
REVIEW ARTICLE

Contrast-enhanced Sonography for Liver Tumours

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ABSTRACT

Detection and characterisation of focal hepatic lesions are important for accurate treatment planning. Although ultrasound is considered a powerful technique for identifying focal liver lesions, its capability for lesion characterisation is suboptimal. Recently, new ultrasound contrast agents have been developed, and their clinical utility is under investigation with a variety of new ultrasound equipment, and results of recent studies are very promising. In this article, several new techniques of grey scale contrast-enhanced imaging such as pulse or phase inversion, coded harmonic imaging, and agent detection imaging are discussed. These contrast-specific grey scale ultrasound imaging techniques are extremely sensitive to the presence of micro-bubble agents and can evaluate microvasculature and the enhancement patterns of hepatic tumours.

Key Words: Contrast agent, Hepatic tumours, Ultrasound

INTRODUCTION

Detection and characterisation of focal hepatic lesions are of equal importance for accurate treatment planning. Although ultrasound (US) is considered a powerful technique for identifying focal liver lesions, its capability for lesion characterisation is suboptimal. Characterisation of hepatic lesions has been based on the grey scale morphologic features and on vascular information from Doppler.¹ With hepatic tumours, knowledge of the vascularity of a hepatic mass is very important for differential diagnosis of the focal liver lesions. For characterisation of liver lesions, the microvascular information is expected to add significant contributions to the diagnostic utility of the US examination. However, fundamental colour Doppler (CD) and power Doppler (PD) US are not always satisfactory for evaluating tumour vascularity compared with dynamic computed tomography (CT) or magnetic resonance imaging (MRI).^{1,2} In previous studies, contrast-enhanced US examinations using various techniques, including CD or PD US and the harmonic Doppler mode, efficiently depicted tumour vascularity.¹⁻¹⁰

At present, a number of manufacturers have produced forms of stabilised microbubbles for use as intravenous

US contrast. Levovist (Schering AG, Berlin, Germany), which has gained regulatory approval in Asia and Europe and is the most widely available agent, is a suspension of galactose microparticles in sterile water. When injected intravenously, the microbubbles (mean diameter, 2 to 3 mm) produce systemic enhancement of Doppler signal for 1 to 5 minutes. In addition to this vascular phase, levovist has a late hepatosplenic parenchymal phase after blood pool clearance.¹

Microbubbles interact with a US beam in a variety of complex ways. At lower acoustic powers, they reflect US echoes. As the acoustic power increases, more complex interactions occur as the bubbles resonate and produce harmonic signals. If the peak pressure of the US beam is sufficiently high, the bubble shell will be disrupted. The effect from sudden loss of correlation due to sudden disappearance of a reflector (i.e., micro-bubble) has been referred to as stimulated acoustic emission.¹ The disruption of the bubbles creates a transient but very strong echo. A disadvantage of this is that there is less contrast left for further imaging. Another limitation of levovist is the short duration of effective contrast enhancement. Multiple injections or continuous slow infusion of contrast agent may prolong the enhancement duration.²

Recently, new US contrast agents with stability, so-called second-generation agents, have been developed, and

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their clinical utility is under investigation with a variety of new US equipment.

In this article, several new techniques of grey scale contrast-enhanced imaging such as pulse or phase inversion, coded harmonic imaging, and agent detection imaging will be discussed. These contrast-specific grey scale US imaging techniques are extremely sensitive to the presence of microbubble agents and can evaluate microvasculature and the enhancement patterns of hepatic tumours without a blooming artifact.

Techniques of Contrast-enhanced Ultrasound *Contrast-enhanced Harmonic Power Doppler Ultrasound*

We recently performed a prospective study to compare contrast-enhanced harmonic PD US with conventional PD US in the assessment of tumour vascularity in hepatocellular carcinoma (HCC).³ In the majority of patients, the intensity of enhanced signals in the tumour and hepatic parenchyma on conventional mode was stronger than that of harmonic mode. However, harmonic mode was superior to conventional mode in terms of PD artifacts at any imaging time. Furthermore, in harmonic PD mode, continuous scanning during the patient's quiet breathing was possible without producing considerable motion-related artifacts.

