Clinical value of contrast-enhanced ultrasonography in the characterization of focal liver lesions: a prospective multicenter trial

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BACKGROUND: Contrast-enhanced ultrasonography (CEUS) is increasingly accepted in clinical settings for diagnostic imaging of focal liver lesions (FLLs). This study aimed to assess the efficacy of CEUS in the characterization of FLLs in comparison with final diagnosis based on gold standard assessment.

METHODS: The study was approved by the local ethics committee and participating patients provided written informed consent. A total of 148 patients with 164 FLLs were studied. Unenhanced ultrasonography (US) and CEUS were performed using fundamental and harmonic imaging, respectively. Contrast enhancement was assessed during the arterial, portal and late vascular phases after intravenous administration of contrast (SonoVue®, Bracco, Italy). Sensitivity, specificity and diagnostic accuracy of US and CEUS were compared in identifying the lesion as benign, malignant or indeterminate and its actual tumor type. Final diagnosis was established by biopsy (129/164), MR imaging (11/164) or medical history (24/164).

RESULTS: When compared to the gold standard, the number of indeterminate diagnoses was reduced from 56.7% (93/164) as assessed by fundamental imaging to 6.1% (10/164) after SonoVue® enhanced US examination. Sensitivity and specificity improved from 49% and 25% at baseline US to 93% and 75% with CEUS, respectively (P<0.01). Diagnostic accuracy of CEUS was 88% in contrast to 41% of baseline US.

CONCLUSION: SonoVue® enhanced US improves the characterization of FLLs and may limit the need for further investigations.

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KEY WORDS: contrast-enhanced ultrasonography; characterization; focal liver lesions

Introduction

Due to its relatively low cost, safety and availability, unenhanced ultrasonography (US) is the most widely used initial imaging modality for patients with known or suspected focal liver disease. In addition, US imaging frequently reveals hepatic lesion as an incidental finding in patients undergoing US for screening purposes or for investigating a non-hepatic disease. Once a lesion is detected it is necessary to know whether it is benign or malignant. Contrast-enhanced computed tomography (CECT) or contrast-enhanced magnetic resonance imaging (CE-MRI) are performed because unenhanced gray scale US only provides information about morphologic features, and color, power, or spectral Doppler US provides information about macro-

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Thus, unenhanced US has limited accuracy in the characterization of focal liver lesions (FLLs) compared with CT and MRI. The introduction of first generation contrast agents with color or power Doppler US has improved tumor vessel visibility even if color signal saturation and blooming artifacts exist. 

The introduction of second generation ultrasound contrast agents, stable microbubbles that can be imaged by using a low mechanical index together with the development of harmonic imaging has enabled us to visualize the microcirculation in real-time and the different vascular phases of the liver (arterial/portal/late) as shown by dynamic CT or MRI. 

The differential enhancement of the focal lesions compared to normal surrounding liver parenchyma during the hepatic arterial and portal venous phases of the contrast can therefore be used to characterize the lesions. In addition, the persistent enhancement of the normal liver parenchyma in the late phase produced by the second generation contrast agents adds to the capability of differentiating benign from malignant lesions. 

CEUS is increasingly accepted in clinical settings for diagnostic imaging of FLLs. Recently, this has prompted a group of experts to issue a specific chapter in the guidelines on the use of contrast agents in ultrasound, for the characterization of FLLs with contrast. 

The document explains the clinical use of contrast ultrasound in diagnosis of liver diseases, in particular for characterization and detection of FLLs and also in monitoring of percutaneous local ablative treatment of primary and secondary liver tumors. 

Afterwards, the American Association for the Study of Liver Diseases (AASLD) issued guidelines which included a recommendation that the diagnosis of hepatocellular carcinoma (HCC) (i.e. characterization of a liver nodule inside a cirrhotic liver as benign regenerative nodule or malignant HCC) could be achieved by consensus of two contrast-enhanced imaging methods from among ultrasound, CT or MRI. 

The aim of this multicenter study was to assess the efficacy of CEUS in the characterization of FLLs in subjects undergoing traditional US examination compared with the final diagnosis obtained from gold standard assessment.

Methods

Patients and study design

This study was a prospective, open-label, non-randomized, multi-centre clinical trial, performed from October 2004 to February 2005 in 11 centers in China on a total of 250 patients with 306 known FLLs.

We present here the data obtained in a subgroup of 148 patients with 164 lesions who had final diagnoses based on the gold standard.

The gold standard for malignant lesions was biopsy (129/164). However, when this was not performed for ethical reason in patients with multiple metastases, a medical history of primary cancer was used as the standard (24/164). Similarly, for benign lesions when biopsy was not available, CE-MRI was used as the standard (11/164).

