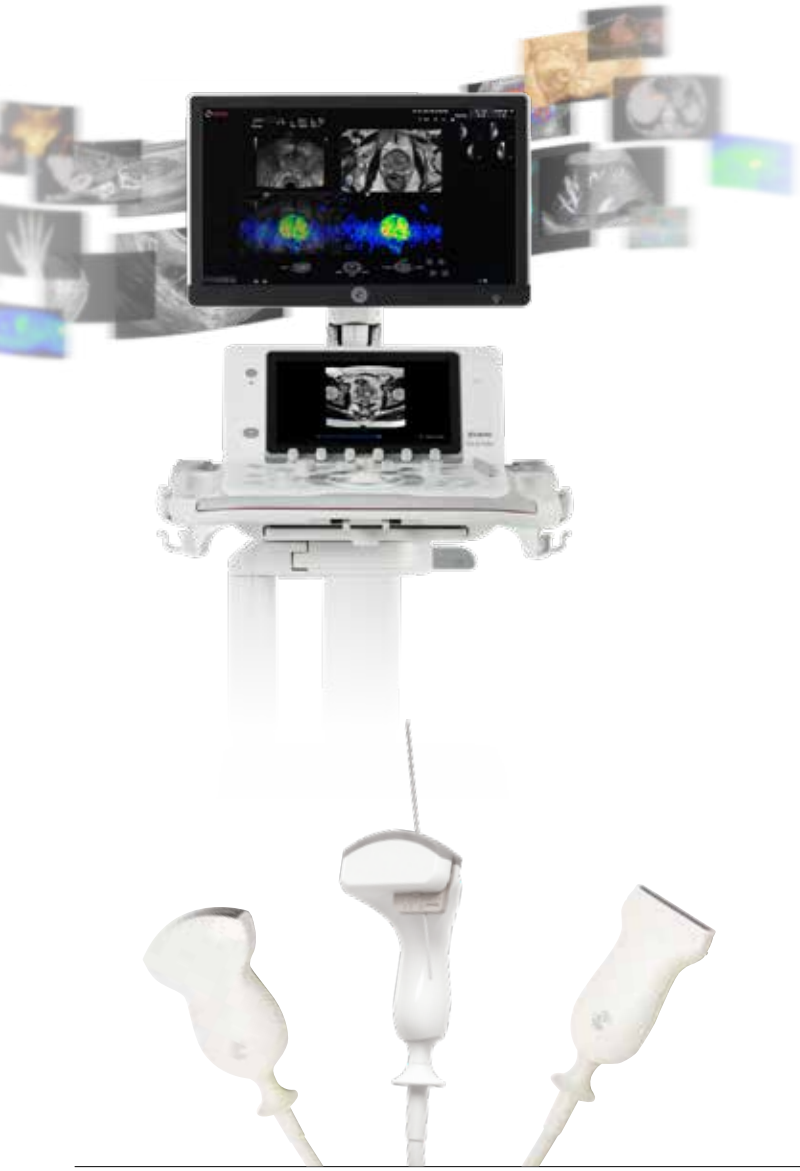
Introduction

Initial screening for a liver condition usually starts with an ultrasound scan and blood tests, and may be followed by other imaging tests, such as CT or MRI to obtain further information. Ultrasound is particularly excellent for differentiating solid masses from liquid ones. Ultrasound examination can also evaluate diffuse liver diseases, like fatty liver or hepatitis. Nowadays, the extended connectivity and the multimodality approach open new horizons in radiology imaging where ultrasound devices may play a central role in Cross-Modality Imaging.



Background

The first real-time sonography device, the so-called “fast B-scan”, was introduced in 1965. Sonography has been an essential part of daily clinical diagnostics for more than 50 years and is guided by the most modern technical developments. Over the last 20 years, many technological advances, such as advanced signal processing and new transducer generation, have been reached to push the limitations of ultrasound technique and provide excellent image quality for screening and monitoring. Furthermore, intensive research and development has led to the creation and integration of new technologies, which can be grouped into three major diagnostic tools:

1) **Contrast Enhanced Ultrasound (CEUS)**

   Using an ultrasound contrast agent, CEUS makes it possible to detect organ perfusion and additionally to characterize liver lesions.

2) **Elastosonography and 2D Shear Wave techniques**

   Using 2D Shear Wave elastosonography as an additional imaging technique enables a stiffness map and gives quantitative assessment of the tissue stiffness.

3) **Fusion imaging**

   By virtue of fusion imaging technology, it is possible to combine an existing CT or MRI dataset with a real-time ultrasound examination.

Following a description of the main technologies used in **screening and monitoring**, these new techniques, briefly outlined here, will be reported in detail below.

Over the past 10 years, ultrasound devices like CEUS, have become invaluable in the follow-up of patients

Ultrasound liver screening and monitoring

Echostructure and vascularization are the two main elements of liver screening. Because of wide interpatient variability (due to the presence of fat, gas or other factors), the quality of the liver visualization and lesion detection may be affected. Esaote has developed specific technologies to overcome the limitations of ultrasound technique and provide excellent image quality even in challenging patients and conditions.

Single Crystal probe technology

Associated with the new generation of signal post-processing, Single Crystal technology enables extended bandwidth to achieve homogenous images even in deep areas **(Fig. 1)**. Furthermore, besides traditional convex probes, Esaote offers a Zero-degree biopsy probe to facilitate the interventional procedure **(Fig. 2)**.

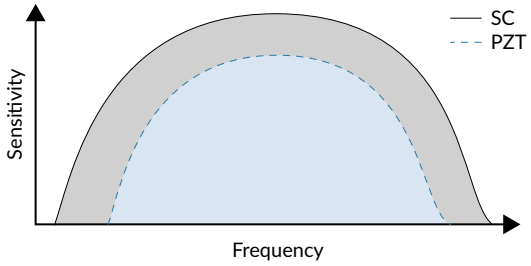


Fig. 1: Sensitivity graph of using a single crystal array versus a PZT technology array