As described earlier,^{2,4} blooming artifact that is the overestimation of the size of contrast-enhanced vessel is evident on conventional PD US. This can be an important problem when we want to know whether any residual viable tumour is present after local treatment for a malignant tumour such as transcatheter arterial chemoembolisation (TACE) or percutaneous ethanol injection (PEI) therapy. In that case, we think that harmonic PD US might be superior to conventional power Doppler US. However, this technique cannot also eliminate blooming artifact completely. Therefore, grey scale contrast-enhanced US techniques were developed.

Pulse Inversion Harmonic Ultrasound

We recently performed contrast-enhanced pulse inversion harmonic US in 20 patients with haemangiomas, 33 with metastases, and 8 with HCC.⁵ The peripheral globular or rim-like enhancement with centripetal fill-in in haemangiomas was striking on the interval delay scanning using pulse inversion harmonic US with a microbubble contrast agent. We therefore believe that the pattern of enhancement on pulse inversion harmonic

US has high sensitivity and specificity for the diagnosis of haemangioma.

In metastases, we found that the varied nature of the primary tumour results in different enhancement characteristics in metastatic tumours. The most common metastatic tumours from gastrointestinal adenocarcinomas most frequently showed rim-like enhancement. HCCs showed homogeneous or heterogeneous enhancement with or without irregular intratumoural enhanced vessels, which was similar to findings on hepatic angiography.

Compared with CT or MRI, there are a few limitations of the US technique used in this study. The first is that dynamic US scanning is possible in only 1 scanning plane. It is therefore not possible to characterise all lesions simultaneously in patients with multiple lesions. Secondly, interval delay scanning in the same area is not easy for unskilled examiners. On the other hand, US is superior to CT or MRI in that immediate, accurate characterisation of a newly detected focal hepatic lesion on US examination can be possible.

Delayed pulse inversion harmonic US obtained approximately 5 minutes after injection of microbubble contrast agent can be used to detect focal liver lesions. Recent studies showed that this technique provided better lesion detection and improved conspicuity and lesion-to-liver contrast of lesions that were seen on unenhanced imaging.^{6,7} Metastatic disease in the liver was seen as a hypochoic area surrounded by the normal liver parenchyma with intense stimulated acoustic emission-related enhancement.

Real-time Harmonic B-Flow (Coded Harmonic Angiography)

This new US technique, coded harmonic angiography (CHA), combines benefits of coded harmonic technology and non-contrast grey scale blood flow (B-flow) image developed by General Electric company (Milwaukee, USA). Coded harmonic technology is able to precisely suppress the unwanted fundamental return signal by transmitting sequence, isolating the coded fundamental return signal, and suppressing this signal. This leaves only the harmonic return signal.⁸

B-flow is a new technique developed to image blood flow. B-flow directly images blood reflectors, providing a real time picture of flow in a display that resembles an angiogram. CHA uses codes to suppress the

fundamental signal, and uses decoding techniques optimised for contrast agents to suppress tissue signal, thus improving sensitivity and uniquely optimising for contrast signal visualisation in dynamic flow states. Therefore, CHA with US contrast agent visualises superb arterial architecture like a digital subtraction angiography.⁹

In our experience, CHA showed excellent dynamic enhancement of tumour vascularity of liver tumours and was useful in characterisation of liver tumours.⁸⁻¹⁰ CHA was approximately equal to MRI scanning in its ability to show peripheral nodular enhancement with centripetal progression, even in small haemangiomas.⁸ In some HCCs, CHA showed blood flow from supplying arterial branches into draining hepatic veins before injection of contrast material. Contrast markedly enhanced these blood flow signals, with peak enhancement 35 to 45 seconds later similar to the enhancement

noted on early phase CT or angiography. Based on our experience, we believe CHA has good sensitivity to weak flow in small vessels, perhaps better than pulse inversion harmonic imaging. Limitations of CHA include inferior imaging resolution due to severe suppression in background grey scale signal, lower frame rate, and significant microbubble destruction. Therefore, we used intermittent scanning and lower mechanical index (output power) to reduce bubble destruction.⁹

Agent Detection Imaging

Agent detection imaging (ADI) is a new microbubble-specific mode that is designed for optimal detection of stimulated acoustic emission from fragile agents such as SH U 508A, and is characterised by its high mechanical index that provides extreme sensitivity to the presence of microbubbles.^{1,10-12} While the pulse inversion harmonic US used 2 identical pulses with reverse polarity, ADI uses coherent pulse formation with precision pulse