The mean age of patients (42 females and 106 males) was 49.5±12.7 years (range 18 to 92 years). Patients older than 18 years and with at least one FLL seen at baseline US examination were enrolled in the study. All subjects underwent CEUS examination, with SonoVue® (Bracco, Italy) to localize and characterize the FLL seen at baseline US and had a CE-MRI performed within 4 weeks before or after the SonoVue® enhanced US. Exclusion criteria comprised subjects with any contraindication to CE-MRI, acute cardiac failure, class III/IV cardiac failure, cardiac rhythm disorders, recent coronary artery intervention or factors suggesting clinical instability, female subjects with a positive pregnancy test, and subjects previously entered in this study or having received an investigational drug within 30 days prior to admission to this study.

The study was approved by the Local Ethics Board. All patients gave their written informed consent to participate in the study, which was performed according to the guidelines provided in the Declaration of Helsinki of 1975, as revised in 1983. After written informed consent was obtained, all patients were monitored for adverse events, until two hours after the administration of contrast.

Imaging equipment

Different ultrasound scanners, all equipped with non-linear imaging capabilities and 2-7 MHz Convex arrays, were used at various centers (in 7 centers: CrtTi Technos MPX DU8 Esato, Genova Italy; in 2 centers: CPS Acuson Sequoia 512, Mountain View, CA; in 1 center Coded PI Logiq 7, GE; and in 1 center: General Contrast Imaging HDI 5000, ATL Bothell, Washington). Technical settings such as mechanical index, frame rate, and focal zone were optimized to obtain images of the best quality.

CE-MRI was performed using 1.0-1.5T Siemens machines (Germany) with gadolinium-based contrast media.

Imaging modalities
Baseline US examinations

Target lesions were first identified using B-mode ultrasound. Then color or power Doppler was carried out to study the vascularization of target lesions and the surrounding parenchyma.

CEUS

The second step of sonography was performed in grey scale with non-linear imaging modes using continuous real time imaging techniques following an intravenous bolus injection of SonoVue® (Bracco, Italy), the second-generation contrast agent. The agent is provided as a sterile, lyophilized powder contained in a septum-sealed vial. A white, milky suspension of sulphur hexafluoride (SF$_6$) microbubbles was obtained by adding 5 ml of physiological saline (0.9% sodium chloride) to the powder (25 mg), using standard aseptic techniques, followed by hand agitation. Each patient received up to 2 intravenous bolus injections of SonoVue® for each lesion for characterization (two boluses of 2.4 ml each) via a 20-gauge intravenous catheter placed in the ante-cubital vein followed by 5 ml of saline flush.

The hemodynamic behavior of SonoVue® during the hepatic arterial (15-25 seconds), portal venous (25-100 seconds) and late vascular phases (100-300 seconds) was evaluated to characterize the lesion. All sonographic examinations were recorded on digital disks.

The location and size of the lesion were assessed on unenhanced and CEUS scans. In addition, the vascularity and pattern of SonoVue® enhancement of the lesion (hypo-echoic, hyper-echoic, iso-echoic) compared with the adjacent liver parenchyma during the hepatic arterial, portal venous and sinusoidal phases were evaluated for the CEUS diagnosis (Table 1).

Therefore, diagnoses in terms of the nature (malignant or benign) and actual histological type of the lesion (such as metastases, HCC, or hemangiomas) were based on a) the pre-contrast fundamental and color power Doppler US, and b) the SonoVue®-enhanced US (CEUS). CEUS and CE-MRI images and/or movie clips were stored for assessment of vascularization patterns in the arterial, portal and late phases. The number, location, size and characterization of the lesions were recorded. Both US and CEUS diagnoses were then compared with the final diagnosis based on the gold standard. One experienced sonographer affiliated with the study center evaluated all the CECT/CE-MRI images in addition to baseline and SonoVue® enhanced images.

Statistical analysis

Summarized descriptive statistics were provided for continuous variables (mean, median, range and standard deviation), and counts and relative frequencies were calculated for categorical data. In addition, 95% confidence intervals (CI) were calculated for the main variables. All statistical comparisons were made as two-sided tests, and significance was declared at the $P\leq0.05$ level. McNemar’s test was used for assessment of accuracy, sensitivity and specificity, at the lesion level. The accuracy of unenhanced and SonoVue® enhanced US in the characterization of FLLs using the gold standard was estimated in terms of the nature of lesion (benign or malignant) and tumor type, and it was defined as the total number of true negatives (TN) and true positives (TP) divided by the total number of benign or malignant lesions identified with the gold standard.

