

Modern Liver Imaging Techniques A New Era in Liver Ultrasound

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Introduction

HCC Epidemiology

Hepatocellular Carcinoma (HCC) is the sixth most common cancer worldwide and the second leading cause of cancer deaths globally ^[1]. In the United States, HCC is the fastest growing cause of cancer mortality, growing by 2.7 percent per year from 2003 to 2012. At this rate, there will be an estimated 78,000 new cases in the United States in 2020 ^[2]. Worldwide, the major risk factors for HCC are Hepatitis B (54 percent) and HCV (31 percent), which is the number one cause in the United States ^[3]. Cirrhosis of any etiology is associated with HCC, and Nonalcoholic Steatohepatitis (NASH) continues to increase with the high prevalence of obesity and metabolic syndromes in the United States ^[4]. Reducing mortality, by diagnosing HCC while the disease is still amenable to medical or surgical treatment, requires effective surveillance tools.

Surveillance Recommendation

Ultrasound is a non-invasive imaging modality widely used to evaluate liver disease. The American Association for the Study of Liver Diseases (AASLD) published practice guidelines on the management of HCC and recommended at-risk groups such as patients with cirrhosis of any etiology or specific hepatitis B carriers to be entered into a surveillance program. Ultrasound is the preferred surveillance tool based on a large randomized controlled trial and the recommended surveillance interval is six months based on doubling time of HCC ^[5].

Semiannual US surveillance recommendation is also supported by cost effective analysis. It is the only cost-effective modality for HCC surveillance ^[6].

Importance of Image Quality

One of the main challenges for ultrasound in HCC surveillance is the variability in sensitivity. The pooled sensitivity of ultrasound to detect early HCC with a size smaller than 5 centimeters was reported to be 63 percent, with a range from 23 percent to 91 percent ^[7]. Ultrasound is operator dependent, equipment and its software can affect image quality, and patient body habitus is also an important factor for the quality. The increased high BMI trend in patients in the United States is a concern. We conducted a retrospective study reviewing 297 ultrasound examinations performed for HCC surveillance, evaluated the image quality and investigated its

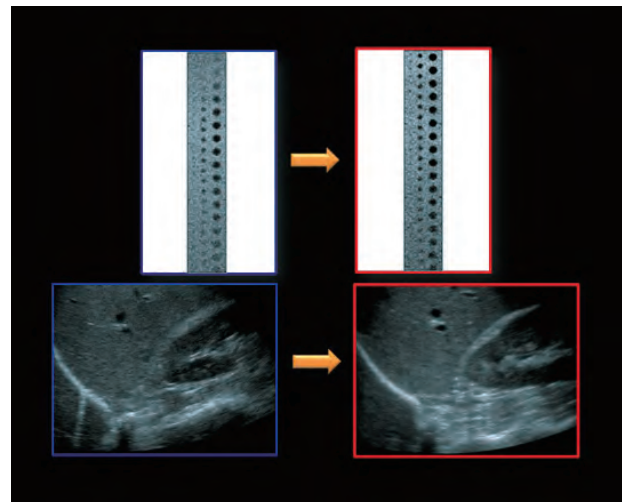


Figure 1. iBeam forming technology generates clinical images with higher resolution and more homogeneity.*

**Compared to DMS transducers*

affecting factors. We found nearly half of the ultrasound examinations (49.3 percent) were of inadequate quality, and multivariate analysis showed BMI to be the largest affecting factor. A one-unit increase in BMI leads to a 30.8 percent increase in the odds of having an inadequate image ratings (Kono Y. et al. unpublished data).

Canon Medical's Aplio™ i-series systems is designed to deliver outstanding clinical performance with enhanced resolution and penetration to improve clinical precision, diagnostic performance and productivity. With the implementation of advanced architecture, iBeam forming technology and Intelligent Dynamic

Micro-Slice technology (iDMS) allows the formation of a shaped, uniform and thin-slice beam that offers clinical images with higher resolution and more homogeneity.* The latest technology offers improvement in contrast resolution, temporal resolution and spatial resolution in all three aspects: axial, lateral and elevation.

Aplio i-series is equipped with a newly developed iDMS ultra-wideband convex transducer, PVT-475BX. The two-in-one ultra-wideband transducer is designed to cover the frequency range normally covered by two transducers, in order to provide both high resolution and penetration.



Figure 2. Intelligent Dynamic Micro-Slice (iDMS) technology provides high-flexibility electronic focusing in the lens direction and improves the elevation resolution.