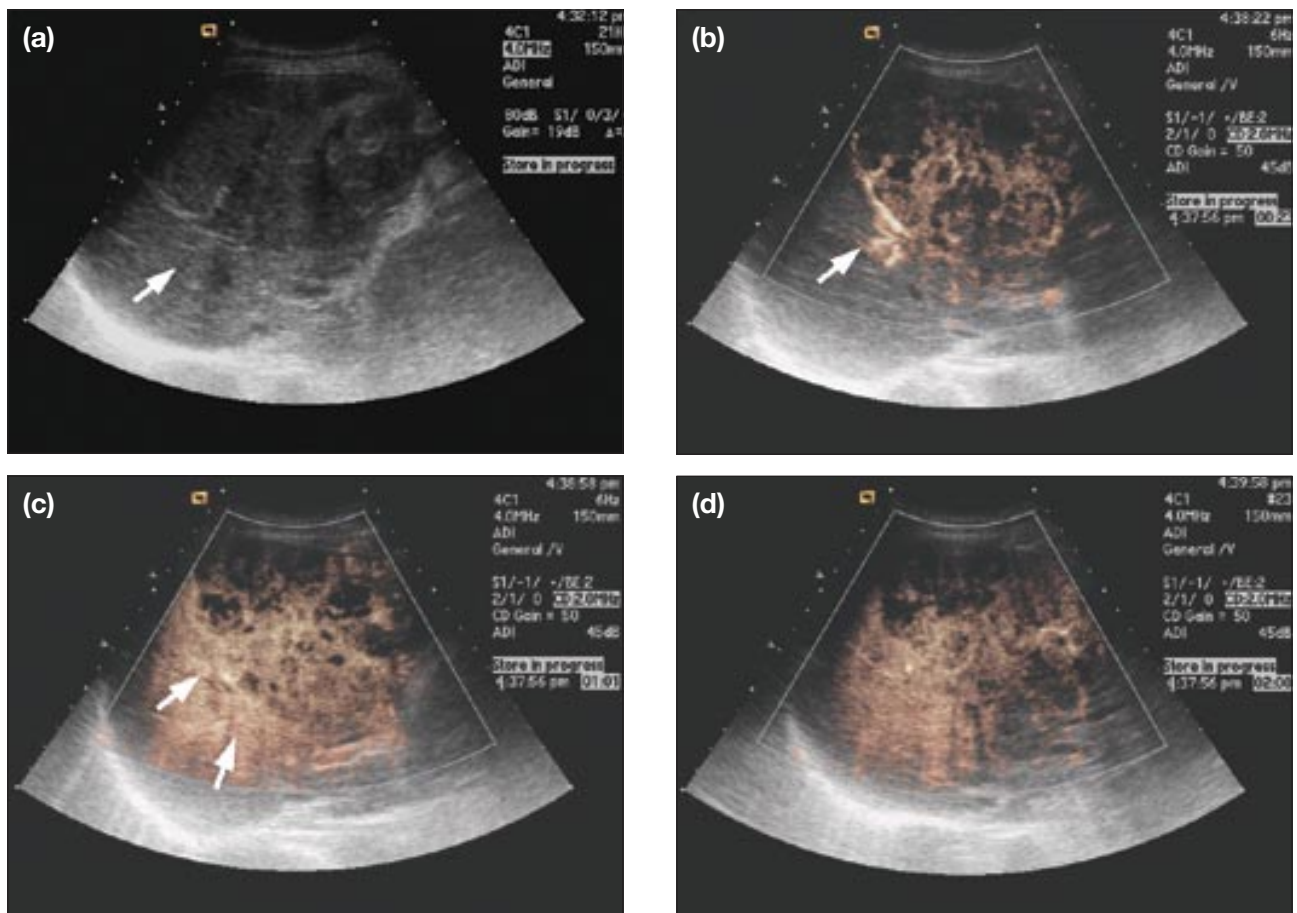


Figure 1. Hepatocellular carcinoma in a 68-year-old man. (a) Grey scale image shows a slightly heterogeneous hypoechoic mass (arrow) in the right lobe of the liver. (b) After administration of levovist, in the vascular phase (23 seconds), the mass is enhanced strongly and heterogeneously. The enhanced feeding vessels (arrow) were also observed well. (c) At 60 seconds after the contrast injection, the surrounding liver parenchyma is homogeneously enhanced. However, the agent in the mass was washed out and the lesion depicted hypoechoic enhancement and subtle capsular enhancement is shown along the periphery of the mass (arrows). (d) At 120 seconds after the contrast injection, the mass is showing less enhancement than the liver parenchyma.

shaping and a single pulse cancellation technique, thus having the advantage of maintaining normal frame rates. On the other hand, because ADI uses conventional colour Doppler display, it can isolate and separate the colour component of the image (representing the micro-bubble) from the grey scale image (representing the tissue). This allows the bubble signature to be toggled on and off so that it can be compared with the exact registered grey scale images to locate the distribution of the SH U 508A very precisely. Also, the enhancement values of a tumour and tumour-to-liver contrast ratio (T/L)

can be calculated from the histogram analysis within region-of-interest at the colour component of the image.