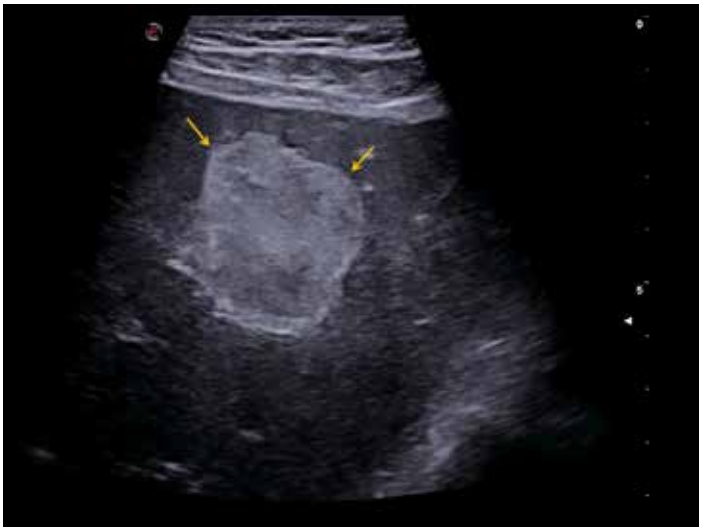


Fig. 2: 36-year-old male patient with large, hyperechoic lesion (yellow arrows) in a non-cirrhotic liver in B-mode ultrasound imaging

microV

Esaote has developed an adaptive algorithm that effectively separates flow signals from overlaying tissue motion artefacts and background noise. microV is the latest technology by Esaote, with a high degree of sensitivity even in very small vessels and detection of slow flows, which enables advanced hemodynamic evaluation with high sensitivity and high spatial resolution **(Fig. 3)**.

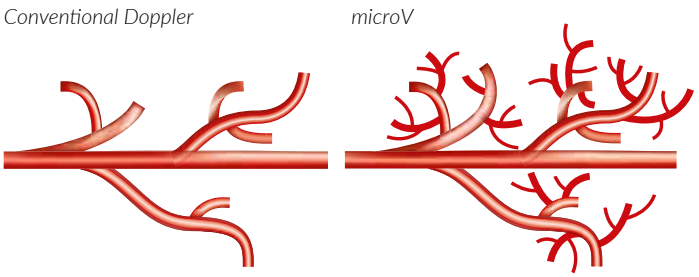


Fig. 3: Image representing sensitivity in terms of vascularization visualization between Power Doppler Technique and microV technology

microV can distinguish between signals coming from flows and other sources with very low flow signal preservation in comparison with conventional Doppler techniques **(Fig. 4)**.

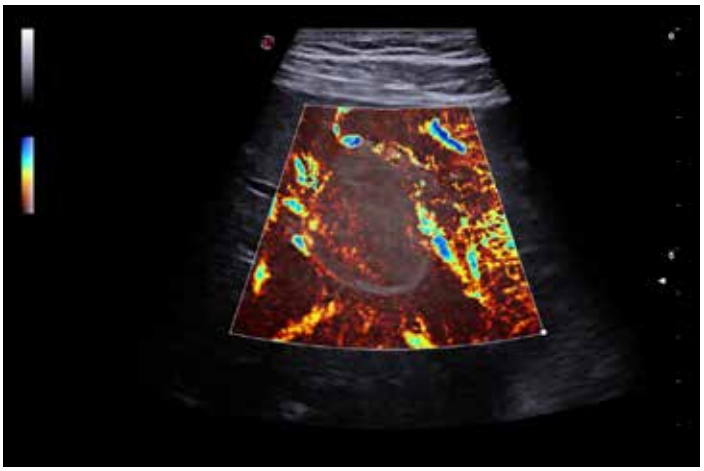


Fig 4: The hyperechoic lesion does not display any increase of vascularization with microV technology

Detection and characterization of liver lesions by contrast agent enhancement

Background

Liver ultrasound scans are commonly used as first-line imaging for evaluating focal liver lesions. It is important to differentiate benign masses from malignant ones because of the effects on appropriate patient management. The liver is the most common site of metastatic lesions. Approximately 25 to 50% of patients with a primary malignancy have liver metastases at the time of diagnosis[1], while the prevalence of focal liver lesions in the general population is only about 5%[2].

Determining further therapy (surgical resection versus interventional therapy) depends on the size, number, and location of the liver metastases[3].

Therefore, accurate detection[4,5] and characterization of hepatic masses is important for determining disease prognosis and making decisions regarding patient management.

Since non-invasive techniques cannot provide a tissue diagnosis, histopathology of core biopsies is the gold standard for the final diagnosis of liver lesions[6].

An enhanced ultrasound examination is also often labelled as a contrast enhanced ultrasound, or CEUS examination. Each examination starts with a patient informed consent form. This form should include information about the potential risks and side effects, such as an anaphylactic reaction. The incidence of allergic reactions is reported in the literature as up to 1/10,000 cases. In comparison with iodine-containing contrast agents used in multislice computed tomography, the risk is much lower[7,8]. There have been no reports of cardio-, nephro–, thyroid or hepatotoxicity following ultrasound contrast agent administration; it is therefore unnecessary to request or check laboratory values before the examination[6,8,9].

In Europe, SonoVue®* from the Bracco Company (Milan, Italy) is available as an ultrasound contrast agent. This contrast agent contains microbubbles 1-10 µm in size, which contain an inert gas known as "sulfur hexafluoride". The bubbles are stabilized by a phospholipid shell. In comparison with the contrast agents for computed tomography and magnetic resonance imaging, which pass into the interstitial space, this ultrasound contrast agent remains in the vascular space. This technique allows us to detect organ perfusion in high resolution in real-time imaging[7,11-13]. Gas components of the ultrasound contrast agent will be eliminated via the respiratory tract.

CnTI™ - Esaote Contrast Enhanced Ultrasound Technology

CnTI™ (Contrast Tuned Imaging) is an Esaote advanced technology for Contrast Enhanced Ultrasound (CEUS) imaging. Based on low mechanical index and real-time scanning, CnTI™ represents the best way to use second-generation contrast media (CM) and prevents the microbubbles from being destroyed too quickly.

Findings and procedure

Due to the high impedance between blood and bubbles, sound waves will be reflected from the surface of the microbubbles. Due to the ultrasound frequency, the microbubbles additionally oscillate and generate a contrast-specific signal with higher frequency components[13,14].

For single CEUS examination, 1.0 to 2.4 cc of the ultrasound contrast agent will be intravenously injected as a bolus. Immediately afterwards, 10 cc of 0.9 % saline is administered as a bolus to flush the IV line[2].
Contrast enhanced ultrasound of the liver has three overlapping vascular phases after the injection of the contrast agent, because of the dual blood supply of the liver, i.e., the hepatic artery and portal vein **(Table 1)**.