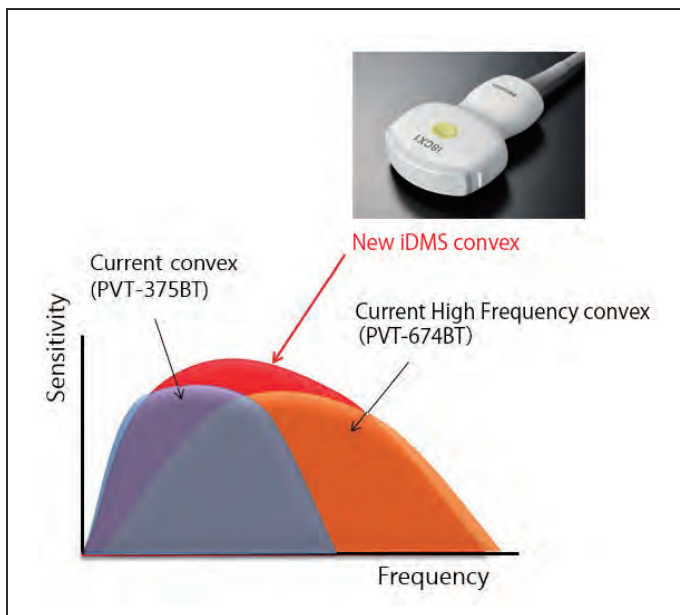
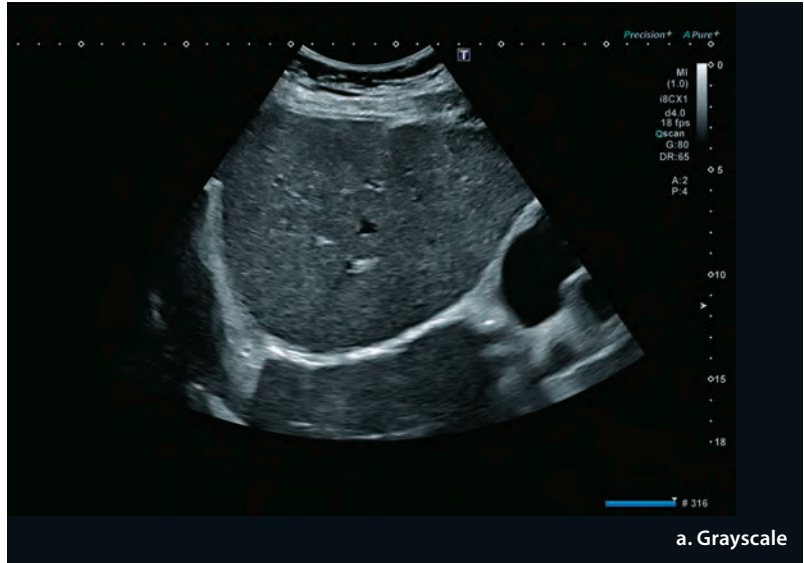


Figure 3. Ultra-wideband iDMS convex transducers

Case Studies

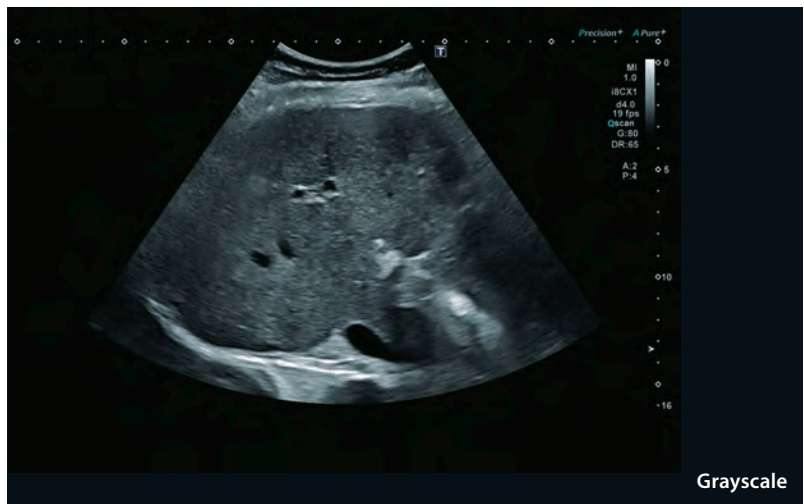
Case 1: Obese patient without known liver disease (BMI 30)

Aplio i-series provides grayscale images with higher resolution, contrast and penetration. With iDMS technology that generates thin-slice beams, homogeneous images throughout the depth can be provided. The increased sensitivity of Doppler images can be demonstrated through Superb Micro-vascular Imaging (SMI). SMI delineates low-velocity minute flows and the detailed vascularity can be visualized.



Case 2: Technically difficult patient with morbid obesity (BMI = 40)

The improvement in penetration and image homogeneity ensures high-resolution in the technically difficult patient. The back of the liver and texture of the liver parenchymal can be clearly visualized.



**Compared to Aplio 500 Platinum*

Figure 5.

Categorization of Focal Liver Lesions using Contrast Enhanced Ultrasound

Contrast Enhanced Ultrasound (CEUS) is capable of providing real time, high-resolution perfusion information and is one of the advanced technologies for differentiation of focal liver lesions. The contrast agents are microbubbles of a few micrometers in diameter and stable enough to circulate in the body with intravenous injection. Modern ultrasound technology with contrast specific imaging is very sensitive to detect circulating microbubbles, and can visualize dynamic contrast enhancement in a real-time manner. The contrast medium Lumason (also known as SonoVue), was recently approved for characterization of focal liver lesions in adult and pediatric patients in the United States.

CEUS LI-RADS®

The American College of Radiology (ACR) endorsed LI-RADS® (Liver Imaging Reporting and Data System) for standardized reporting and data collection of computed tomography (CT) and magnetic resonance (MR) imaging for HCC in 2011. With the recent approval in the United States of microbubble-based agents for US liver imaging, LI-RADS® was expanded to include CEUS in August 2016. The LI-RADS imaging criteria are used to classify liver observations on high-risk patients from definitely benign (LR-1) to definitely HCC (LR-5) based on imaging criteria^[8]. We expect a categorization algorithm with well-defined CEUS criteria would reduce imaging interpretation variability and errors, and improve communication with referring clinicians and facilitate quality assurance and research. Please note LI-RADS only applies to high-risk patients for HCC.