Our preliminary results showed that single level dynamic (SLD) US using ADI was potentially useful in diagnosing HCC with excellent demonstration of intra- and peritumoural vascularity, early tumour staining and, sometimes, delayed capsular enhancement (Figure 1).¹⁰

In our recent study, SLD US scanning would cover the optimal time windows and duration for demonstrating

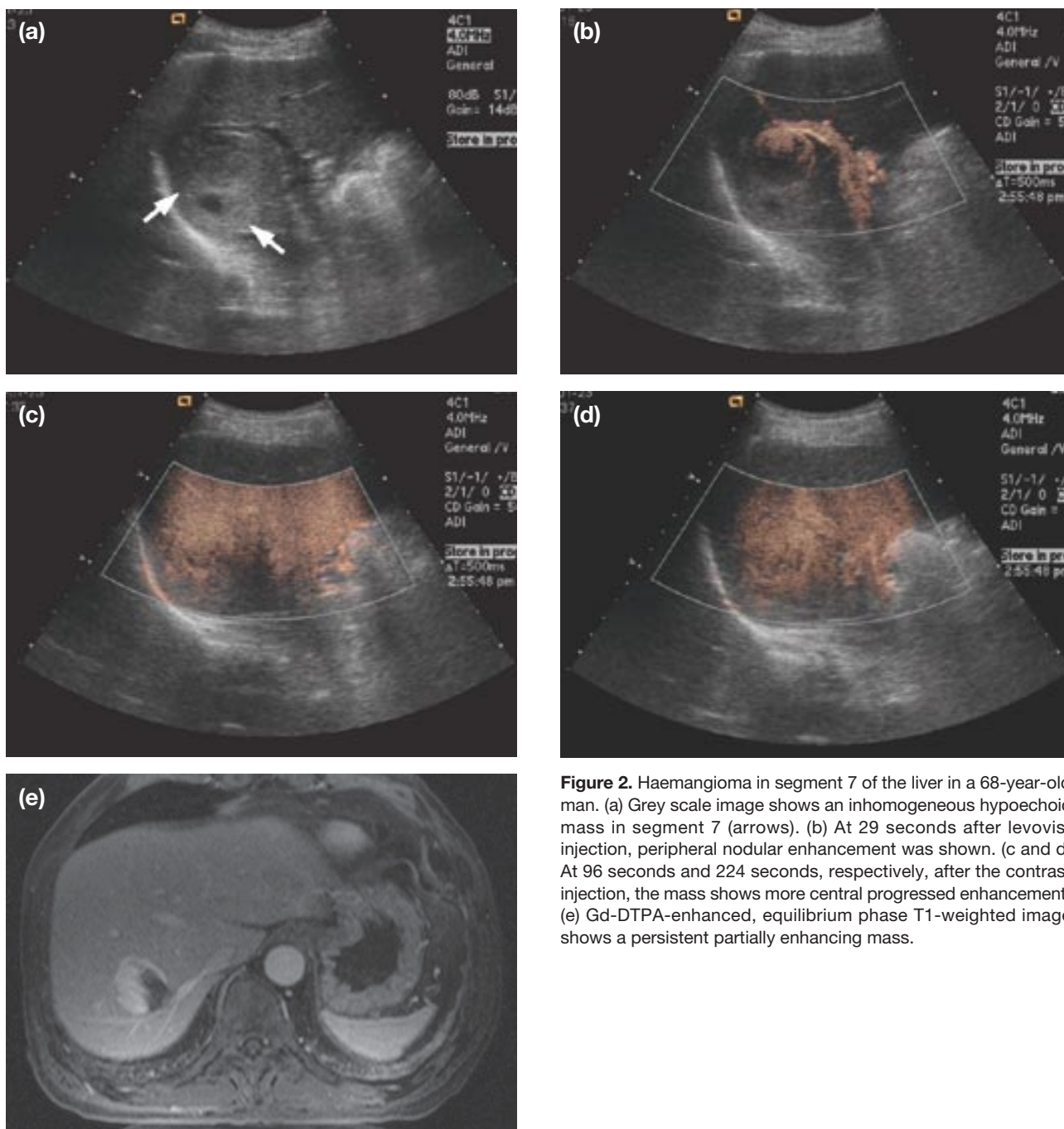


Figure 2. Haemangioma in segment 7 of the liver in a 68-year-old man. (a) Grey scale image shows an inhomogeneous hypoechoic mass in segment 7 (arrows). (b) At 29 seconds after levovist injection, peripheral nodular enhancement was shown. (c and d) At 96 seconds and 224 seconds, respectively, after the contrast injection, the mass shows more central progressed enhancement. (e) Gd-DTPA-enhanced, equilibrium phase T1-weighted image shows a persistent partially enhancing mass.

HCC.¹² Therefore, maximal conspicuity of each HCC could be increased despite the individual variation of the circulation time and the tumour's relative vascularity. With individual optimisation of the scan delay time, SLD US is useful for depicting the hypervascularity of HCC during the arterial phase.¹²

A recent study also showed that levovist-enhanced ADI revealed distinctive enhancement characteristics in focal liver lesions that would contribute positively to

the characterisation of these hepatic lesions (Figure 2).¹ Minimally invasive interventional techniques such as TACE, radiofrequency (RF) ablation, and PEI have been used increasingly with favourable results for the treatment of malignant hepatic masses. However, high recurrence rates have been reported after therapy, and they are considered limitations of these minimally invasive treatments compared with surgical tumour resection. Therefore, to attain better survival for patients who have recurrent or residual tumours after undergoing such

