

● Review

CONTRAST-ENHANCED ULTRASOUND OF FOCAL LIVER MASSES: A SUCCESS STORY

STEPHANIE R. WILSON,^{*} PETER N. BURNS,[†] and YUKO KONO[‡]

^{*} Department of Radiology, and Division of Gastroenterology, Department of Medicine, University of Calgary, Foothills Medical Centre, Calgary, Alberta, Canada; [†] Department of Medical Biophysics, University of Toronto, Imaging Research, Sunnybrook Research Institute, Toronto, Ontario, Canada; and [‡] Department of Medicine, Division of Gastroenterology and Hepatology, University of California San Diego, San Diego, CA

(Received 8 September 2019; revised 17 December 2019; in final form 19 December 2019)

Abstract—The epidemic of increasing fatty liver disease and liver cancer worldwide, and especially in Western society, has given new importance to non-invasive liver imaging. Contrast-enhanced ultrasound (CEUS) using microbubble contrast agents provides unique advantages over computed tomography (CT) and magnetic resonance imaging (MRI), the currently established methods. CEUS provides determination of malignancy and allows excellent differential diagnosis of a focal liver mass, based on arterial phase enhancement patterns and assessment of the timing and intensity of washout. Today, increased use of CEUS has provided safe and rapid diagnosis of incidentally detected liver masses, improved multidisciplinary management of nodules in a cirrhotic liver, facilitated ablative therapy for liver tumors and allowed diagnosis of hepatocellular carcinoma without biopsy. Benefits of CEUS include the dynamic real-time depiction of tumor perfusion and the fact that it is a purely intravascular agent, accurately reflecting tumoral and inflammatory blood flow. CEUS has many similarities to contrast-enhanced CT and MRI but also unique differences, which are described. The integration of CEUS into a multimodality imaging setting optimizes patient care. (E-mail: Stephanie.Wilson@ahs.ca) © 2020 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Contrast-enhanced ultrasound, Liver blood flow, Liver tumors, Hepatocellular carcinoma, Contrast-enhanced ultrasound Liver Imaging Reporting and Data System, Ultrasound contrast agents, Liver guidelines.

INTRODUCTION

Liver disease has always been a major object of attention in the health care setting. Recent years have witnessed a marked acceleration of this interest, propelled by two factors. One is the growing epidemic of obesity in the developed world and the related impact of non-alcoholic fatty liver disease (NAFLD). The second is the identification of associated liver inflammation and liver cirrhosis, and the increased risk for development of hepatocellular carcinoma (HCC). The principal implication for imaging is the increased incidence of liver and biliary cancers, which has been overwhelming. Between 2000 and 2016, in the United States, the rate of death from liver cancer increased by 43% (Villanueva 2019),

while other cancers have declined in incidence and mortality over the same period (Siegel et al. 2015).

For liver imagers, the impact of this change over recent decades has been dramatic. Non-invasive image-based diagnosis and management of liver tumors is now commonplace, international guidelines for imaging performance are routine and development of formal diagnostic algorithms, such as LI-RADS (Liver Imaging Reporting and Data System), has been implemented to guide performance and interpretation of imaging studies so as to standardize patient management.

Historically, ultrasound (US) has not played a significant role in liver mass diagnosis, as gray-scale imaging, even with the addition of Doppler, does not provide the information on tissue perfusion needed to allow confident differential diagnosis of liver tumors. However, the advent of microbubble contrast agents has transformed the capability of US imaging. Here we describe the major clinical indications, principles and techniques of liver mass contrast-enhanced ultrasound (CEUS) and

Address correspondence to: Stephanie Wilson, University of Calgary Department of Diagnostic Imaging, Foothills Medical Centre, 1403-29 Street NW, Calgary, Alberta T2N2T9, Canada. E-mail: Stephanie.Wilson@ahs.ca

highlight how its performance now places US imaging firmly alongside contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) for liver diagnosis.

This review was invited on the basis of expertise on the subject of CEUS of liver tumors. Cited prospective studies had institutional review board (IRB) approval and informed consent. The cited retrospective studies had IRB approval with consent or waiver of it. Publications without IRB approval are in compliance with the Declaration of Helsinki, Version 2013.