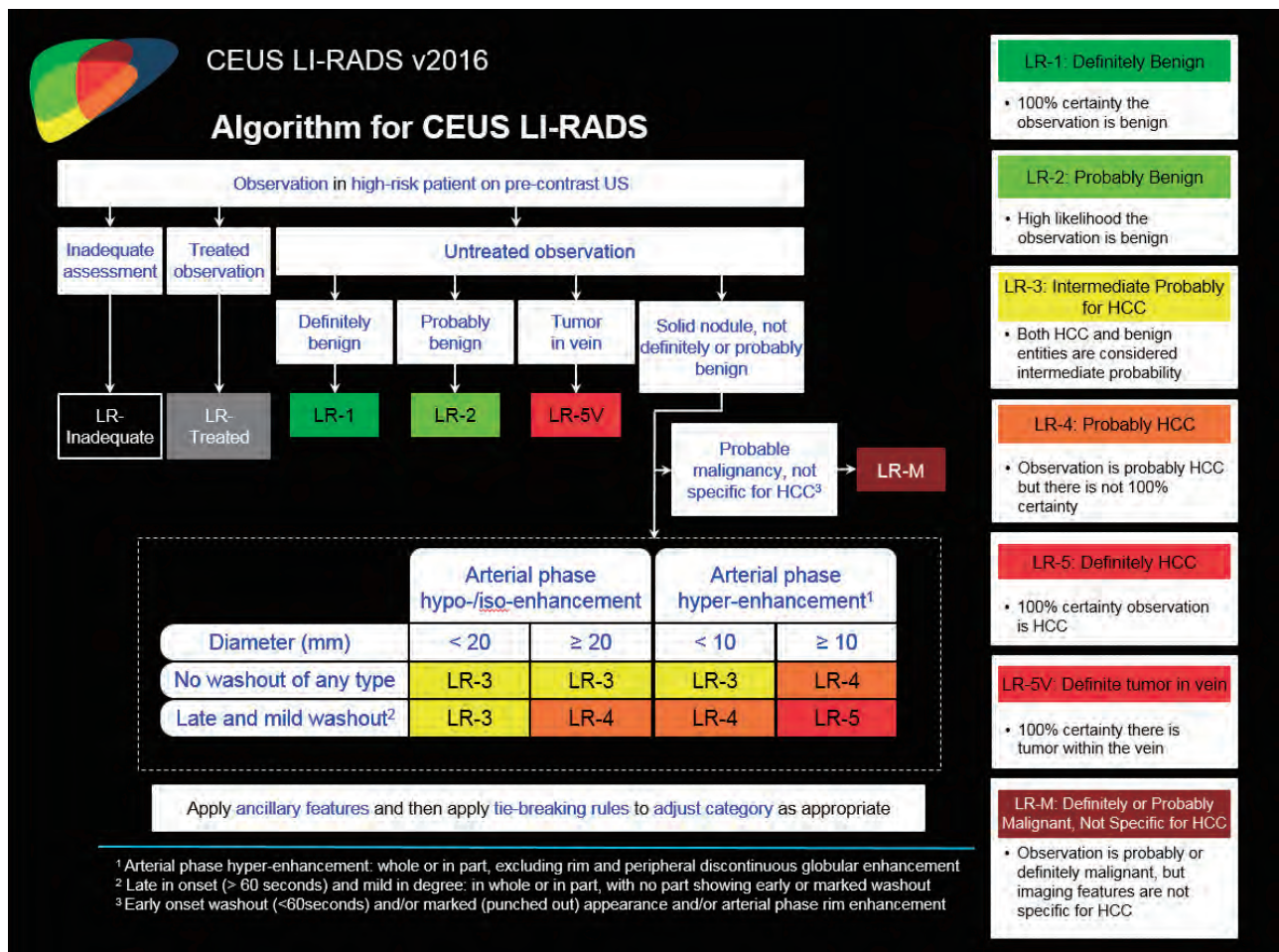


Figure 6. Algorithm and categorization of CEUS LI-RADS®

Case Studies

CEUS is a very powerful tool to observe perfusion pattern of focal liver lesions in real time during arterial phase, portal venous phase and delayed phase, which enables characterization.

Hemangioma

Hemangioma is one of the most common benign liver lesions. The grayscale image from a 50-year-old male shows a heterogeneous hypoechoic lesion in the left hepatic lobe, measuring 3.6 centimeters in diameter. In the grayscale image, the border and the internal structure of the lesion is clearly depicted. In Color Doppler Imaging (CDI), a dilated and distorted portal vein can be observed. Utilizing SMI, low-velocity minute vessels inside the lesion can be visualized at

high frame rates (47 fps) and the lesion demonstrated high vascularity. Focal liver lesions can be clearly seen on non-contrast ultrasound with good image quality. Vascularity can be evaluated to some extent. However, diagnosis cannot be made without the use of contrast agent. This is the same for CT or MRI, which also require multiphasic imaging with contrast injection.