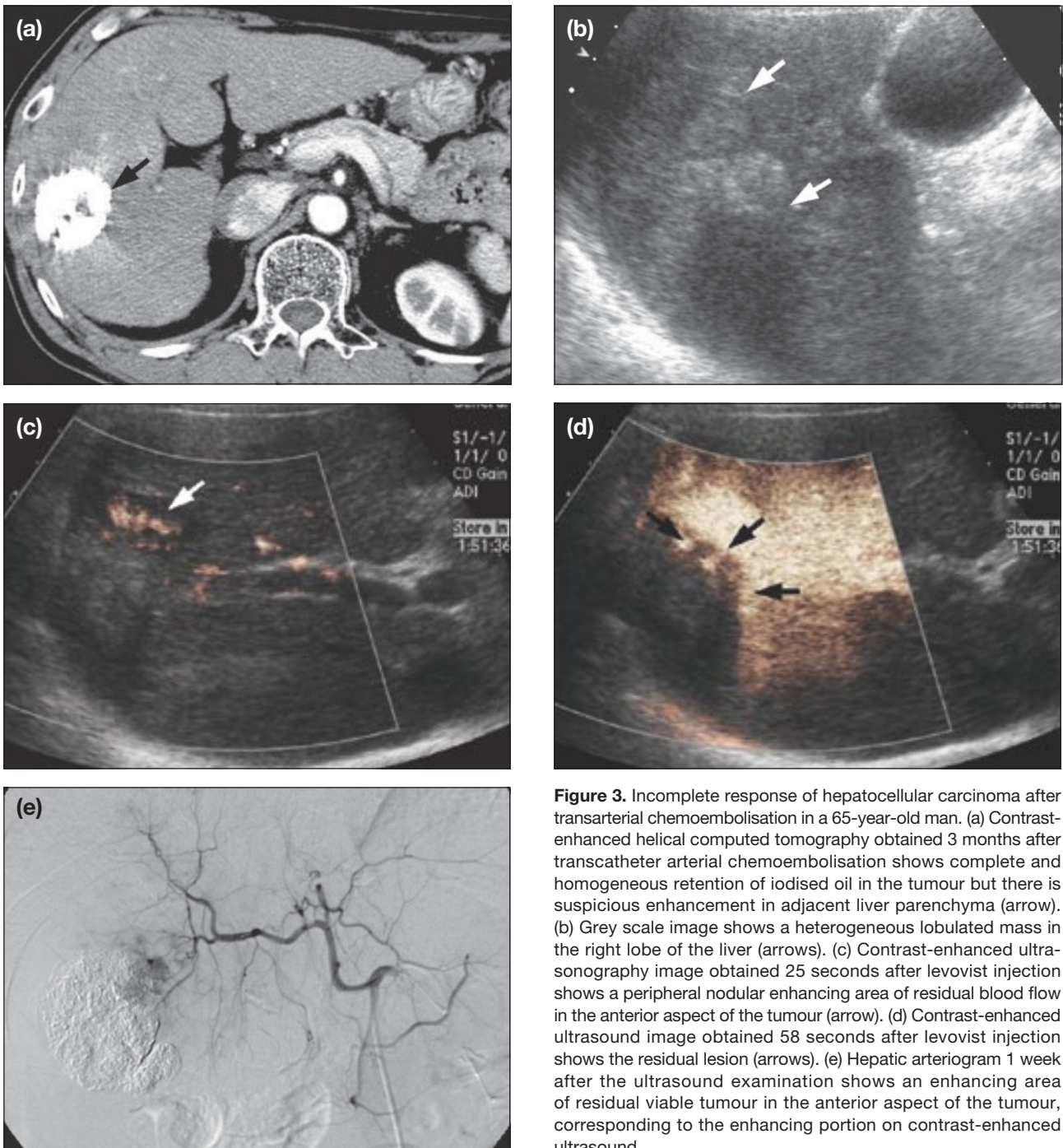


Figure 3. Incomplete response of hepatocellular carcinoma after transarterial chemoembolisation in a 65-year-old man. (a) Contrast-enhanced helical computed tomography obtained 3 months after transcatheter arterial chemoembolisation shows complete and homogeneous retention of iodised oil in the tumour but there is suspicious enhancement in adjacent liver parenchyma (arrow). (b) Grey scale image shows a heterogeneous lobulated mass in the right lobe of the liver (arrows). (c) Contrast-enhanced ultrasonography image obtained 25 seconds after levovist injection shows a peripheral nodular enhancing area of residual blood flow in the anterior aspect of the tumour (arrow). (d) Contrast-enhanced ultrasound image obtained 58 seconds after levovist injection shows the residual lesion (arrows). (e) Hepatic arteriogram 1 week after the ultrasound examination shows an enhancing area of residual viable tumour in the anterior aspect of the tumour, corresponding to the enhancing portion on contrast-enhanced ultrasound.

interventional procedures, it is necessary to detect residual tumours or recurrences at an early stage when conditions for additional treatment with PEI, RF ablation, or TACE are favourable. For that purpose, various imaging modalities, including CT, MRI, angiography, Doppler US, and biopsy, have been used to evaluate treatment response. CD or PD US have been reported to be less sensitive for revealing residual areas or recurrence of hepatic tumours after ablation. Nevertheless, detection of residual or recurring regions of hepatic tumours by US is extremely important because additional local therapy is usually performed with US guidance.¹³