FOCAL LIVER DISEASE

Focal liver disease comprises virtually all of the tumors that occur in the liver, both benign and malignant, as well as inflammatory and infiltrative conditions appearing in a mass-like form.

Benign liver tumors

Benign liver tumors are most often detected incidentally, that is, at imaging performed for another indication. Hemangioma, a tumor of the liver blood vessels; focal nodular hyperplasia (FNH), a tumor-like condition composed of liver cell components; and hepatic adenoma, a tumor of the liver cells or hepatocytes, are the benign tumors that are most frequently seen on CEUS imaging of the liver. Hemangioma and FNH are very common, and their identification on imaging is routine. Their typically benign course makes them inconsequential, and their confirmation on CEUS is generally sufficient, reducing the need for more expensive downstream imaging. Their identification followed by confirmation of diagnosis is as important for excluding malignancy as for the benign diagnosis. Adenomas are much more important, as these benign liver cell tumors infrequently undergo malignant transformation and may also rupture with catastrophic consequences. However, they are very rare, and as they occur in identifiable clinical circumstances, they are often suspected on clinical grounds (Tsilimigras et al. 2019).

Malignant liver tumors

Liver masses in at-risk patients. A liver mass may be found on imaging as part of a focused search motivated by a patient's symptoms or by known risk factors for metastatic disease or in the cohort of patients with chronic liver disease, who have increased risk for HCC or other malignancies. In these situations, the likelihood of malignancy is high, but regardless of the circumstances of detection or discovery, the presence of a focal liver mass will most often require its characterization, as clinical presumption of diagnosis is not generally acceptable in those with a cancer risk.

Hepatocellular carcinoma. Hepatocellular carcinoma is the most common primary liver cancer and a major cause of morbidity and death worldwide. It is the second most lethal cancer after pancreatic cancer, with a 5-y survival rate of 18%. It is the sixth most common cancer and the fourth cause of cancer death. It is estimated that more than 1 million patients will die of liver cancer in 2030 (Villanueva 2019).

More than 90% of HCCs arise from cirrhosis. This can have multiples causes, but there is a higher prevalence of HCC in patients with cirrhosis associated with hepatitis B and hepatitis C infection. Incidence of NAFLD is rising with obesity and has become the most common cause of liver dysfunction worldwide. It will soon be the leading cause of both cirrhosis and HCC in many countries (Younossi 2019).

The detection, diagnosis and treatment of HCC are complex, and the integration of imaging at all stages of tumor management has led to the development of liver imaging specialists devoted to the patient at risk for the development of HCC. This in part has resulted in the development of CEUS LI-RADS, discussed below.

Non-hepatocellular tumors. Primary tumors of the liver that do not originate from the liver cells (hepatocytes) include metastases; intrahepatic cholangiocarcinoma (ICC), which arises from the peripheral biliary ductules; lymphoma; and epithelioid hemangioendothelioma, a rare tumor of vascular origin. From an imaging perspective, the category of non-hepatocellular tumors is most helpful as they share many common imaging features. Their definitive diagnosis, however, requires biopsy before treatment or their removal.

Liver metastasis. Liver metastases are the most common malignant liver tumors and are a manifestation of progression of primary cancers of many organs including lung, colorectum and breast. Their detection on CEUS is facilitated by scanning the liver in large sweeps during the portal venous phase (PVP) and late phase when the liver parenchyma exhibits diffuse vascular enhancement, thereby increasing the conspicuity of the metastases, which, after their washout, appear as black holes throughout the enhanced parenchyma (Albrecht et al. 2003).

Although screening protocols established for surveillance of cancer patients include imaging, it is generally in the form of PVP CT scan. CT is widely available and can quickly handle the large populations of patients requiring this procedure. CEUS facilities are not equipped for these large surveillance populations. However, CT and magnetic resonance (MR) scans in this population can yield indeterminate results, and the ability of CEUS to resolve these successfully is a high point for its role. For example, CT revealing one or more low

attenuation nodules on PVP imaging is indeterminate, whereas CEUS will resolve an explanatory cyst and easily differentiate it from a metastasis.

LIVER MASS CHARACTERIZATION

Liver mass characterization, as distinct from liver mass detection, is an approved indication for CEUS worldwide, and it is this straightforward application that has yielded its greatest success (Claudon *et al.* 2013). The clinical impact of the characterization of a focal liver mass is enormous, as an identified mass may indicate either a benign tumor or a malignant tumor, both of which can be found in a wide variety of clinical situations.