| Table 1. Diagnostic criteria for malignant and benign FLLs based on CEUS vascular patterns |
|----------------------------------|-----------------------------------------------|
| Lesion                           | CEUS criteria                                 |
| Malignant                        |                                               |
| HCC                              | Diffuse enhancement in arterial phase; washing out at PV and late phases |
| Metastasis                       | Peripheral rim or complete enhancement in arterial phase and hypo- or non-enhancing in PV and late phases |
| Cholangiocellular carcinoma      | Peripheral enhancement in arterial phase and hypo- or non-enhancing in PV and late phases |
| Benign                           |                                               |
| Cyst                             | Non-enhancing at any contrast vascular phase |
| Hemangioma                       | Peripheral nodular enhancement, no central E in arterial phase; centripetal filling during PV phase; marked contrast uptake during late phase |
| FNH                              | Central spoke wheel-shaped enhancement at arterial phase becoming homogeneous during PV phase; iso- or hyper-enhancing at late phase |
| HCC                              | Diffuse homogeneous or heterogeneous enhancement at arterial phase; iso- or hypo-enhancement at PV phase; iso-enhancement at late phase |
| Regenerative nodule              | Iso-enhancing during all phases               |

PV: portal-venous.
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The sensitivity was calculated as the percentage of true malignant lesions over the total number of malignant lesions; in the estimate of sensitivity, undetermined lesions were classified as being wrongly diagnosed as benign, with the consequence of underestimated TP and overestimated false negatives (benign+undetermined).

The specificity was calculated as the percentage of true benign over the total number of benign lesions; in estimation of specificity, undetermined lesions were considered as wrongly diagnosed as malignant, with the consequence of underestimated TN and overestimated false positives (malignant+undetermined).

Results

According to the gold standards 48/164 lesions (29%) were benign and 116/164 (71%) were malignant. With unenhanced US, a total of 71/164 lesions (43%) were characterized: 12/48 (25%) were correctly characterized as benign and 56/116 (48%) as malignant. After dynamic examination with SonoVue®, total lesions characterized were 154/164 (94%); of these, 36/48 (75%) were correctly characterized as benign and 108/116 (93%) as malignant (Table 2).

Evaluation of diagnostic performance versus gold standard showed that the accuracy of SonoVue® (88%) was markedly higher than that of the fundamental method (41%) \( (P<0.01) \). The specificity and sensitivity of SonoVue® were also higher than those of the fundamental method \( (P<0.01) \) (Table 3).

CEUS increased the number of correct diagnoses, as demonstrated by the consistent reduction obtained with CEUS in the number of undetermined lesions in comparison to baseline US, i.e. from 93/164 (57%) at baseline to 10/164 (6%) after contrast (Table 2).

As to the characterization of lesion type, among benign lesions, concordance of fundamental imaging with the gold standards for hemangiomas was 43% (6/14), whilst after SonoVue® this increased to 93% (13/14). Among malignant lesions, concordance in the diagnosis of HCC increased from 48% (32/66) with fundamental imaging to 95% (63/66) after SonoVue® administration, and for metastases concordance improved from 50% (16/32) with unenhanced imaging to 91% (29/32) with contrast (Table 4).

Hence, the level of agreement with the gold standards in the characterization of the lesions was higher with SonoVue® (126/164 lesions, 77%) than with fundamental imaging (62/164 lesions, 38%). However, 4 lesions were misdiagnosed as benign by CEUS, two of which were revealed to be cholangiocellular carcinomas, one was classified as a suspicious malignant lesion and the other was a mixed cell carcinoma at biopsy.

Discussion

The incidental detection of a liver lesion that needs to be characterized is one of the most common clinical issues.\[20, 21\] FLLs are found incidentally during more than 50% of autopsies, hemangiomas being the most common (up to 20%), followed by focal nodular hyperplasia (3%).\[22\] Small liver tumors detected in asymptomatic patients are usually benign, even in patients with a history of malignant tumors, especially when the diameter of the lesion is less than 15 mm.\[23\]

\[\text{Ultrasound is the first choice of imaging investigation for a number of abdominal disorders. However,}\]
baseline US lacked specificity in characterizing FLLs; its specificity in differentiating benign from malignant lesions ranges between 23% and 68% on a baseline study. Colour and spectral Doppler US is limited in the detection of tiny vessels and/or low-flow states in all FLLs. CEUS characterization of liver lesions was based on the comparison of enhancement level of the lesion to normal liver parenchyma during all three vascular contrast phases, i.e. arterial, portal-venous and late (Figs. 1-3).

The gold standard for tissue characterization is histology. However, the sensitivity of fine-needle aspiration cytology (FNAC) for detecting hepatic malignancy is reported to be 90%-93%.[25,26] Similar to the diagnostic accuracy obtainable with radiological investigations, including CEUS, which have an up to >90% sensitivity.[4,27,28] Furthermore, biopsy of hepatic adenomas, focal nodular hyperplasia, and hemangiomas also carries an increasing bleeding risk. Several studies have demonstrated the value of CEUS in the characterization of FLLs.[27-32]

In a large study on 452 patients with 452 lesions undetermined by baseline US, Quaia et al.[21] reported that the diagnostic accuracy for FLL characterization increased from 49%-51% at baseline examination to 85%-88% after CEUS. The sensitivity and specificity increased from 53% and 41% to 83% and 95% after contrast study, respectively. In 126 lesions in 124 patients with FLL detected by baseline US, examination with CEUS was able to improve the sensitivity from 78% to 100% and the specificity from 23% to 92%.[15]

In another study by Catala et al.[28] on 77 patients, CEUS provided a correct diagnosis in 90% of FLLs, with a sensitivity, specificity and accuracy of 91%, 90%, and 91%, respectively.
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The use of contrast-enhanced ultrasound in the characterisation of focal liver lesions

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ABSTRACT

Purpose: To determine the potential application of contrast-enhanced ultrasound in the characterisation of focal liver lesions encountered in radiological practice at a district general hospital.