The lesion showed a typical enhancement pattern for a hemangioma with an initial peripheral nodular enhancement and centripetal enhancement pattern in the arterial phase. The perfusion of the lesion can be seen clearly. The hemangioma continues to show complete hyper-enhancement in the portal venous phase, and iso-enhancement in the delayed phase. This is a typical pattern of a benign lesion without any type of washout in the portal venous phase or delayed phase.

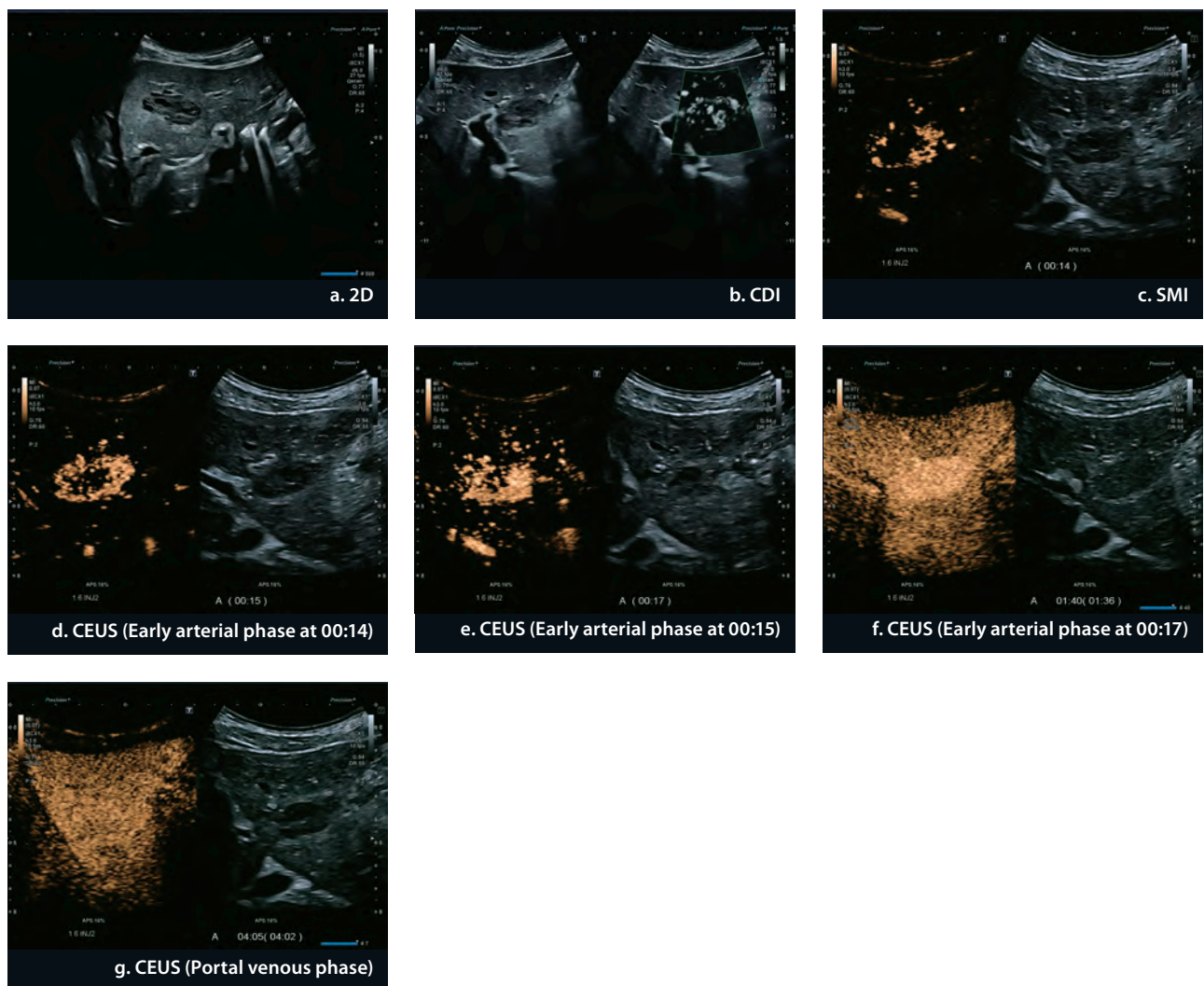


Figure 7.

Hepatic Adenoma

This case is a 25-year-old female with multiple hepatic adenomas. The largest lesion is 3.5 centimeters in diameter, located in segment six. Although the lesion locates deep at 10 centimeters and is nearly isoechoic to the parenchyma, the image quality in grayscale allows clear observation of the lesion. At a depth of 10 centimeters, the arterial phase hyper-enhancement and its vascular pattern, can be easily visualized with a peripheral, diffuse pattern towards the lesion center. It is

an important diagnostic point to distinguish a hepatic adenoma from a benign focal nodular hyperplasia (FNH) as FNH has similar imaging appearances but enhances from inside to outside. Iso-enhancement in both the portal venous and delayed phases demonstrate the lesion is benign. Lesions with iso-enhancement can be difficult to track during the late portal venous or delayed phases, however, the clear visualization of the lesion in the 2D image helps with confident tracking of the lesions.