Although CT and MR scans are fully established as imaging techniques for liver mass characterization, CEUS has exhibited equivalence or superiority in multiple studies (Burns and Wilson 2007; Seitz *et al.* 2009). Additionally, CEUS offers more than another equivalent contrast imaging modality, providing unique contributions to the diagnosis of liver masses and to the determination of malignancy. These include real-time dynamic imaging of enhancement patterns, typically with superior temporal resolution and vessel discrimination. CEUS also uses a purely intravascular contrast agent, removing the pseudo-enhancement frequently seen on CT and MR scans when contrast agent diffuses into the tumor interstitium. CEUS should therefore be added to the imaging toolbox for this indication.

Incidental liver masses

Incidental liver masses are those discovered unintentionally while imaging for another indication. Their detection is a regular event when using US for abdominal imaging. Although historically these lesions have been characterized on subsequent CT or MR scans, today, they are optimally characterized using CEUS, thereby reducing time to diagnosis. As these masses are incidental, they are likely to be benign, although on occasion a malignant mass may be found incidentally as well. The CEUS diagnosis of liver masses at the time of their detection improves outcomes in a shorter time, reduces costs (Faccioli *et al.* 2007), allays patient anxiety and reduces the necessity of downstream imaging (Seitz *et al.* 2009). In today's era of cost containment and expanding non-invasive diagnosis of focal liver masses, CEUS is recognized as a major contributor.

IMAGING FOCAL LIVER MASSES WITH CEUS

Methods

Whereas the initial indication for intravenous contrast agents in the liver was as an echo-enhancer for Doppler signals (Cosgrove 1996), CEUS imaging of the liver as we know it today only began around 2000. It

relies on the combination of second-generation (*i.e.*, low-solubility gas) agents and bubble-specific imaging methods that can detect and image microbubbles in real time at a transmit power sufficiently low to avoid destroying them (Burns *et al.* 1998). Early efforts in the 1990s to image perfusion in the liver using harmonic imaging (Claudon *et al.* 2013; Dietrich *et al.* 2014) relied on disrupting the bubbles, partly because the imaging systems could not operate effectively at low mechanical index (MI) and partly because the air-based microbubble agents of the time were relatively unstable. The advent of multipulse bubble-specific imaging methods, such as pulse inversion (Hope Simpson *et al.* 1999), (Burns *et al.* 2000) opened the way to real-time, low-MI imaging of enhancement patterns in liver and tumor parenchyma (Albrecht *et al.* 2003; Burns and Wilson 2006). In subsequent years, imaging of the liver has become the most popular and most successful non-cardiac application of CEUS (Claudon *et al.* 2013).

Currently approved CEUS agents for liver imaging can be divided into those that are “blood pool” and do not leave the vascular system and those that are taken up by phagocytosis in the liver and therefore exhibit post-vascular or “Kupffer cell” enhancement. Commonly used blood pool agents include SonoVue/Lumason (Bracco Imaging S.p.A., Milan, Italy) and Definity/Luminy (Lantheus Medical Imaging, Billerica, MA, USA). Currently less widespread in their availability are agents that combine a blood pool and Kupffer phase such as Sonazoid (GE Healthcare, Amersham, UK). Numerous studies have reported the excellent safety profile of these agents, with an adverse event rate comparable with or lower than that of contrast-enhanced MRI (Claudon *et al.* 2013).

All agents require an US imaging system with a dedicated, low-MI contrast-specific imaging mode. The function of this mode is to suppress tissue echoes and reveal enhancement caused by the bubbles in real time (Burns and Wilson 2006). The operating parameters of the system should be optimized by the manufacturer for the specific agent being used and be available as a preset mode on the system. The agent is administered through an intravenous cannula, no smaller than 22 gauge, and followed by a 10-mL saline flush *via* a three-way stopcock. Small boluses (*e.g.*, 0.2 mL for Definity, 2.4 mL for SonoVue) are preferred, making it possible to have multiple boluses from a single vial. An on-screen timer is initialized at the start of the saline flush. Cine loops are recorded covering the arterial phase in real time, beginning at the arrival of the first bubble in the field of view and continuing to just beyond the peak of arterial phase enhancement. Subsequent scanning is continued intermittently throughout the portal and late phases, to about 5 min (it should be noted that there is no interstitial