Materials & Methods: Retrospective analysis of 68 sequential patients undergoing contrast-enhanced ultrasound (CEUS) of liver. All patients were referred for CEUS following identification of 1 or more focal liver lesions on conventional ultrasound or CT imaging. After baseline US examination (Acuson), a bolus of 1.0-2.4 ml of SonoVue (Bracco, UK) was administered intravenously. CEUS images were obtained during arterial, portal venous and delayed phases. Patients were followed up for a mean period of 6 months. The CEUS diagnosis was compared to that indicated by other imaging modalities, histopathology, and clinical follow up.

Results: CEUS correctly identified malignant liver lesions in 19 patients, with the final diagnosis confirmed by histopathology in 5 cases and clinico-radiological follow up in 14 cases. 47 patients were correctly identified with benign liver lesions on CEUS imaging, with all these cases confirmed on clinico-radiological follow up. In the detection of malignancy, the sensitivity was 95.0% and the specificity was 97.9%.

Conclusions: In our experience to date, contrast-enhanced ultrasound imaging is highly accurate in characterising malignant and benign focal liver lesions. It therefore has significant potential for utilisation in most general radiology departments.

INTRODUCTION

The effective non-invasive detection and characterisation of focal liver lesions (FLL) can significantly alter patient management. Early detection of primary or secondary liver malignancies increases the possibility of curative surgical resection or successful percutaneous ablation. It is becoming increasingly evident that contrast-enhanced ultrasonography (CEUS) using non-destructive low-acoustic-power ultrasound scanning with second generation contrast agents, such as perfluorocarbon or sulphur hexafluoride-filled microbubbles, allows improved characterisation of solid focal liver lesions. CEUS has high sensitivity in the detection and characterisation of hyper- and hypovascular liver malignancies with an accuracy comparable, and in some cases superior to, helical CT. CEUS may also enable definitive diagnosis of haemangiomas and focal nodular hyperplasia (FNH).

The aim of this study was to determine the potential application of contrast-enhanced ultrasound in the characterisation of focal liver lesions encountered in radiological practice at a district general hospital.

METHODS

This study retrospectively reviewed the radiological yield and clinical outcome of 68 sequential patients who underwent CEUS of the liver in Antrim Hospital, a district general hospital in Northern Ireland. The patients were found to have one or more FLLs on conventional ultrasound or contrast-enhanced CT before being referred for CEUS. Information was collated by review of ultrasound examinations, case-notes, and CT and/or MRI investigations. After baseline ultrasound (Acuson, Mountain View, USA), continuous ultrasound images were obtained with the “Coherent Contrast Imaging” setting after the administration of a bolus intravenous injection of 1-2.4 ml of SonoVue (Bracco, UK), followed by a 5 ml saline flush. Images were obtained during arterial (15 – 25 seconds following injection), portal venous (45 – 90 seconds), and “late” (180 seconds onward) phases.

Patients were followed up for a mean period of 6.3 months, using case-notes and further Ultrasound, CT and/or MRI scans as evidence of disease progression or diagnosis confirmation. Comparison was made between the working diagnosis as indicated by clinical follow-up and further imaging, and the original CEUS diagnosis.

RESULTS

Of the 68 patients, 41 were female and 27 male. Ages ranged between 17 and 83 years, with a mean age of 56.5 years. CEUS
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Correctly identified malignant liver lesions in 19 patients, with the final diagnosis confirmed by histopathology in 5 cases and clinico-radiological follow up in 14 cases. One patient with a metastatic liver deposit confirmed on clinico-radiological follow up was incorrectly diagnosed by CEUS as a benign lesion (haemangioma). 47 patients were correctly identified with benign liver lesions on CEUS imaging, with all these cases confirmed on clinico-radiological follow up. One patient with a haemangioma confirmed on clinico-radiological follow up was incorrectly diagnosed as a benign lesion (haemangioma). 47 patients were correctly identified with benign liver lesions on CEUS imaging, with all these cases confirmed on clinico-radiological follow up. One patient with a haemangioma confirmed on clinico-radiological follow up was incorrectly diagnosed by CEUS as a benign lesion (haemangioma). The different diagnoses encountered are listed in tables I (benign) and II (malignant). In the 68 cases where focal liver lesions were characterised, CEUS demonstrated a sensitivity of 95.0% and a specificity of 97.9% in the detection of malignancy. The positive predictive value was 95.0%, and the negative predictive value was 97.9%.