- The arterial phase provides information on the degree and pattern of the arterial vascular supply of a focal liver lesion.
- The portal venous phase represents the arrival of ultrasound contrast agent through the portal system, resulting in diffuse and maximal enhancement of the normal liver parenchyma.
- The late phase lasts until the ultrasound contrast agent is cleared from the circulation and depends on the dose, total scanning time, acoustic power output, and the sensitivity of the ultrasound system.

Phase	**Start** (sec.)	**End** (sec.)
Arterial	10 – 20	30 – 45
Portal venous	30 – 45	120
Late	>120	bubble disappearance (approx. 4 – 8 min)

Table 1: Vascular phases in CEUS of the liver (visualization of post-injection time)[15]

The potential applications of CEUS imaging include all liver lesions. The lesions can be divided into benign **(Table 2)** and malignant liver lesions **(Table 3)**. Additionally, the liver tissue perfusion and liver vessels can be monitored. In addition to primary diagnostics and intervention, CEUS imaging can be used in the operating room or in the intensive care unit.

* Sonovue® is a trademark of Bracco Group

Tumor	Arterial phase (10-30 s)	Portal venous phase (10-30 s)	Late phase (10-30 s)
Hemangioma **Fig. 5, 6, 7**	Peripheral nodular enhancement	Partial/complete centripetal fill-in	Incomplete or complete enhancement
Focal nodular hyperplasia **Fig. 8, 9, 10**	Hyper-enhancement from the center, complete, early	Hyper-enhancement	Iso-/hyper-enhancing
Hepatocellular adenoma	Hyper-enhancement complete	Iso-enhancement	Iso-enhancement
Focal fatty infiltration	Iso-enhancement	Iso-enhancement	Iso-enhancement
Focal fatty sparing	Iso-enhancement	Iso-enhancement	Iso-enhancement
Abscess	Peripheral nodular enhancement, no central enhancement	Hyper/Iso-enhancement rim, no central enhancement	Hypo-enhancing rim, no central enhancement
Simple cyst	Non-enhancing	Non-enhancing	Non-enhancing

Table 2: Typical enhancement patterns of benign focal liver lesions[15].

Tumor	Arterial phase (10-30 s)	Portal venous phase (10-30 s)	Late phase (10-30 s)
Metastasis **Fig. 11, 12, 13**	Rim enhancement	Hypo-enhancement	Hypo-/non-enhancement
HCC (Hepato carcinoma)	Hyper-enhancement from the center, complete, early	Iso-enhancement	Hypo-/non-enhancement
CCC (Cholangio-carcinoma)	Rim-like hyper enhancement	Hypo-enhancement	Hypo-/non-enhancement

Table 3: Typical enhancement patterns of malignant focal liver lesions[15].

Conventional ultrasound is the most frequently used modality for the primary imaging of abdominal organs, including the liver, but is less sensitive in the detection of focal liver lesions than contrast-enhanced-CT (CECT) and contrast-enhanced-MRI (CEMRI). Several studies[16–24] have reported that CEUS has a considerably higher sensitivity of up to 80%-90% in detecting liver metastases, comparable to that of CECT[24] and CEMRI.[15,17]

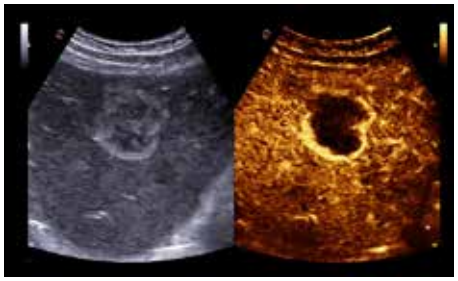


Fig. 5: Peri-nodule enhancement in arterial phase

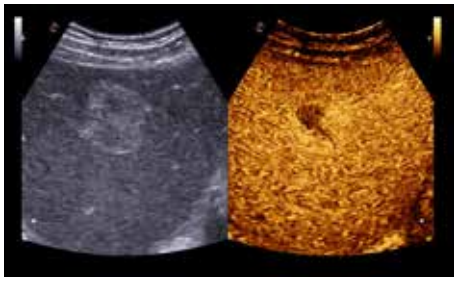


Fig. 6: Peri-nodule enhancement with nearly complete filling in the portal venous phase

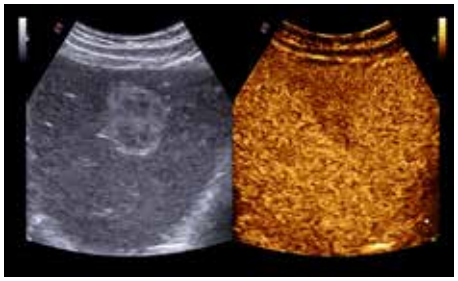


Fig 7: Complete filling of the lesion in the late phase; final diagnosis: hemangioma

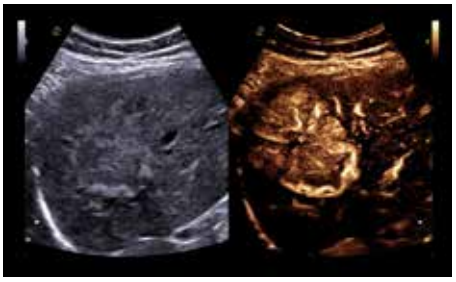


Fig. 8: Strong early enhancement of the lesion in the arterial phase

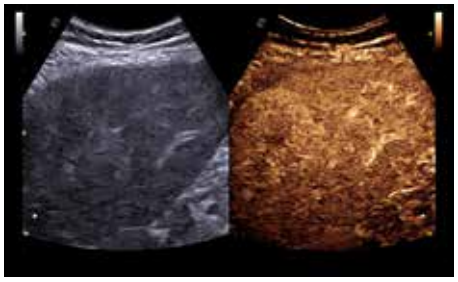


Fig. 9: Hyper-enhancement of the lesion in the portal veinous phase with central scar

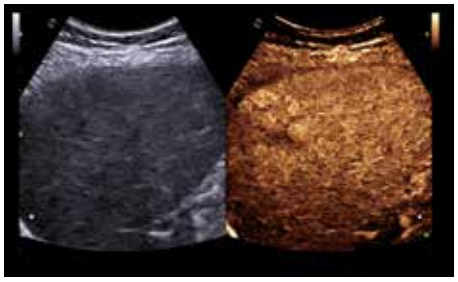


Fig. 10: Hyper-enhancement in the late phase with central scar; final diagnosis: FNH

