New real-time image fusion technique for characterization of tumor vascularisation and tumor perfusion of liver tumors with contrast-enhanced ultrasound, spiral CT or MRI: First results

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Abstract. Aim: Evaluation and characterization of the vascularisation and perfusion of liver tumors by means of image fusion of dynamic contrast-enhanced ultrasound (CEUS), multidetector-CT (MD-CT) or magnetic resonance imaging (MRI) with the ultrasound navigation technique.

Material: For interventional planning a real-time image fusion involving CEUS (LOGIQ E9, GE) was performed in 20 patients (12 men, 8 women, age 43–69 years, median 54) with histologically confirmed malignant liver tumors (9 × hepatocellular carcinoma (HCC), 5 × metastases, 2 × hemangiomas, 1 × cholangiocellular carcinoma (CCC), 1 × lymphoma, 1 × neuroendocrine tumor, 1 × focal nodular hypoplasia (FNH)). In 17 patients the real-time CEUS was fused with contrast-enhanced MD-CT and in three patients with contrast-enhanced MRI (Gd-DTPA and liver-specific contrast medium Resovist®). All of the ultrasound examinations were performed by an experienced examiner with a multi-frequency probe (2–5 MHz, LOGIQ E9, GE); dynamic image sequences up to 3 minutes in true agent detection mode of contrast harmonic imaging (CHI) were documented. An evaluation of the tumor was performed by the characterization of the dynamics of the contrast medium and microperfusion with CEUS, fused with MD-CT or MRI.

Results: In 18/20 cases there was an accurate agreement with respect to the segmental localization of the tumor lesion. In 2/20 cases the localization was comparable with the image fusion of CEUS and reference imaging (a total of at least 65 lesions: 3 × 1 lesion, 5 × 2 lesions, 8 × 3 lesions, 2 × 5 lesions, 1 × 8 lesions, 1 × at least 10 lesions (multifocal)). With image fusion a certain characterization was attained in 17/20 cases. In 3/20 cases (lymphoma after liver transplantation, multifocal CCC, metastases of a neuroendocrine tumor) the diagnosis was at first doubtful and had to be confirmed histologically. In patients with HCC an evaluation of the tumor perfusion was feasible in all 9 cases (8/9 after local trans-arterial chemoembolization (TACE), 1/9 after radio frequency ablation (RFA)). A tendency toward the identification of more lesions with image fusion of CEUS and CT than with contrast-enhanced CT alone could be recognized (p = 0.059).

Conclusion: Applying a new real-time fusion technique of MD-CT or MRI with CEUS new possibilities for the evaluation, intervention and monitoring of the therapy of liver lesions were made possible, since the method also comprised the dynamic microperfusion.

Keywords: Real-time image fusion, contrast-enhanced ultrasound (CEUS), liver lesions, CT, MRI

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1. Introduction

The detection and characterization of liver tumors can frequently only accomplished by combining different imaging techniques. The imaging modality of first choice in liver imaging is ultrasound including dedicated vascular imaging. However contrast-enhanced ultrasound (CEUS) is required for the detection of smaller liver lesions with sufficient confidence [1–6]. A certain disadvantage of ultrasound is the fact, that the method is dependent on the experience of the examiner. Contrast-enhanced multidetector-CT (MD-CT) can detect and characterize liver lesions with a high degree of diagnostic certainty since it involves imaging during the arterial and portal-venous contrast phase. On the other hand it is not possible to monitor the contrast enhancement of the lesions continually. This is not even possible with contrast-enhanced MRI. Additionally there are several contra-indications for contrast media application in CT and MRI [5]. Nevertheless, ultrasonic contrast media can be used even if the kidney function is reduced. Additionally, CEUS is being employed increasingly to determine the dynamic vascularisation and perfusion, and thereby to characterize liver lesions which cannot be detected by CT or MRI [7–12]. Frequently there are different numbers of lesions detected by CEUS, CT and MRI. This is especially the case with hypervascularised foci of hepatocellular carcinomas (HCC). Consequently a real-time fusion of CEUS with MD-CT or CEUS with MRI would be a perfect method to combine the continuous dynamics of CEUS with the tumor perfusion data and the high spatial resolution obtained with MD-CT and MRI. This could be applied for detection, characterization and monitoring of interventions.