There were 16 cases of metastases, most of which appeared as hypoechoic nodules in contrast to the enhanced background of normal liver parenchyma (fig 1). One case of metastasis demonstrated diffuse enhancement in the arterial phase, suggesting that it was hypervascular, and showed subsequent rapid wash-out of contrast, the lesion becoming hypoechoic to the surrounding liver in the late phase (fig 2). CEUS identified one patient as having metastatic disease, when CT and biopsy confirmed the diagnosis was hepatocellular carcinoma with metastatic liver disease. In the one case of metastasis misdiagnosed as haemangioma, there was a hypoechoic mass which appeared to gradually fill-in during the late phase.

Of the two hepatocellular carcinomas, one demonstrated peripheral enhancement during the arterial phase, followed by isoechogenic enhancement with the liver during the portal venous phase, and finally became hypoechoic in the late phase. The other demonstrated isoechogenic enhancement with the remainder of the liver in the arterial and portal venous phases, and became hypoechoic during the late phase. The lymphomatous deposit, demonstrated in one patient in whom there was a previous history of lymphoma, remained hypoechoic throughout all phases of CEUS. In the final patient with malignancy, a histologically-proven cholangiocarcinoma was erroneously reported as a metastatic deposit, demonstrating hypoechogenicity throughout all phases of CEUS.

Of the 27 haemangiomas detected, 19 (70%) demonstrated typical appearances of hyperechoic focal lesions on conventional B mode ultrasound (fig 3a), showed rapid peripheral filling-in during the arterial phase of contrast enhancement (figure 3b), and subsequently became isoechogenic with the surrounding liver in the portal venous and late phases (figure 3c). A further haemangioma was initially hypoechogenic, but demonstrated rapid peripheral filling-in to become isoechogenic with the surrounding liver in later phases of the examination.

Seven haemangiomas demonstrated atypical behaviour, and were reported as being likely atypical haemangiomas but further follow up was recommended to confirm or exclude metastases. Of these, six haemangiomas demonstrated persistent hypoechoic areas with circumferential filling-in. The other atypical haemangioma demonstrated slow filling-in of peripheral enhancement, and was shown to be unchanged on ultrasound six months later.

Another of the haemangiomas demonstrated peripheral enhancement in the arterial phase with rapid wash-out of contrast in the portal venous and late phases, and was therefore thought to be a metastasis. However, MRI and clinical follow up confirmed this lesion to be a haemangioma.

Focal fatty sparing was shown in 3 patients to be a hypoechogenic, well-defined area on B mode which became isoechogenic with the surrounding liver during all phases of CEUS. Focal fatty infiltration was shown in two patients to be a hyperechoic lesion on B mode which became isoechogenic with the surrounding liver during all phases of CEUS. There were four cases of simple hepatic cysts. A focal regenerating nodule was seen to be a well-defined hyperechoic lesion on B mode, and was obscured when CEUS was performed. The diagnosis was confirmed with repeated ultrasonography and CT. The one case of focal nodular hyperplasia demonstrated early central

Table I. Benign focal liver lesions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemangioma</td>
<td>27</td>
</tr>
<tr>
<td>Focal fatty sparing</td>
<td>13</td>
</tr>
<tr>
<td>Focal fatty infiltration</td>
<td>2</td>
</tr>
<tr>
<td>Simple cyst</td>
<td>4</td>
</tr>
<tr>
<td>Regenerating nodule</td>
<td>1</td>
</tr>
<tr>
<td>Focal nodular hyperplasia</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
</tr>
</tbody>
</table>

Table II. Malignant focal liver lesions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>16</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma deposit</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20</strong></td>
</tr>
</tbody>
</table>

Fig 1. Typical hypoechoic appearance of a metastatic deposit on a background of enhanced normal liver parenchyma.
DISCUSSION

Accurate characterisation of focal liver lesions is essential for the utilisation of new treatment strategies in the management of focal liver malignancies.

Ultrasound is a widely used modality for imaging liver pathology. It is relatively inexpensive, does not expose the patient to ionising radiation, and is widely available. However there are limitations to conventional grey scale B mode ultrasound in the detection of focal liver lesions, especially when the lesions are small (<2cm), in the setting of cirrhosis, or in patients undergoing chemotherapy. Colour and power Doppler has increased sensitivity for focal lesion detection compared to conventional B mode, but sensitivity is still inferior to contrast-enhanced spiral CT and MRI.