ADI (at a high mechanical index) could detect the existence of a contrast agent in the vascular bed of a residual or recurring lesion by showing prominent enhancement in a completely devascularised lesion. In a recent study, contrast-enhanced ADI enabled radiologists to evaluate the therapeutic effects of interventional therapeutic procedures confidently compared with helical CT in malignant hepatic masses.¹³ Moreover, the information provided by the segmented display produced by this technique may be used to successfully target additional percutaneous US-guided treatment in patients with lesions showing incomplete tumour responses after the first treatment (Figure 3).

CONCLUSION

US findings for levovist-enhanced images of liver tumours with the use of several currently available imaging techniques and different manufacturers' equipment have been presented. These include CD and PD US, harmonic PD US, pulse inversion harmonic US, CHA, and ADI. Each of these has its advantages and drawbacks, and each may work differently with different contrast agents.

In our experience, pulse inversion harmonic US has definite advantages when compared with PD US, including the absence of Doppler artifacts, the ability to examine lesions near the heart, and enhanced evaluation of patients who cannot hold their breath. Recently introduced CHA and ADI are better than pulse inversion harmonic US. CHA is highly sensitive to weak signals from small vessels and has no artifact. Therefore,

this technique is excellent for detailed evaluation of fine vasculature of liver tumours. ADI is a disruptive bubble imaging with high mechanical index. Therefore, ADI is very good for vascular volume assessment and evaluation of tumour stain and haemodynamics, including wash-in, wash-out pattern. Further investigations will help identify potential roles of these new sonographic techniques and the usefulness of different contrast agents.

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