With the development of a new ultrasound transducer together with a navigation system and dynamic positioning system (“Vnav”) it is becoming possible to combine current ultrasonic images with uploaded CT or MRI data. That enables us to combine the advantages of diverse imaging procedures within the framework of an ultrasonic examination and to enhance the certainty of a diagnosis. Modern probe technologies and very sensitive contrast-enhanced ultrasound imaging (amplitude modulation) with a low mechanical index (low MI technique) thereby afford us the prerequisites for an image fusion that enables an improved visualization of the microcirculation. There are only a few studies about imaging fusion with native US and CT or MRI [13–17].

The aim of this study is to present the first clinical results concerning the evaluation and characterization of the vascularisation and perfusion of liver tumors by means of real-time image fusion of CEUS and MD-CT or MRI with the help of a new ultrasound navigation technique.

2. Materials and methods

For the interventional planning in 20 patients (12 men, 8 women, age 43–69 years, median 54) with histologically confirmed malignant liver tumors (9 × HCC, 5 × metastases, 2 × hemangioma, 1 × cholangiocellular carcinoma (CCC), 1 × lymphoma, 1 × neuroendocrine tumor, 1 × focal nodular hypoplasia (FNH)) an image fusion involving contrast-enhanced sonography (LOGIQ E9, GE) was performed. In 17 cases real-time image fusion was performed with contrast-enhanced MD-CT and in three cases with contrast-enhanced MRI.

For the MD-CT (Sensation 16, Siemens) we acquired two different contrast phases (arterial, portal-venous) with a calculated axial slice thickness of 5 mm employing a bolus triggering technique (flow 4 ml/s, 130 ml Imeron 300, Bracco, Italy). For MR imaging (1.5 T, Avanto, Siemens, Germany) we employed two different contrast medias, whereby the liver-specific contrast agent Resovist® was applied after the administration of Gd-DPTA. The complete examination protocol included transverse T2-weighed
Half Fourier single shot turbo spin echo (HASTE), T1-weighted fast low angle shot (FLASH) in- and opposed-phase, T2-weighted turbo spin echo (TSE) in BLADE-technique with fat suppression, 3D volume interpolated breathold examination (VIBE) for the measurement of the Gd-DPTA contrast enhancement as well as T1-weighted FLASH with fat suppression in transverse and coronal orientation. After the administration of Resovist® axial T2*-weighted FLASH sequences were acquired. The slice thickness of the 3D VIBE sequence was 3 mm, whereas the thickness in all of the other transverse measurements was 6 mm with a 10% interslice gap; for the coronal acquisitions slice thickness was 5 mm with a 20% interslice gap. For the image fusion the dynamic 3D VIBE during the Gd-DPTA administration (0.1 mmol/kg bodyweight – measurement time for a 3D data set: 17 s) was utilized. Those lesions that could be identified with certainty were employed as reference and for follow up (≥ 3 months).

In HCC and neuroendocrine tumors the arterial phase is used for the image fusion, whereas in metastases of colorectal carcinomas the portal venous phase is employed. In hemangiomas and FNH the phase is chosen in which the tumors can be easily localized.

All of the ultrasound examinations were performed by an experienced examiner with a multifrequency probe (2–5 MHz, LOGIQ E9, GE) carried out with documentation of dynamic image sequences up to 3 minutes, flow documentation with color-coded duplex sonography (CCDS), native power Doppler and the perfusion in true agent detection mode of contrast harmonic imaging (CHI). An evaluation of the tumor was performed by the characterization of the dynamics of the contrast medium and microperfusion with CHI, fused with MD-CT or MRI.

For the image fusion volumetric MD-CT or MRI data, which was stored in DICOM format, were uploaded in the fusion mode (VNav) of the ultrasound system. Magnetic tracking systems determine the position of moveable sensors relative to a fixed transmitter within a defined operating volume. The sensors precisely measure the magnetic field from a transmitter that is configured to generate a known set of field patterns. These transmitted patterns are arranged such that the system can resolve a unique spatial position and orientation from the values measured by each sensor. The low frequency pulsed DC fields are unaffected by body tissues and most non-ferrous metals. The magnetic tracking system in the LOGIQ E9 employs Transient Electromagnetic (TEM) signal generation and processing which allows reduced sensor size, improved interference rejection, lower noise, higher update rates, and improved accuracy compared with earlier systems. The system generates a precisely known current waveform, which is sent through a transmitter located adjacent to the operating volume. The transmitter converts this current into a magnetic field, which is detected by a sensor and output as a small voltage. This tiny signal is then carefully amplified and digitized by a 21 bit, 800KSPS A/D converter. The data stream is processed by an FPGA and 2 floating point DSP’s that analyze the amplitude, shape and frequency content of the data stream. Mathematical corrections are applied to remove conductive metal effects, external noise and other errors. The values are then fed into an algorithm that determines the position and orientation of the sensor relative to the transmitter (“VNav”).