Ultrasound examination with intravenous contrast agents allows dynamic assessment of focal liver lesions, improving the diagnostic performance of conventional sonography. Perfluorocarbon or sulphur hexafluoride-filled microbubble contrast agents, such as SonoVue, can be used with non-destructive low acoustic power ultrasound scanning. In this way, real-time assessment of contrast enhancement in focal liver lesions is possible. CEUS therefore has the potential to provide firm diagnostic information without the need for other imaging modalities such as CT or MRI. In district general hospitals where imaging resources may be limited, CEUS can be incorporated into radiological practice with a relatively small cost.
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increase in equipment and operator expenditure.

The results of this study indicate that CEUS in our practice has high sensitivity and specificity in determining if focal liver lesions are malignant. Most of the lesions exhibited definite enhancement patterns on dynamic scanning. As demonstrated in previous studies, the principal difference between benign and malignant liver lesions is their appearance during the late phase of contrast enhancement. Malignant lesions are usually hypoechoic compared to normal liver parenchyma in this phase, whereas benign lesions are usually hyperechoic or isoechoic. In this study, nearly all of the metastases remained hypoechoic throughout all phases, although one case showed arterial enhancement with rapid wash-out. The two hepatocellular carcinomas showed variable enhancement characteristics in arterial and portal venous phases, but were also markedly hypoechoic relative to normal liver parenchyma in the late phase. The hepatic lymphoma and cholangiocarcinoma encountered in our study were correctly identified as malignant, although the enhancement characteristics were indistinguishable from hepatic metastases.

The majority of haemangiomas in our series demonstrated the usual pattern of peripheral enhancement in the arterial phase, followed by central filling-in on the delayed images (fig 3). A few haemangiomas exhibited slightly atypical enhancement patterns, but were correctly identified as benign. CEUS enabled the accurate characterisation of focal fatty sparing and focal fatty infiltration as the cause of liver lesions in several patients. Focal nodular hyperplasia was identified in only one patient in our series, with the classic features of early central spoke wheel-shaped enhancement and isoechoic appearance on late phase imaging.

CONCLUSION

Contrast-enhanced non-destructive ultrasonography using a low mechanical index is the sonographic modality of choice for the detection of liver malignancy. In our experience, contrast-enhanced ultrasound imaging is highly accurate in characterising malignant and benign focal liver lesions. The equipment and expertise required for this investigation can be incorporated into most general radiology departments. Contrast-enhanced ultrasonography therefore has significant potential for utilisation in district general hospitals as well as specialist centres.

Conflict of Interest – none declared.

REFERENCES

Abstract

In patients with known malignancy, correct detection and characterization of liver lesions has important therapeutic consequences. Conventional sonography is the most commonly used modality for liver imaging in tumor patients. However, it has a lower sensitivity for the detection of liver metastases compared to contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI). The majority of liver metastases are hypoechoic and well defined in baseline ultrasound (US), while detection of isoechoic or small liver metastases <1 cm is difficult and the differentiation of liver metastases from benign liver lesions and other malignant liver tumors can be impossible with baseline US. The use of microbubble-based ultrasound contrast agents and contrast-specific imaging techniques advanced the accuracy of ultrasound in liver imaging. Levovist and SonoVue are the US contrast agents approved for liver imaging in Europe. Compared to Levovist, SonoVue allows continuous imaging of the liver in real-time over a period of up to 5 minutes. As a result, SonoVue became the preferred contrast agent for liver imaging in the recent years, while Levovist became less important. Important for the detection of liver metastases are the portal venous and late phases in which metastases show a wash-out and can be detected as hypoechoic lesions in homogeneous enhanced liver parenchyma. The detection of hepatic metastases is substantially improved by CEUS compared to conventional B-mode sonography. Several studies showed sensitivity in detecting liver metastases comparable to that of contrast-enhanced CT and MRI. Furthermore, the typical enhancement patterns of the different benign and malignant liver lesions allow reliable characterization and differentiation from liver metastases in the majority of cases. This paper provides information about the advantages and expedient application of contrast-enhanced ultrasound (CEUS) in tumor patients.
Imaging of Focal Liver Lesions
Low-Mechanical-Index Real-time Ultrasonography With SonoVue