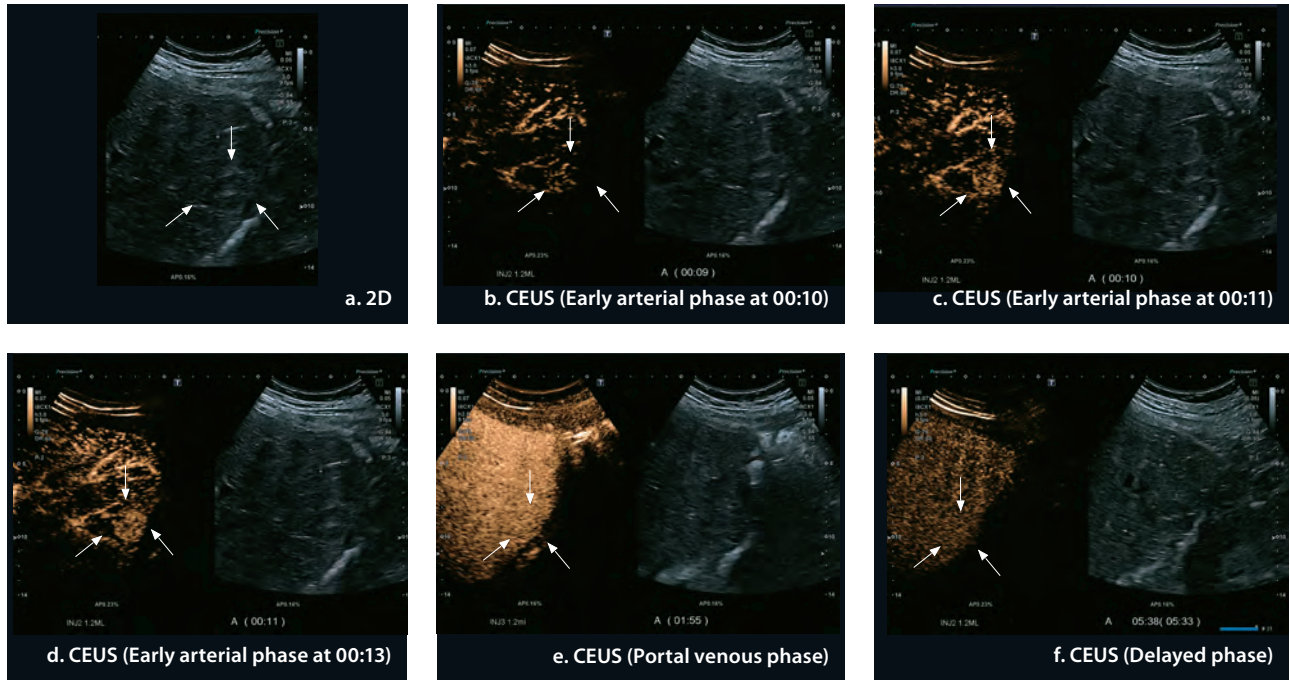


Figure 8.

LI-RADS 5 HCC

A 63-year-old female with alcoholic cirrhosis presented with a 3 centimeter liver lesion. The boundary of the isoechoic lesion and its hypoechoic halo can be clearly depicted on a grayscale image. Using color Doppler, intra-tumoral vascularity can be detected. Rich vascular structure can be delineated with SMI and distorted vessels can be shown, suggesting a malignant lesion. After contrast injection, in the arterial phase, the lesion shows homogeneous hyper-enhancement, associated with the

feeding vessels. No washout is seen at one minute and at two minutes. In the delayed phase at 3.5 minutes, mild washout can be observed. Washout slowly progresses and becomes clearer at five minutes. Late (greater than or equal to 60 seconds) and mild washout is one of the major features for LI-RADS 5, and is very important to differentiate from LI-RADS M which shows early (less than 60 seconds) and/or marked washout. As a result, the lesion is categorized as CEUS LI-RADS 5. The CEUS LI-RADS categorization corresponds to the LI-RADS on CT.