At the beginning of the image fusion the axial sections in the medial line of the body between the CT or MRI and the primary B-scan are adapted. After this plane registration an additional point registration is carried out to enable a more precise adaptation. Especially vascular structures such as the branching of the portal vein, the liver veins, the celiac artery or the mesenteric vessels are thereby chosen as anatomical landmarks. Afterwards the different imaging modalities are superimposed (overlay mode) and manually adjusted. This becomes feasible by positioning the patient similar to the scanning position in the CT or MRI.

After the registration in the medial line in axial sections the dynamic adaptation of the direction of the sections that run at an angle is double-checked so that a connection between the CEUS and the CT or
MRI images is attained. Especially the sections that include the parts of the liver close to the diaphragm, which are difficult to visualize, are optimized. Then the documentation of the tumor vascularisation is performed with the help of CCDS or power Doppler in order to register the arterial vessels feeding the lesions. Additionally thrombosis of the portal vein or AV-shunts can be excluded.

The dynamic CEUS with a bolus injection of 2.4 ml SonoVue® was performed with a reduced mechanical index (MI < 0.2) applying the contrast harmonic imaging technique (CHI) using the true agent detection mode. The complete examination of the whole liver was done with the sweep technique, whereby digital image sequences of a duration of at least 2.5 min were stored (sweep technique, duration ca. 10 s per sweep). When a lesion was localized, an adaptation as precise as possible was performed to enable the lesion to be characterized with CEUS and CT or MRI; this involved an additional registration of points in VNav image fusion mode. After virtual markers were placed as precisely as possible in the center of the lesion, the variable increase or decrease of the lesions (also in sectional planes running at an angle) in different contrast-medium phases of CEUS could be assigned to the CT or MRI images. If improved tumor detection possibilities in modified sections came about during the course of the dynamic examination, a second bolus injection with 2.4 ml SonoVue® was used to perform a tumor perfusion analysis. We applied a maximum of 5 ml SonoVue® i.v. via a cubital vein and flashed the syringe with 10 ml NaCl.

Reduced renal function and adverse reaction to contrast media in the past were regarded as contraindications. Written informed consent was obtained in all patients.

The digitally stored raw data allowed a retrospectively independent evaluation, leaving the option of an additional quantitative perfusion analysis open.

For statistic evaluation we used SPSS (version 16.0 SPSS for windows, LEAD technologies). For the evaluation of the distribution patterns, the Wilcoxon signed rank test was employed. Differences with \( p < 0.05 \) were considered as statistically significant.

3. Results

In all cases it was feasible to upload the volumetric MD-CT (17/20 cases) or MRI (3/20 cases) data. Additionally the data was registered correctly with the real-time CEUS. Image fusion along the cranio-caudal direction of the uploaded volumetric CT or MRI data could be achieved by using real-time B-scan (Figs 1–7).

After the additional registration of three landmarks ("point registration") using an overlay of vascular structures, an image fusion with visualization of the moving oblique slices in CT or MRI with the real-time B-scan was realized in all of the cases. A size adjustment from the B-scan to the CT or MRI of tumor structures could be achieved with an overlay marked in a different color in 16/20 cases.

In 4/20 cases the demarcation of the liver tumors in the B-scan could not be defined with sufficient confidence. Therefore an adjustment of the size was not possible.

In all of the 20 cases a dynamic contrast-enhanced examination in the true agent detection mode of the CHI was feasible in the fusion mode (VNav); digital cinematic sequences of approximately 3 min (range 2.5–3.5 min) could be recorded. In 18 cases the marking of the lesions in real time could be performed in VNav mode during the dynamic contrast-enhanced examination. In these 18 cases an exact correspondence was achieved, which means that the lesions could be assigned to particular segments. In 2/20 cases a comparable localization of the lesions was not attainable in the image fusion due to the different positioning of the patient and major respiratory motions.
Fig. 1(a). Small neuroendocrine tumor lesions (<1 cm) visible by image fusion with CEUS/MRI after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®).