phase for blood pool agents). Intermittent scanning is used as continuous insonation of stationary or very slow moving bubbles will result in their eventual destruction, even at low MI. Thus, continuous scanning can artifactually reveal lesions with slow-moving blood (*e.g.*, a hemangioma) as washing out (Dietrich *et al.* 2014). It is also important for HCC diagnosis to preserve bubbles in liver parenchyma. Continuous insonation shortens the duration of liver parenchymal enhancement and may miss late and mild washout of HCC. Most systems have a dual-screen display to exhibit simultaneous images of tissue and contrast agent, side by side. This helps in the identification of a lesion in the tissue-suppressed contrast-specific image, clearly localizes altered enhancement (either hyper- or hypo-) of a designated nodule, and is particularly useful in guiding interventions such as transjugular intrahepatic portosystemic shunt (TIPS), biopsy and ablation. Finally, as the depiction of vessel morphology in the arterial phase is of diagnostic importance, a vessel-tracking technique known as temporal maximum intensity projection (MIP or “accumulation”) is commonly used (Wilson *et al.* 2008). This takes advantage of the fact that the bubbles provide relatively bright, discrete echoes whose path traces that of the vessels that contain them. The method simply overlays successive frames, with a result analogous to the long-exposure photographs taken of moving lights at night. It is, however, most susceptible to tissue motion, so is usually performed over a few seconds of breath hold. MIP examples are shown with their associated images.

Practical advice on machine settings and handling of the contrast agents for liver examinations can be found in many publications (Durot *et al.* 2018).

FUNDAMENTALS OF LIVER MASS DIAGNOSIS

The interpretation of focal liver masses on CEUS has two major objectives: determination of malignancy and correct lesion diagnosis. The principles for interpretation listed here are based on ethics-approved research publications and are intended to be used as guidelines. They recognize, of course, that there are always exceptions. Nonetheless, they are easily implemented and quickly allow for the reliable interpretation of CEUS studies (Burrowes *et al.* 2017). They incorporate the observations outlined in our algorithm (Fig. 1).

Principle 1

The enhancement level in a CEUS image reflects the number of microbubbles in the field of view. As these are exclusively within blood vessels, echo-enhancement is therefore indicative of the volume of blood, and its change with time is indicative of the rate of perfusion in a region of interest (Figs. 2 and 3).

Principle 2

Most malignant masses are identified by washout of the mass in the portal venous or late phase (Wilson and Burns 2006). Washout refers to the decline in the enhancement of a mass relative to that of the adjacent liver


















| BENIGN | AP - APHE | | PVP/LP - SUSTAINED ENHANCEMENT | |
|---------------------------|---|---|--|--|
| Hemangioma |  | |  |  |
| Focal Nodular Hyperplasia |  | |  |  |
| Adenoma |  | |  |  |
| MALIGNANT | AP - VARIABLE | | PVP/LP - WASHOUT | |
| Hepatocellular |  |  | Early<1min  | Late>1min  |
| Non-Hepatocellular |  |  |  |  |
| CDM | | | | |

Fig. 1. Schematic algorithm of enhancement of focal liver masses with CEUS. AP = arterial phase; PVP = portal venous phase; LP = late phase. APHE = arterial phase hyper-enhancement.

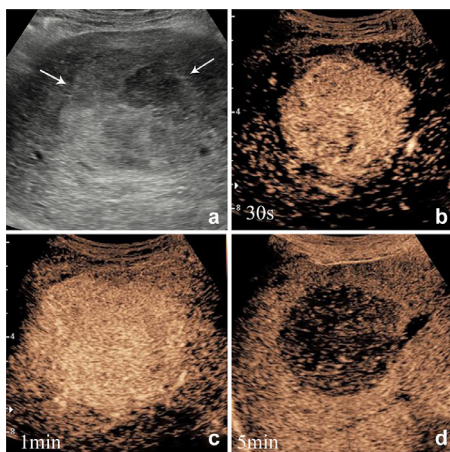


Fig. 2. The interpretation of contrast-enhanced ultrasound relies on the differences in signal intensity, which reflects the volume of microbubbles in the region of interest over time. (a) A gray-scale image reveals a focal liver mass (*arrows*). (b) In the early arterial phase, at 30 s, the tumor is bright because of greater vascular volume and more rapid perfusion. (c) At 1 min, the liver parenchyma, perfused by both the hepatic artery and the portal vein, has now increased in brightness although the tumor remains brighter. (d) At 5 min, the mass is now dark relative to the liver by a process referred to as washout. Washout is the most reliable predictor of malignancy. Here, the washout is weak as microbubbles are still evident within the washout region. This weak washout suggests hepatocellular carcinoma.