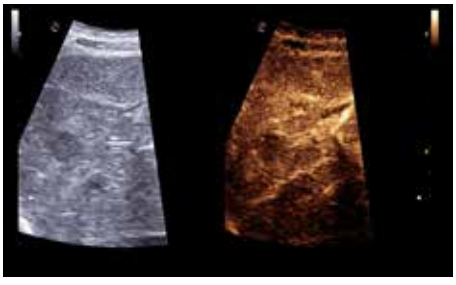


Fig. 11: Hypo-enhancement in the arterial phase

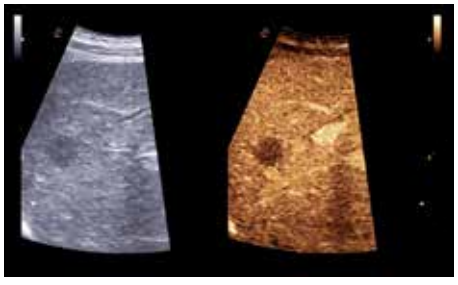


Fig. 12: Washout in the portal venous phase

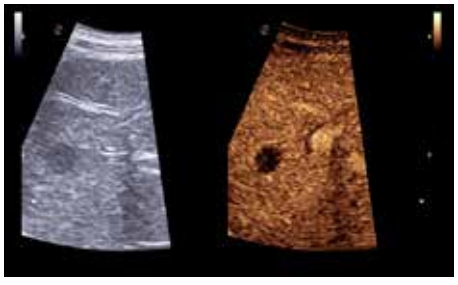


Fig. 13: Complete washout in the late phase; final diagnosis: liver metastasis

Liver Fibrosis Assessment

Background

Ultrasound elastography has established itself as an additional imaging technique for characterizing liver tissue properties in radiological diagnostics. This technique makes it possible to visualize the relative stiffness of a tissue or the relative elongation of a tissue. The origin of this method is based on manual palpation, one of the oldest examination methods in medicine. Palpation aims to detect pathological changes based on the differences in the tissue elasticity between pathological and healthy tissue. It is mentioned in the Edwin Smith Surgical Papyrus dating from the seventeenth century B.C.[26].

In the past, a liver biopsy was considered to be the gold standard for an accurate assessment of the severity of liver inflammation and the degree of fibrosis. However, due to some limitations, such as cost, sample size, or complications of an invasive technique, over the last two decades, elastographic techniques have rapidly become the method of choice for assessing liver fibrosis, replacing liver biopsy for diagnosis, evaluation, longitudinal safe monitoring of the disease progression, and treatment monitoring.

Esaote QElaXto 2D technology

QElaXto 2D is a Shear Wave Elastosonography (SWE) technique from Esaote that alternates multiple perturbations and reading phases, making it possible to detect stiffness in a small tissue sample. The system creates multiple shocks beside the box that will induce some shear waves. Then it tracks the radiofrequency (RF) signal of the tissue displacement on different sample stripes inside the box and measures the Shear Wave velocity for each strip. Secondly, the velocity is associated with a color map and then QElaXto 2D codes each strip with color pixels to enable a colored representation of the stiffness in the sample **(Fig. 14)**. The operator has the possibility of changing the scale of the stiffness representation, which can be reported in units of either m/s or kPa[35-36].

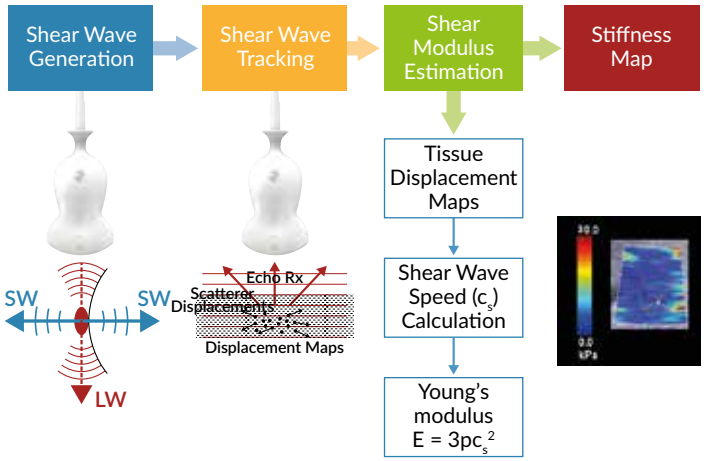


Fig. 14: Basic physics of SWE. In the first step of the process, the shear waves are using an energetic RF pulse; they propagate perpendicularly to the primary US wave at a lower velocity. In the second step, tissue displacement is calculated, and finally tissue displacements are used to calculate Shear Wave velocity (Cs).

Consequently, clinicians can perform a quantitative measurement inside the box, placing the ROI in an area free of vessels, bile ducts and artefacts.

QElaXto 2D can provide the following measurements to clinicians:

- Median (MED) in kPa or m/s
- IQR/MED in %

Beside these, the software also gives additional measurements such as:

- Average (AVG) in kPA or m/s
- Standard Deviation (SD) in kPpa or m/s
- Interquartile Range (IQR) in kPa or m/s

According to the guidelines, 3 to 5 valid measurements are adequate in the presence of a quality assessment provided by the manufacturer.
The session (ended after five valid acquisitions) can be considered reliable when IQR/MED <30% **(Fig. 15)**.
To help clinicians obtain reliable measurements, QElaXto 2D offers some further tools, namely the dispersion map and the rejection parameter. The dispersion map is the computation of the standard deviation of the value of each pixel in comparison with the surrounding ones.

- Green means that the reliability is good
- Orange means that the reliability is weak

It can be enabled beside the stiffness imaging in a dual mode visualization.
The rejection parameter indicates to the algorithm the rejection level for the artefacts, vessels and weak Shear Waves. With rejection activated, the algorithm does not include the pixels from the rejected areas in the computation of the values.