Fig. 1(b). Small neuroendocrine tumor lesions (<1 cm) visible by image fusion (CEUS/MRI) with VNav navigation in the arterial phase after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®).
Fig. 1(c). Small neuroendocrine tumor lesions (<1 cm) visible by image fusion CEUS/MRI with color coded overlay for planning intervention.

Fig. 1(d). Small neuroendocrine tumor lesions (<1 cm) planning the biopsy in B-scan after successfully image fusion with CEUS/MRI.
Fig. 2(a). Intratumoral micro-vascularization of a HCC in segment VIII of the liver in the arterial phase of image fusion CEUS/CT after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®).

Fig. 2(b). Intratumoral micro-vascularization of a HCC in segment VIII of the liver in the late portal venous phase similar the liver parenchyma at image fusion CEUS/CT after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®). Visualization with GPS marker in VNav mode.
Fig. 3. Detection of a malignant liver lesion in segment V of the liver near the falciforme ligament not clearly visible in CT scan but by image fusion CEUS/CT after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®).

Fig. 4. Intratumoral micro-vascularization after partial TACE of a HCC lesion in segment IV of the liver in the portal venous phase of image fusion CEUS/CT after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®).
Fig. 5. Intratumoral micro-vascularization after complete TACE of a HCC in segment VI of the liver in the portal venous phase of image fusion CEUS/CT after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®). GPS markers are helpful to assign the target of the HCC lesion (arrow).

Fig. 6. Detection of HCC lesions with image fusion CEUS/CT after i.v. bolus injection of 2.4 ml contrast agent (SonoVue®). With CEUS (left) more lesions are visible in the arterial phase in comparison to CT (right).
In total 65 lesions could be definitely identified with the real-time image fusion with CT/MRI (3 × 1 lesion, 5 × 2 lesions, 8 × 3 lesions, 2 × 5 lesions, 1 × 8 lesions, 1 × at least 10 lesions (multifocal)). The sizes of the lesions were 1.6 cm in the average (range 0.5–5.2 cm, standard deviation 0.63 cm). In 17/20 cases a certain characterization of the lesion was achieved with the image fusion. In comparison to the follow up 6 additional lesions were observed with image fusion (CEUS and CT) which were not seen with CT alone. Between image fusion (CEUS and MRI) and MRI alone there was no difference (Table 1).

In 3/20 cases (lymphoma after liver transplantation, multifocal CCC, metastases of a neuroendocrine tumor) the diagnosis was only made after the histological confirmation. In all patients with HCC (n = 9) an evaluation of the tumor perfusion was feasible (8 cases after local trans-arterial chemoembolization (TACE); one case after radio frequency ablation (RFA)) (Fig. 8).

The statistical evaluation with the Wilcoxon test did not show any significant differences between the number of lesions which could be documented with image fusion compared with MRI and the reference methods (biopsy and/or operation results) and follow up examinations with CT or MRI. However, a tendency toward the identification of more lesions with the real-time image fusion of CEUS and MD-CT compared with the two phase contrast-enhanced CT alone could be identified (p = 0.059).

4. Discussion

Using CEUS it is feasible to detect and to characterize liver lesions with a high degree of diagnostic certainty [1–4,7–12]. Even lesions that are smaller than 1 cm can be ascertained with this method. In general, malignant liver lesions show a reduced uptake of contrast medium in the portal venous phase and the late venous phase [1,2]. In HCC, atypical hemangiomas, adenomas, FNH and metastases of neuroendocrine tumors the arterial phase can therefore prove decisive for the tumor characterization, since these tumors can be concealed in the portal venous or late phase [1,10]. For the detection of liver tumors and the visualization of the tumor vascularisation MD-CT with at least two contrast phases is
Table 1
Tumor entities and number of lesions detected with contrast-enhanced CT, MRI and image fusion with the dynamic CEUS technique

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required; using MRI a dynamic contrast-enhanced study must be carried out. In addition a liver-specific contrast medium must be administered if necessary [11]. However the dynamics of the contrast medium can only be registered at certain points of time, whereas CEUS enables a continuous documentation of the perfusion of the tumor. With image fusion a parallel scanning is possible, whereby the advantages of the different imaging modalities can be exploited [13–17].