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Objective. The purpose of this study was to evaluate the usefulness of a contrast-enhanced contrast-specific ultrasonographic technique with a low mechanical index for characterization of focal liver lesions. Methods. Contrast-specific ultrasonography was used to assess 144 patients with 147 focal liver lesions: 87 primary liver carcinomas, 27 hemangiomas, 16 focal nodular hyperplasias, 5 hepatic abscesses, 3 inflammatory pseudotumors of the liver, and 9 metastases. A sulfur hexafluoride gas-based contrast agent was used with a mechanical index of 0.08 to 0.11. Results. On contrast-enhanced ultrasonography, the typical hemodynamic pattern of primary liver carcinoma was the whole-lesion enhancement or mosaic enhancement in the arterial phase with an enhancement defect in the late phase (sensitivity, 92.0%; specificity, 86.7%). The most common enhancement pattern of hemangioma was that enhancement appeared in the periphery first and progressively filled into the lesion center (sensitivity, 96.3%; specificity, 97.5%). The enhancement pattern of focal nodular hyperplasia was that the whole lesion enhanced early and rapidly in the arterial phase with a centrifugal radiating configuration and appeared isoechoic or hyperechoic until the late phase (sensitivity, 87.6%; specificity, 94.5%). The central scar was detected in 31.3% of cases in the late phase. The specific enhancement of a hepatic abscess was the honeycomblike enhancement in all phases (sensitivity, 80.0%; specificity, 100%). No enhancement of a lesion in all phases was specific for an inflammatory pseudotumor of the liver. Conclusions. Contrast-enhanced real-time ultrasonography is a promising approach in the noninvasive characterization of focal liver lesions and can be useful as a first-line imaging technique clinically when a focal liver lesion is detectable on ultrasonography. Key words: contrast media; liver neoplasms; low mechanical index; microbubbles; ultrasonography.

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Abbreviations
CT, computed tomography; MI, mechanical index; MRI, magnetic resonance imaging

Ultrasoundography is the most widely available imaging modality for the screening of liver disease and the detection of small incidental hepatomas in high-risk patients. However, conventional color and power Doppler ultrasonography does not allow levels of sensitivity for hepatic lesion characterization compared with those of contrast-enhanced axial imaging (computed tomography [CT] and magnetic resonance imaging [MRI]). The introduction of gas microbubble agents in ultrasonographic examination has had a remarkable impact on the evaluation of tumoral vascularization. The combination of a contrast agent and harmonic technology has been reported to be...
Contrast enhanced ultrasonography (CEUS) is a new imaging modality offering new perspectives in the management of abdominal disease. The objectives of this review are to expose briefly principles of CEUS signal acquisition, to illustrate second generation of contrast agent signal, to give a short overview of current clinical applications of CEUS, and to discuss CEUS feasibility.

Key-words: Ultrasound (US), contrast media – Abdomen, US.

Contrast enhanced ultrasonography (CEUS) is no new modality as the first description of an increase in blood backscattering dates back 1968 when cardiologists observed, during cardiac catheterization, a gas cavity phenomenon, after saline solution injection into the aorta (1).

For a long time, radiologists have known that air acoustic impedance prevents propagation of ultrasound at the frequency used in medicine. Air interface has a classical hyperechoic sonographic aspect and no sonographic information is available behind this interface.

This is the reason why it is impossible to explore by sonography pulmonary tissue or bowel internal wall (when gas is present).

It has been demonstrated that air microbubbles do not stop completely ultrasound propagation and that it is possible to observe microbubbles motion under the form of echoic dots in case of aerobily or aerporty (2, 3).

The great idea, heart of the development of sonographic contrast agents, was to use air or gases (with the same acoustic properties than air), in the form of injectable microbubbles, to increase blood backscattering (4).

US contrast agents

The challenge for the industry was to provide microbubbles injectable through an easy way (venous access), optimised to increase the blood reflectivity, sufficiently small (diameter < 7 µm) to cross the lung bed after intravenous injection, sufficiently stable over time to produce persistent enhancement during several minutes after intravenous injection, and well tolerated without clinical adverse effect.

To satisfy the specifications of an ideal contrast agent, the initial rough saline solution of Gamiak and Definy (Albunex, Mallinkrodt), galactose + surfactant (Levovist, Shering) or phospholipids (SonoVue, Bracco and Definity, Bristol–Myers Squibb Medical Imaging), bubble solubility reduction by the use of other gases than air like perfluorocarbon (Definity, Bristol) or sulfur hexafluoride (SonoVue, Bracco).

During the last decade, the most popular contrast agent available on the market was Levovist® from Shering (Berlin). It is interesting to notice that the majority of the articles dedicated to CEUS accuracy were published in the international literature by German authors.

Today, in Europe, for five years Levovist has been replaced by a second-generation contrast agent, SonoVue®, produced by Bracco (Milan) and, similarly, from the beginning, most of the experienced authors are Italian.

In 2007, Sonovue® from Bracco is approved in Europe, Asia and Canada. In the United States, the Food and Drug Administration has not yet approved microbubbles for non-cardiac use.

In Belgium, Sonovue® is approved by the National Drug Commission and reimbursed, under certain restrictive conditions, by the National Health Insurance.

Contrast agents properties

Microbubbles are true blood pool agents presenting a pure intravascular distribution without passage through the vascular endothelium into the interstitium. 10 to 15 min after injection, the microbubble gas content is exhaled via the lungs, while the components of the shell are metabolised or filtered by the kidney and eliminated by the liver (5).

Safety of contrast agents is high: no serious adverse effects have been mentioned over the last 10 years (> 2 millions injections in Europe).

Rare mild allergic types of reactions were occasionally described.

There is no nephro- or cardiotoxicity (6).