parenchyma, after initial arterial phase enhancement. Therefore, if washout is present, malignancy should be considered likely (Fig. 2d; Supplementary Video 3, online

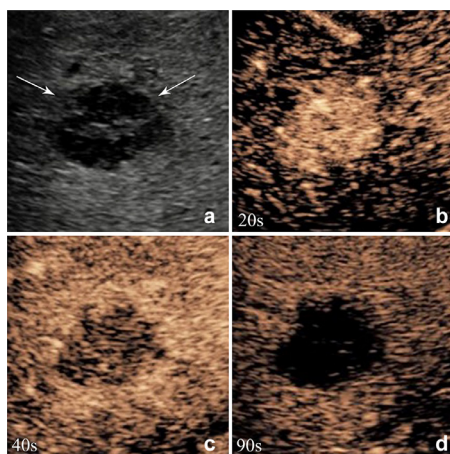


Fig. 3. Importance of washout. (a) A gray-scale image reveals a central focal hypo-echoic mass (*arrows*). The appearance is non-specific. (b) At 20 s, the peak of the arterial phase, the mass exhibits hyper-enhancement relative to the liver. (c) At 40 s, the mass already exhibits washout, which appears weak at the time of first observation. (d) By 90 s, the mass is totally devoid of microbubbles and appears as a black hole. This is marked washout, which suggests non-hepatocellular malignancy. This is intrahepatic cholangiocarcinoma. (See Supplementary Video 3, online only.)

only). Conversely, if washout is not present and the mass exhibits sustained enhancement, there is a high likelihood that it is benign (Friedrich-Rust *et al.* 2013).

Principle 3

The timing and intensity of washout discriminate between HCC and non-hepatocellular malignancy (Bhanyana *et al.* 2010). HCC tends to exhibit late (later than 1 min) and weak washout (so that some bubbles remain within the washout zone) (Fig. 1), whereas all non-hepatocellular malignancies, including ICC, lymphoma and metastasis, are characterized by rapid (earlier than 1 min) and marked washout, so that all bubbles are absent from the nodule, making it appear as a black, punched out hole (Figs. 3 and Fig. 4; Supplementary Video 3, online only) (Kong *et al.* 2014; Sporea *et al.* 2014).

Principle 4

A natural consequence of the two previous principles is that the PVP is the optimal time to detect metastases, when their conspicuity will be increased relative to the enhanced background parenchyma (Figs. 2d and 3) (Murphy-Lavalle *et al.* 2007).

Principle 5

An essential imaging technique for all CEUS examinations where malignancy is suspected is to sweep the liver in the portal venous phase. This can reveal washout of previously undetected malignant lesions (Fig. 5). This technique is performed with a full

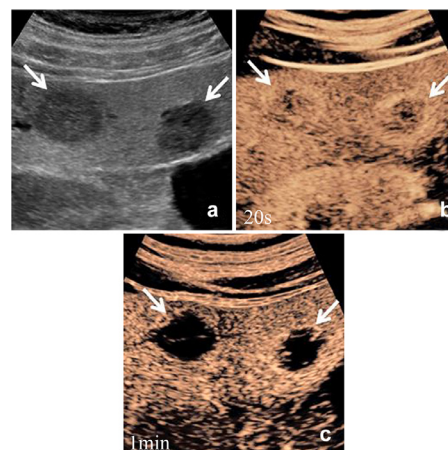


Fig. 4. Optimal time to detect metastatic disease. (a) A gray-scale image of the liver reveals two focal hypo-echoic masses (*arrows*). (b) At 20 s, there is bright rim enhancement with lower-level central enhancement (*arrows*). (c) At 1 min, there is marked washout, such that the lesions appear completely black and “punched out.” The conspicuity of liver metastases is greatest during the portal venous and late phases, as lesion conspicuity increases with washout, allowing for detection of more and smaller lesions.