The technique used in this study enables a fusion of MD-CT or MRI and real-time CEUS. Thus the advantages of the different imaging modalities, for example the dynamic continuous recording of CEUS and the high spatial resolution of MD-CT or MRI, can be combined and jointly exploited to enable an optimal detection and characterization of liver lesions. With additional markers in the VNav mode it is possible to mark even small lesions and to characterize them in respect to their contrast-medium dynamics in various imaging modalities. Especially in the restructuring of the liver that occurs in cirrhosis, lesions smaller than 1 cm cannot be delineated and characterized with sufficient confidence using either MD-CT, MRI or conventional ultrasound [7].

Based on major technical improvements in contrast-enhanced ultrasound it is possible to detect and characterize even smaller liver lesions at depths greater than 10 cm with the help of CHI with amplitude modulation; this can even be done with lower transmitting power and a reduced mechanical index (MI) <0.2 employing small amounts of the ultrasound contrast media of the second generation (ϕ = 1 ml) [1,2]. Multi-frequency probes with high resolution matrix technology, which are increasingly available in frequency ranges from 2–5 MHz, have proven to be advantageous for this purpose.
The storage of digital raw data for dynamic image sequences over 3 min duration is now available in high-performance ultrasound devices. This is a decisive advantage over contrast-enhanced CT or MRI, in which the documentation generally only comprises a fixed point in time during the arterial, portal venous and late venous or parenchymal phase of the liver. Even by means of bolus triggering it is not possible to compensate for, among other things, mixed phenomena, for example AV shunts, which frequently occur in cirrhosis. Other reasons for inhomogeneous contrasting are reduced heart rate or a thrombosis of a portal vein. For the characterization of adenomas, of FNH or of atypical hemangiomas it can be necessary to comprise a later venous phase in addition to the portal venous phase [1,2,10–12]. For the diagnosis of malignant lesions in patients with HCC or the detection of a high flow hemangioma, in which the arterial contrast phase only enables the detection of a minor part of the lesions, it is of decisive importance to include an early arterial phase. The technique of image fusion between CT, MRI and CEUS, which is presented here for the first time, enables a lesion-specific characterization in uncertain CT or MRI findings. It also allows to localize with conventional CEUS in the absence of fusion, for example those near the diaphragm. It is much easier to find these lesions with CEUS when performing real-time image fusion with CT or MRI. Based on these findings the optimal angle for the ultrasound waves can be utilized. This has the potential of enabling secure, ultrasound-guided access for punctures, improved therapy monitoring or a more precise intervention, for example for TACE or RFA of malignant liver tumors [2–4,6,8,14].

Studies with larger numbers of cases will be necessary to determine whether the method of image fusion affords advantages for the detection of liver lesions. Therefore especially in HCC intra-operative ultrasound would be the reference method during the procedure while a histopathological examination after a liver transplantation could be the standard of reference. Even in contrast-enhanced MRI with liver-specific contrast media it is not feasible in all cases to clearly differentiate between regenerative, dysplastic and HCC lesions in cirrhosis. Still it remains a critical point to what extent the detection of lesions smaller than 1 cm can be improved by real-time image fusion [7,8,10–12].

Certainly a decisive advantage of the method is the potential to dynamically record the microperfusion of liver lesions with CEUS, in addition to the vascularisation with MD-CT and MRI [1,2,11,12]. Quantitative perfusion measurements based on the raw data can then be utilized for an advanced tumor characterization [1]. Additionally the method of image fusion with CEUS can also be employed when contra-indications prevent the usage of contrast media in CT or MRI [1,5,9–12]. Even with reduced renal function ultrasonic contrast media can be employed. In therapy monitoring image fusion with the initial examination enables a more precise evaluation and, ultimately, a way to reduce radiation exposure by reducing follow-up CT examinations at short intervals. Since the amounts of ultrasound contrast media can be reduced by high-resolution probe technology ($\varnothing = 1$ ml), it is possible to save on the costs for these substances as well.

One disadvantage is that for an optimal image fusion the positioning of the patient must be comparable to that in CT or MRI. Displacements resulting from breathing motions must also be taken under consideration. Additionally for optimal contrasting it is necessary to have a sufficient access to a vein. Additionally, as in all applications of contrast media, the written consent of the patient is required. Even though the method of real-time image fusion with CEUS is still under development and the experience of the ultrasound examiner is of decisive significance, the great potential of this technique for evaluation of tumor microcirculation is already evident.
References