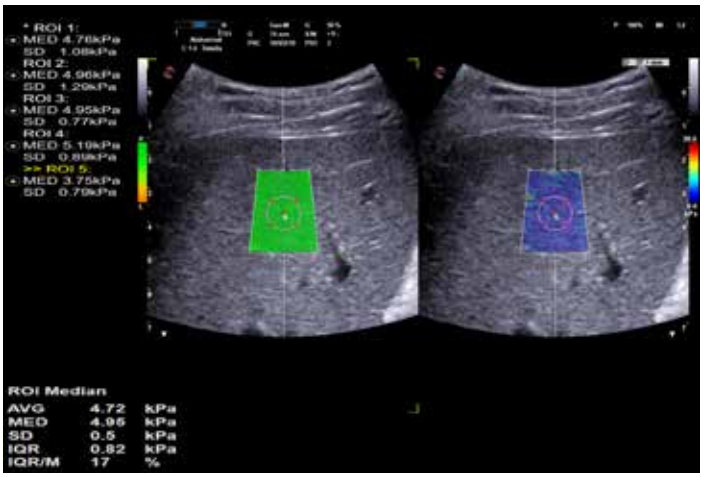


Fig. 15: 2D-SWE examination in a healthy patient with a median value of 4.72 kPa and IQR/m of 17%. The Quality map on the left side of the image is highlighted in green to indicate a high-quality examination.

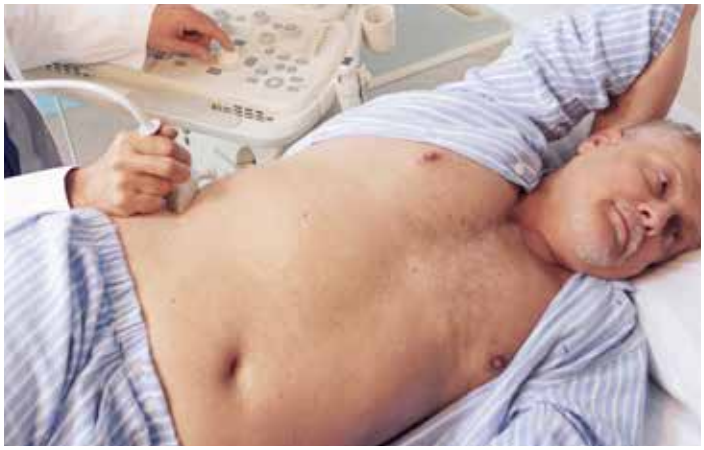


Fig. 16: Patient position for a 2D-SWE examination – Patient in decubitus position with his right arm above his head and the convex probe on the intercostal access.

General recommendations according to the EFSUMB Guidelines and Recommendations[30]

- Measurement of liver stiffness by SWE should be performed through the right intercostal space in supine position, with the right arm extended, with the patient holding their breath, avoiding deep inspiration prior to holding their breath **(Fig. 16)**.
- Measurement of liver stiffness by SWE should be performed by experienced operators.
- Measurement of liver stiffness by 2D-SWE should be performed at least 10 mm below the liver capsule.
- Patients should fast for a minimum of 2 hours and rest for a minimum of 10 minutes before undergoing liver stiffness measurement (LSM) with SWE.
- The major potential confounding factors (liver inflammation indicated by AST and/or ALT elevation >5 times the normal limits, obstructive cholestasis, liver congestion, acute hepatitis, and infiltrative liver diseases) should be ruled out before performing LSM with SWE, to avoid overestimation of liver fibrosis and/or should be considered when interpreting the SWE results.
- SWE within the normal range can rule out significant liver fibrosis when the clinical and laboratory background allows.
- Adequate B-mode liver imaging is a prerequisite for 2D-SWE measurements.
- For 2D-SWE a minimum of three measurements should be obtained; the final result should be expressed as the median together with the interquartile range. An IQR/M ≤ 30% of the measurements is the most important reliability criterion.
- The results with the lowest variability 2D-SWE systems may be obtained at a depth of 4–5 cm from the transducers.

Guidelines and latest update to the Society of Radiologists in Ultrasound Consensus Statement on Liver Elastography

As suggested by the latest guidelines, the evaluation of the progression of liver diseases and the staging of liver diseases are the most important factors for evaluating the prognosis, monitoring and treatment indications, because fibrosis is a dynamic process and patients with a higher stage of liver fibrosis (F3-F4) are at higher risk of clinical complications. A consensus panel recently suggested the "rule of four" (5, 9, 13, 17 kPa) for the energetic RF pulse techniques for viral etiologies and for NAFLD as described in the table below **(Table 4)**.

For other etiologies, such as alcoholic hepatitis, primary biliary cirrhosis, Wilson disease, autoimmune hepatitis, sclerosing cholangitis, and drug-induced liver disease, there is as yet insufficient data to give the same indication.

Liver Stiffness	Recommendations
≤ 5 kPa (1.3 m/sec)	High probability of being normal
< 9kPa (1.7 m/sec)	Without other clinical signs, rules out cACLD. In presence of clinical signs, may need further test for confirmation
9-13 kPa (1.7-2.1 m/sec)	Suggestive of cACLD but needs further test for confirmation **(Fig. 17)**
17 kPa (2.4 m/sec)	Suggestive of CSPH

Table 2: Rule of 4 established for the use of 2D-SWE technique in ultrasound for the assessment of fibrosis stages
Key: cACLD = compensated advanced chronic liver disease, CSPH = clinically significant portal hypertension

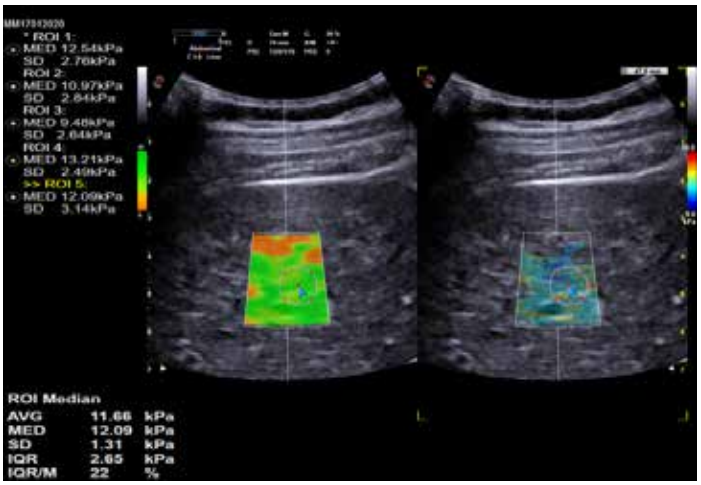


Fig. 17: 2D-SWE examination of a patient with known hepatitis C, a median value of 11.66 kPa and IQR/M of 22% was measured. The quality map confirmed the quality of the examination.