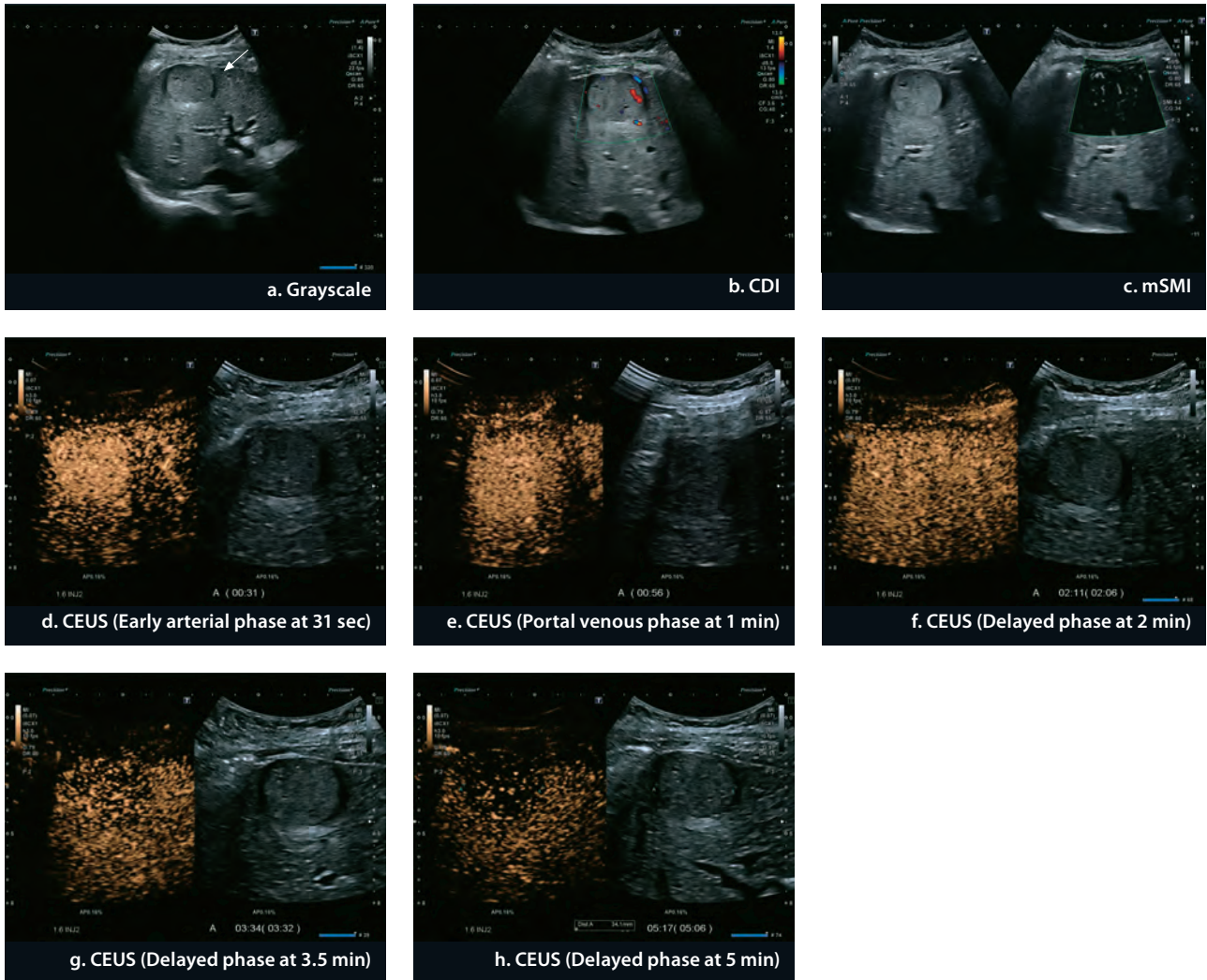


Figure 9.

HCC post treatment assessment

A follow-up exam was performed on a 79-year-old male with Hepatitis B cirrhosis complicated with HCC after trans-arterial chemoembolization (TACE) therapy. A new lesion was detected adjacent to the post-TACE lesion. On the grayscale image, the new lesion is clearly seen, but it is difficult to detect the HCC recurrence in the post-TACE lesion. Using the color-coded SMI (cSMI), rich vascularity can be seen inside the new lesion. CEUS was performed to evaluate the treatment outcome. By

using CEUS, both the new lesion and HCC recurrence in the post-TACE lesion can be investigated easily. The new lesion shows arterial phase hyperenhancement and no washout up to five minutes, therefore, it is a LI-RADS 4 lesion, probable HCC by LI-RADS criteria. Feeding vessels can be observed clearly in the early arterial phase. For the post-TACE treated lesion, the majority of the lesion does not enhance, however, the hyper-enhancing area was observed in the arterial phase at the upper side of the treated lesion, indicating the HCC recurrence.