Consequently, contrast agents may be used in case of iodine allergy or renal insufficiency.

The only restriction concerns patients with unstable ischaemic heart disease where CEUS is not indicated. CEUS is not recommended in case of pregnancy and in children.

CEUS: principles of signal acquisition (5, 6)

The increase in backscattered ultrasound signal up to 20 dB of the blood was exploited, at the beginning, to improve Doppler studies, so-called “Doppler rescue”.

However, the response of microbubbles to an ultrasound beam is more complex because gases are compressible when exposed to an ultrasound pulse: gases vibrate at a particular frequency, their resonance frequency.

When insonated by fundamental frequency (2.5-3 MHz), microbub-
Monitoring of local ablative treatment

Today, for the monitoring of liver tumor radio-frequency ablation, several authors are proposing CEUS, either during the procedure or after the procedure (37-39).

And during the procedure, CEUS improves tumor delineation and facilitates targeting and positioning of the needle (40).

After the procedure, CEUS seems to be particularly efficient for the immediate assessment of treatment and is also useful for the delayed assessment of local recurrence.

Other potential clinical applications of CEUS concern the spleen: characterization of focal lesions, detection of perfusion troubles, diagnosis of traumatic lesions especially in emergency department, detection of septic or vascular complications (intensive unit) (41).

The pancreas has been also explored by CEUS: in case of focal pancreatitis or chronic pancreatitis mass, by showing an inflammatory parenchymography, CEUS can make the differential diagnosis versus neoplastic lesion (absence of signal) (42).

In severe acute pancreatitis, CEUS is interesting for the assessment of necrosis (43).

In case of neoplasm, CEUS can assess the arterial and late perfusion pattern and make a locoregional and hepatic staging (during the same procedure).

Other potential fields of interest of CEUS concern intraoperative assessment of hepatic additional metastasis, evaluation of bowel perfusion (intensive care, Crohn disease), evaluation after abdominal solid organ injuries (blunt trauma) (44). CEUS is particularly recommended in patients with an impaired renal function and patients in the intensive care difficult to move to the CT suite.

Other intra-abdominal organs have been explored successfully by CEUS like kidney, uterus, ovaries, and prostate.

Feasibility of CEUS

Drawbacks

The main criticism we can make about CEUS is its operator and technical dependence: it is a manual modality requiring expertise for CEUS.

This is the reason why EFSUMB in 2004 and the American Institute of Ultrasound in Medicine in 2007 have published recommendations for the use of CEUS insisting on the importance of examination procedures, equipment criteria, safety and training (45).

Sensitivity and NPV of CEUS / CT or MRI for the detection of liver metastasis is also a negative argument for CEUS, but this problem is still under discussion.

CEUS remains a semi-aggressive modality, compared to US alone.

Experience with CEUS in clinical practice is still limited and more investigations are needed to improve the general CEUS accuracy.

Finally, a big drawback, in Belgium, is the restrictive reimbursing by INAMI-RIZIV of Sonovue® for limited indications.

Advantages

Real time imaging is the main advantage of CEUS: the high temporal resolution is particularly useful in case of rapidly changing enhancement and the vascular distribution of the contrast without "equilibrium" phase gives an "angiography-like" video sequence. Thanks a good spatial resolution, CEUS is able to depict dysmorphic intratumoral arteries.

The second advantage is the specificity of US contrast agents as true blood pool agent, giving a high concordance with CT and MR images for arterial phase.

Another big quality of US contrast agents is its safety, compared to CT or MR agents.

The direct accessibility to the CEUS modality could be a useful advantage, but it depends on the US unit organization and requires technical and personnel adaptations.

Psychological impact of CEUS on patient management is significant, by giving the opportunity to the radiologist to answer directly the question of the nature of a liver mass, especially in young patient.

Finally, economical impact of CEUS has to be mentioned.

In Belgium, for example, the total cost for one abdominal examination (contrast included) is 138,04 Euro for CEUS, 221,70 Euro for angioCT, and 214,07 Euro for angioMRI.

Leen summarized perfectly the feasibility of CEUS in 2004: accurate diagnosis, safety, speed, comfort, convenience, and cost-effectiveness (46).

Future of CEUS

Beside the clinical applications described before, two interesting new modalities using CEUS are already available or under research: functional imaging, using enhancement curves, for the follow-up of antiangiogenic treatment and molecular imaging using targeted microbubbles to specific antigens in case of neangiogenesis, tumor or thrombi (47, 48).

Volumetric sonography including CEUS is another new field of interest.

Conclusion

CEUS is a new imaging modality coming to maturity, offering new perspectives in the management of abdominal disease, particularly liver tumors.

Thanks to its high accuracy, it is expected to replace many computed tomography and magnetic resonance imaging examinations in the near future.

The broad potential range of applications of CEUS offers to radiologists an exciting and promising opportunity to promote contrast ultrasonography in their clinical practice.

References