Fusion imaging with Virtual Navigator

Background

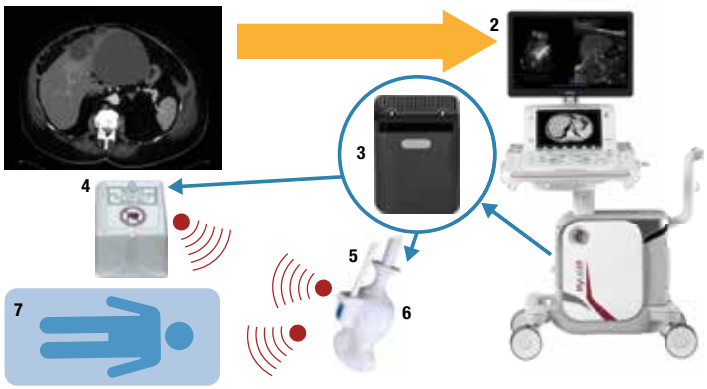
By providing an additional image from the reference series, fusion imaging enables real-time correlation of anatomy between several imaging modalities, thus making it possible to display continuously reformatted plans from the reference series matching the ultrasound sections. A second modality can be any series coming from CT, MR, US, or PET.

It has been possible to fuse existing CT or MRI data on Esaote ultrasound devices since 2004.[44,45]. The technology consists of an real-time ultrasound scanner equipped with an electromagnetic tracking device for localizing ultrasound transducers and providing their position and orientation in space during a standard ultrasound scan of the liver. The information from the tracking device and the 3D dataset from the second modality is combined to compute a reformatted slice image that is spatially consistent with the real-time ultrasound image displayed.[47]

This advanced ultrasound technique can be useful for complicated liver diseases, especially in the following cases[47,48]:

- Lesions better identified with CT, MRI, or PET or not visible on US
- Lesions only seen during arterial phase enhancement
- Follow-up of local tumor after ablation or resection
- New lesions after previous surgery or ablation
- Lesions hidden during treatment (US gassed out)
- Composite ablations requiring multiple needle insertions
- Complex geometries or difficult treatment plans to identify a safe pathway to the target, such as a difficult US "window", or complex angle of insertion.

Fusion imaging can also be helpful in young patients and patients with contraindications for CT scans or unclear CT findings, reducing the exposure to radiation as well as to nephrotoxic contrast agents[49-51].



1 *Second Modality Series (CT-scan/MRI)*
2 *Esaote Ultrasound Scanner*
3 *Cable connector on the US scanner*
4 *Electromagnetic Tracking Device (Transmitter)*
5 *Electromagnetic Tracking Antenna (Receiver)*
6 *Ultrasound Probe*
7 *Patient*

Fig. 18: Tracking solution on Esaote ultrasound system

Materials

Virtual Navigator is an Esaote fusion imaging technology. The hardware of the ultrasound system needs an additional magnetic field generator and a position sensor known as an antenna for the ultrasound transducer to perform image fusion. The antenna makes it possible to detect the position of the transducer in a three-dimensional field created by the electromagnetic transmitter. Then the software Virtual Navigator enables the co-registration of the datasets from a DICOM[47,48] (digital imaging and communication in medicine) second modality and the real-time ultrasound **(Fig. 18)**.

Fusion imaging Procedure

The procedure is split into 3 steps:

1. Preparation phase

The operator imports into the ultrasound device one or more DICOM second modalities, such as MRI, CT, and PET CT directly from the PACS or from an external support, such as a CD or USB stick. Inside the VNav environment, if there is more than one second modality, the operator can use the automatic alignment function to align the series **(Fig. 19)**. Then, the physician will identify the target and fix it inside the reference volume by selecting "Ball target" or "Auto-contour" on the touchscreen of the VNav menu.

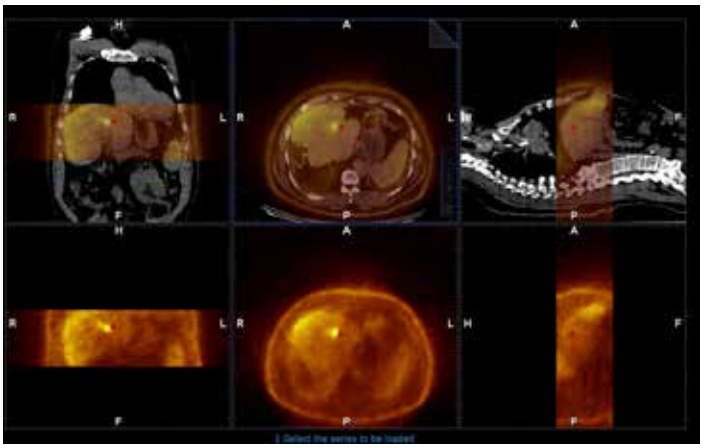


Fig. 19: Preparation of a fusion imaging procedure with automatic alignment of different DICOM modality datasets and target set

2. Ultrasound/2nd modality dataset co-registration

Once the preparation phase has been completed, the system is ready to start the fusion procedure between MRI or CT and real-time US data. The easiest way is to perform single-plane registration selecting the same plane in axial view both on the US scan and on the MRI/CT dataset. After confirmation that the system has registered the two modalities, the system will compute a reformatted slice image of the 3D dataset according to the movements of the US transducer. It is recommended to confirm the registration in the same patient of the acquisition using the second modality to increase the accuracy of the alignment. Therefore, some adjustments can be performed to optimize the co-registration closer to the target area. VNav offers different possibilities:

- One-point alignment consisting of real-time selection of the same point on the US scan and on the MRI/CT volume dataset.
- Fine-tuning consisting of real-time selection of the same plan on the US scan and MRI/CT dataset.
- Internal marker alignment using a trigonometry plan in both modalities, by selecting at least 3 points.

Usually, the same anatomical landmarks are selected on the US and second modality dataset to perform the alignment adjustment, such as vessels, trying to pick a target where the hepatic vascular pattern presented a bifurcation.

3. Navigation phase and interventional procedure

The system is ready to navigate through the 2 modalities. If more than one second modality dataset has been uploaded, the operator can switch between them at any time as the reference modality. VNav also offers the possibility to enable a layout with 3 modalities together. The clinician can proceed to the biopsy or the treatment procedure guided by the second modality **(Fig. 20)** to reach the lesion with more confidence.