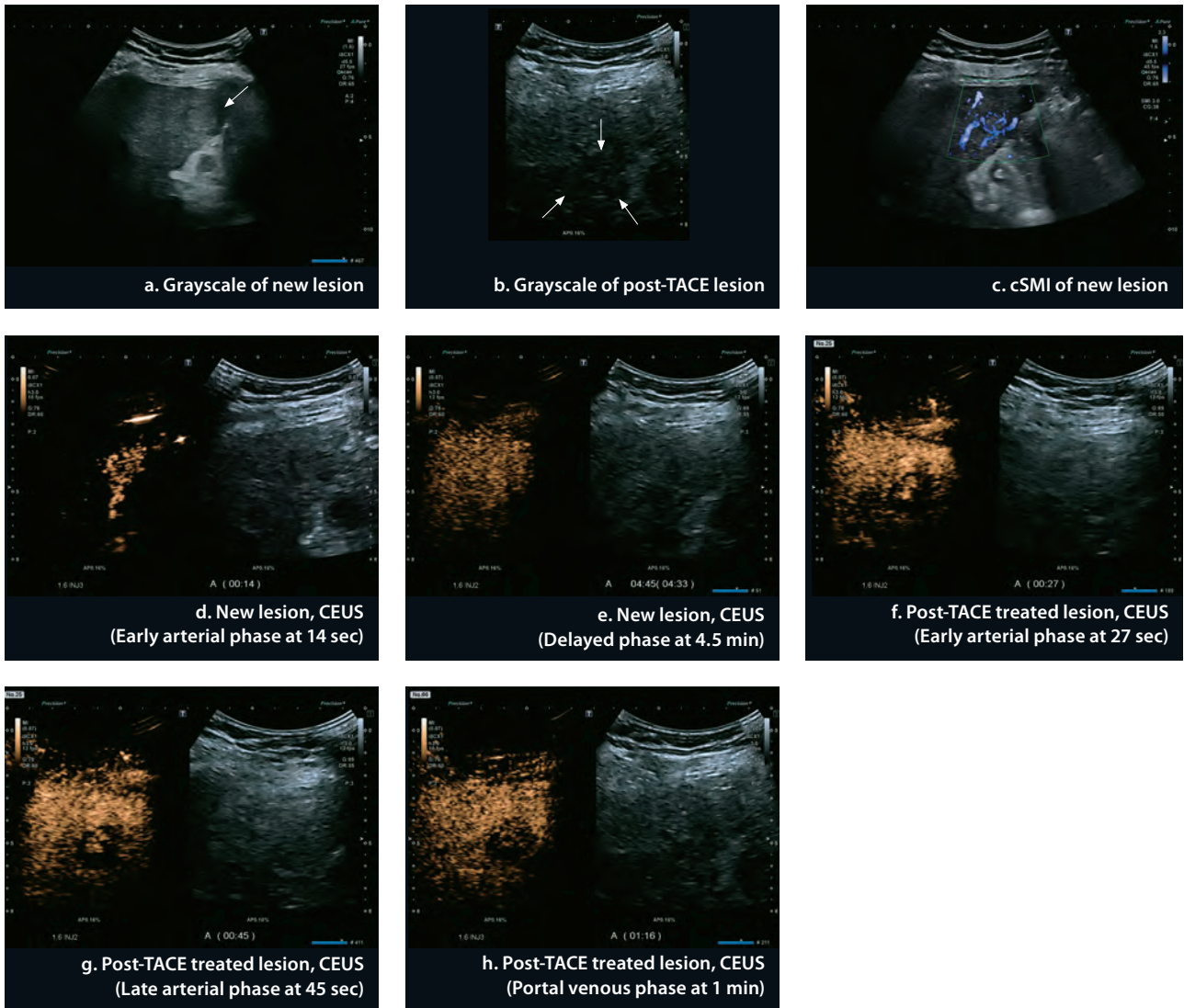


Figure 10.

LI-RADS 4 multiple HCCs

This is a case of a 60-year-old female with decompensated HCV cirrhosis with ascites. In the grayscale image two lesions, 21 millimeters and 10 millimeters respectively, are detected in segment five. Since Canon Medical shear wave is performed by push pulse, shear wave examination can be performed on patients with ascites. In the early arterial phase, homogeneous hyper-enhancement can be observed

in both lesions. The lesions are isoechoic in the portal venous and late phases, no washout was observed at six minutes post injection, therefore these lesions were categorized as LI-RADS 4, probable HCC. It is important to know LI-RADS 5 is an HCC with 100 percent certainty, and it does not require biopsy. Significant numbers of LI-RADS M (probably or definitely malignant, but not specific to HCC) and LI-RADS 4 (probable HCC) are actually HCC.

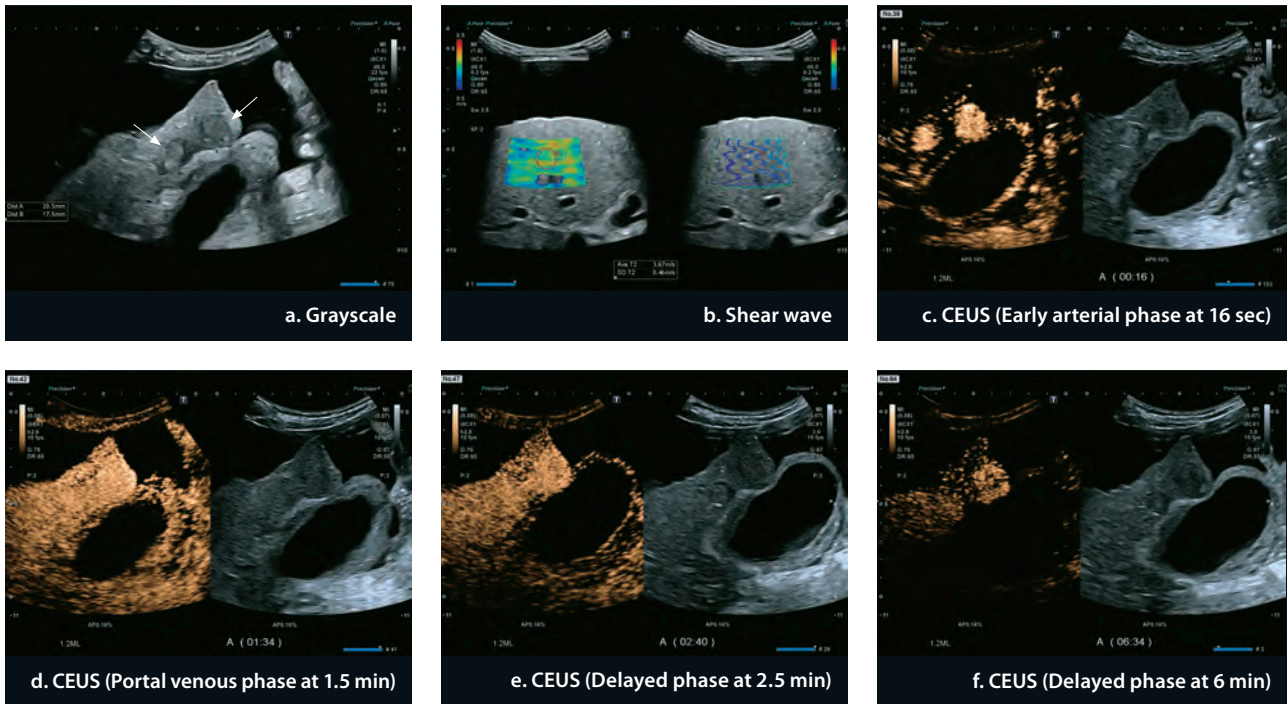


Figure 11.

LI-RADS 5 multiple HCCs

A 23 millimeter lesion was detected in the right hepatic lobe of a 70-year-old female with HCV cirrhosis. Detailed vascular structure and the feeding vessel are clearly depicted with CEUS in the early arterial phase and during portal venous phase, and the lesion is iso-enhancing. This lesion is a typical LI-RADS 5 lesion for its size, hyper-enhancement in the arterial phase and late and mild washout seen at three minutes post injection.

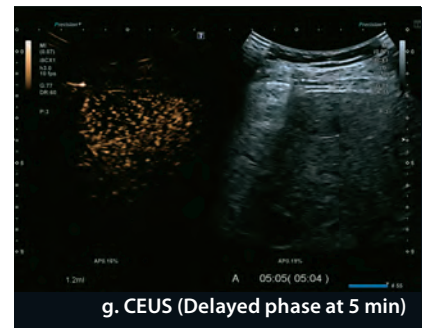
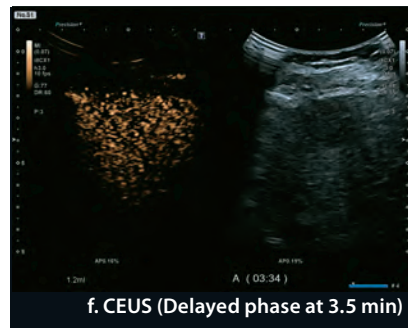
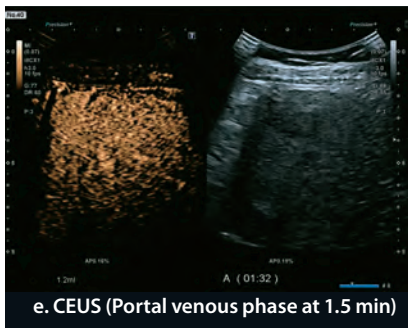
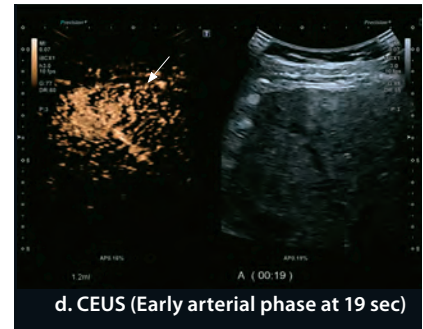
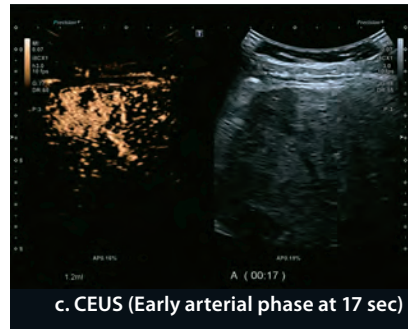
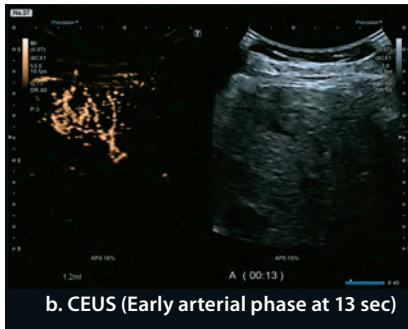


Figure 12.

Conclusion

Aplio i-series systems provide excellent imaging clarity and definition while significantly enhancing penetration to help overcome difficulties in imaging obese patients and small HCCs. Better image quality even on obese patients is critical to improve HCC surveillance outcome.

Contrast-enhanced ultrasound allows for the differentiation of malignancy of focal liver lesions enabling CEUS LI-RADS® categorization. Diagnostic performance and productivity are highly improved based on the high image quality. In addition, the CEUS is

a cost-effective method for categorization of focal liver lesions without ionizing radiation in adult and pediatric patients. For patients with acute and chronic kidney injury, there is high risk of contrast induced nephropathy by CT contrast agents, and nephrogenic systemic fibrosis by Gadolinium-based MRI contrast agents, and CEUS is a safe alternative as there is no nephrotoxicity.* Health care reform is transforming the United States from volume-based care to a value-based health care system. As that transition continues, CEUS for characterization of focal liver lesions can emerge as an example of a cost-effective and high-value clinical tool.

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The clinical results described in this paper are the experience of the author. Results may vary due to clinical setting, patient presentation and other factors.

*See Lumason prescribing information:
http://imaging.bracco.com/sites/braccoimaging.com/files/technica_sheet_pdf/us-en-2017-01-04-spc-lumason.pdf

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