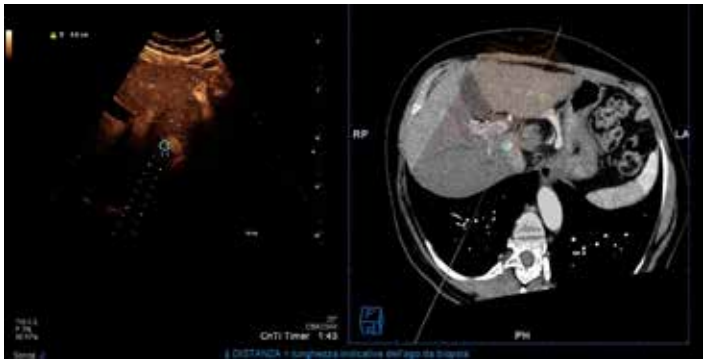


Fig. 20: Navigation phase enabling the biopsy channel/line on both modalities for performing the interventional procedure

Advanced features

VNav technologies offers several advanced tools to facilitate the fusion procedure.

1. Automatic movement correction

Using the motion sensor, the operator can place a sensor on the patient that will detect any patient movements after co-registration and will automatically correct the changes to maintain the same alignment between the US and the second modality dataset.

2. Breathing compensation

The motion sensor can be also used to detect the patient's respiratory phases since breathing determines a rototranslation of the liver that can lead to a mismatch of considerable size. A traffic light will indicate the best matching breathing position while an interpolation algorithm will make the second modality breathe synchronously **(Fig. 21)**.

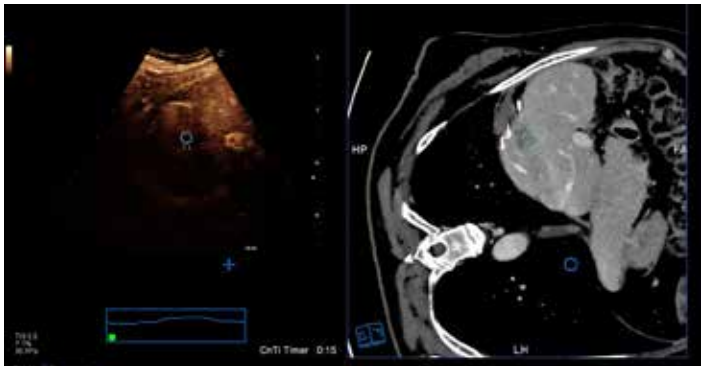


Fig. 21: Fusion imaging procedure using Breathing synchronization tool to increase the accuracy of the alignment

3. Automatic registration based on hepatic segmentation

The Autoregistration algorithm works simultaneously on the US and the second imaging modality volume dataset. It is based on automatically matching the vessels visible in both modalities. Automatic registration with hepatic anatomical markers, usually the vascular tree, was carried out acquiring a US plan with color doppler of the hepatic vascular tree, and the automatic vessels detection tool of the MRI/CT dataset.

4. Automatic registration with OmniTRAX™*

VNav is compatible with CIVCO disposables, OmniTRAX™ available for MRI and CT acquisition. OmniTRAX™ must be used as the second modality of acquisition from the patient. Once the patient arrives for the fusion procedure with the OmniTRAX™ in strictly the same position, all the operator needs to do is position the sensor on the OmniTRAX™ and confirm the co-registration.

5. Needle tracking

Needle Tracking Esaote technology is an additional support for interventional procedures. This feature will enable the virtual path of the needle **(Fig. 22)** to find the best approach and insertion point to reach the target.

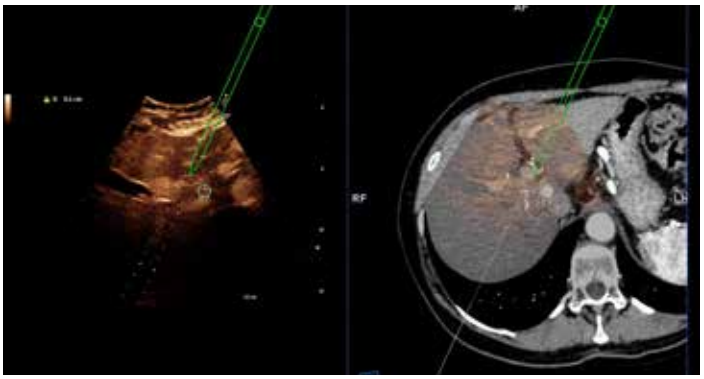


Fig. 22: Needle Tracking tool to identify the best path to reach the target

6. Planning

VNav offers the option to plan the focal treatment and enable the treated areas according to the chosen therapy.

Liver Total Approach solution

Furthermore, the Virtual Navigator makes it possible to combine different ultrasound Esaote technologies, such as Color and Power Doppler, microV, QElaXto 2D and CnTI™ in real-time during fusion imaging.

Using all the different ultrasound imaging techniques in real-time enables comprehensive imaging and characterization of the vascularization of liver lesions[52,53].

* OmniTRAX™ is a trademark of CIVCO Medical Solutions

Liver Total Approach solution - Case report

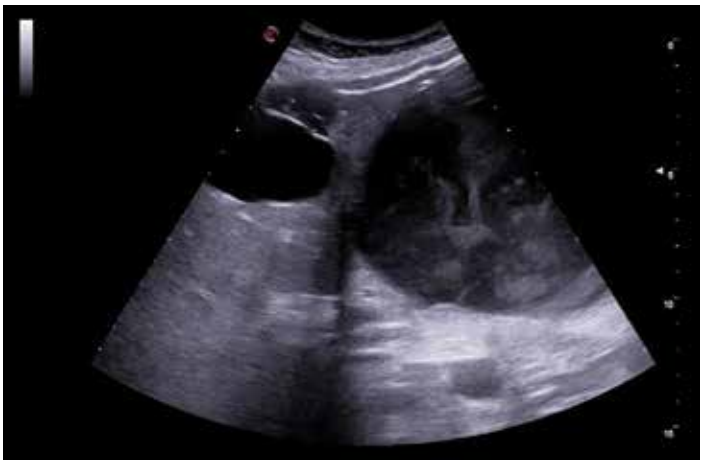


Fig. 23: Complex liver lesion in grayscale obtained with ultrasound examination

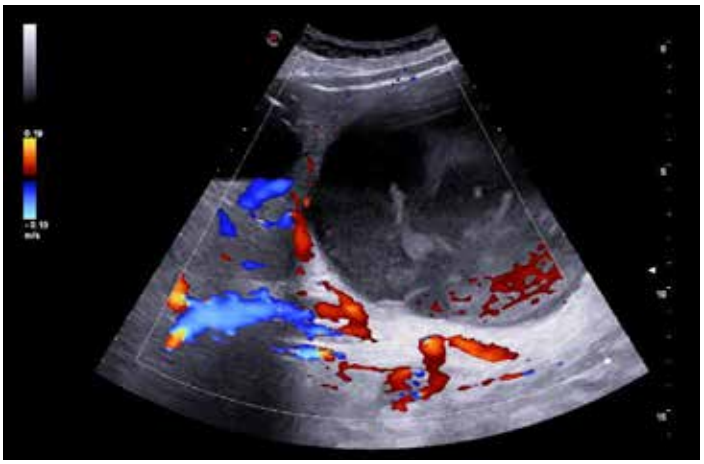


Fig. 24: No vascularization in color Doppler mode

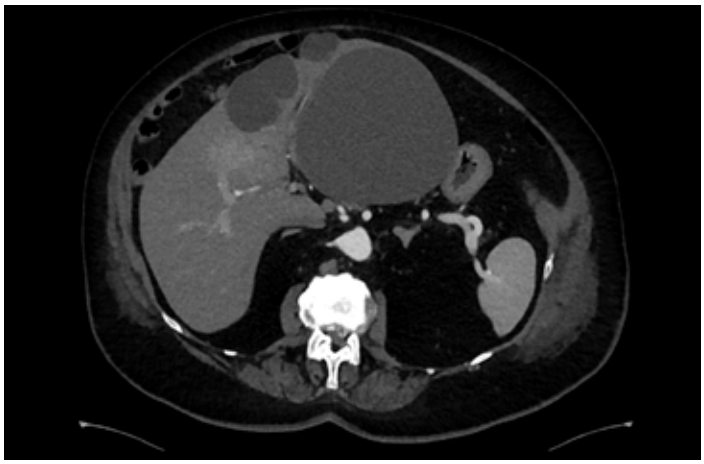


Fig. 25: Same liver complex lesion detected by CT

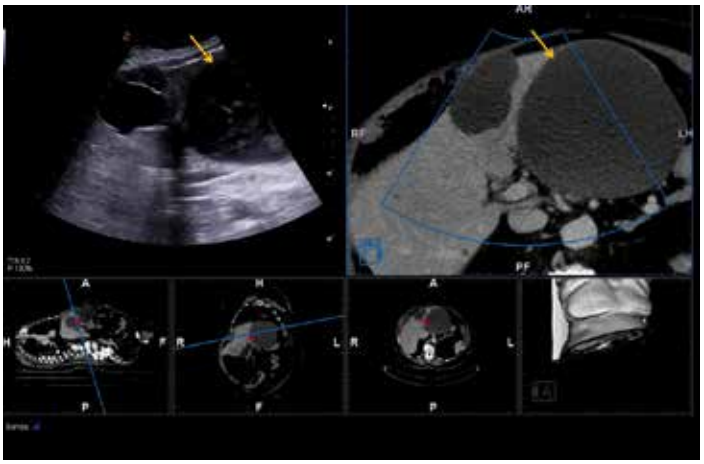


Fig. 26: Image fusion with B-Mode and CT-data in the side-by-side setting. Patient was referred for ultrasound examination due to increased HE value of the liver cyst in CT. B-Mode sonography of the liver cysts with inhomogeneous multiple septa (yellow arrow). With the help of image fusion, the cyst can be easily detected with multiple septa and thickened walls (yellow arrow) in comparison with MS-CT.

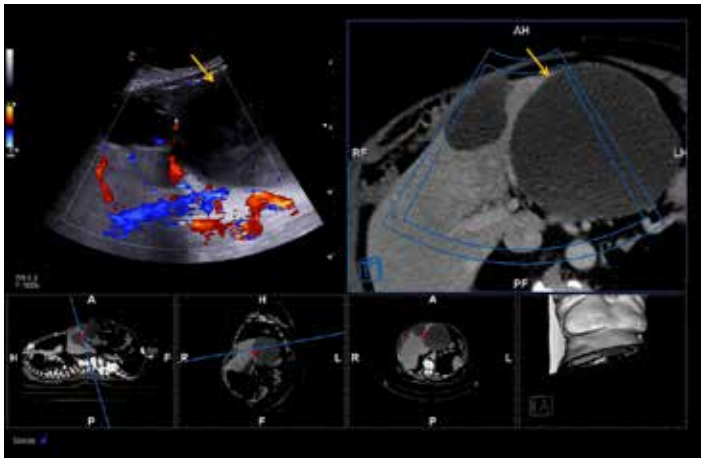


Fig. 27: Image fusion with color Doppler and CT data in the side-by-side mode. Color Doppler reveals no vascularization of the liver cyst in comparison with CT

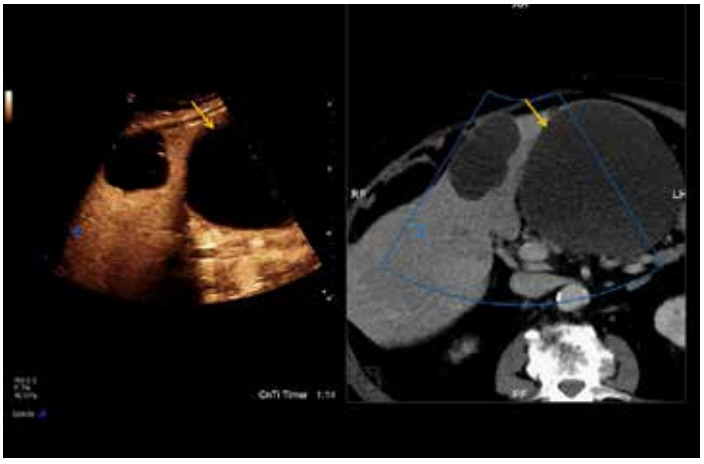


Fig. 28: CEUS reveals no vascularization of the liver cyst in the side-by-side mode, which is in line with a hemorrhagic liver cyst (yellow arrows)

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