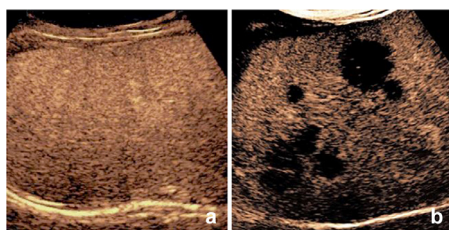


Fig. 5. Value of sweeping the liver in the portal venous and late phases. (a) Still image taken from a portal venous phase sweep of the right lobe of a normal liver. We see homogeneous enhancement with no alteration. (b) In a different patient, an image from a portal venous phase sweep reveals multiple small black masses throughout. These are metastases that were occult on the baseline scan. Conspicuity increases after rapid washout allowing for improved detection, revealing both more and also smaller tumors versus baseline imaging.

suspended inspiration and sweeping of the imaging plane to include all of the liver parenchyma within two to three multiframe acquisitions.

Principle 6

All commonly encountered benign tumors are characterized by specific enhancement patterns in the arterial phase (Laumonier et al. 2012). This allows the investigator to be suspicious of their presence as soon as the examination begins. Patterns include peripheral nodular discontinuous enhancement for hemangiomas (Fig. 6;

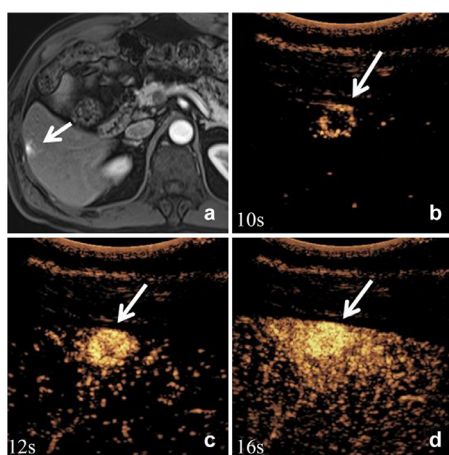


Fig. 6. Improved temporal resolution on real-time dynamic contrast-enhanced ultrasound resolves enhancement details confirming benign diagnosis in a 55-year-old man with hepatitis B virus and risk for hepatocellular carcinoma. (a) An arterial phase magnetic resonance image reveals a small indeterminate hyper-vascular focus in the right lobe of the liver (arrow). A sequence of contrast-enhanced ultrasound arterial phase images taken at (b) 10 s, (c) 12 s and (d) 16 s reveal peripheral nodular enhancement with progressive centripetal filling, diagnostic of flash-filling hemangioma. (See Supplementary Video 6, online only.) Imaging to 5 min reveals sustained enhancement with no washout (not shown). Reprinted with permission, from Jo et. al (2017).

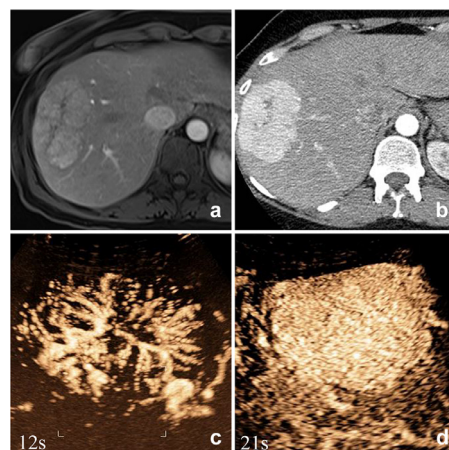


Fig. 7. Focal nodular hyperplasia as an explanation for an incidentally detected liver mass. (a) Magnetic resonance and (b) computed tomography images reveal a hyper-enhancing lesion in the arterial phase. (c) Contrast-enhanced ultrasound (CEUS) at 12 s using a bubble-tracking technique reveals stellate vessels and obvious filling from the center of the mass toward the periphery. (d) At peak arterial phase imaging, 21 s, CEUS is concordant with computed tomography/magnetic resonance imaging. Exquisite vessel morphology is a unique feature of CEUS. (See Supplementary Video 7, online only).

Supplementary Video 6, online only), stellate vessels with centrifugal filling for FNH (Fig. 7; Supplementary Video 7, online only) and the somewhat less reliable sign of

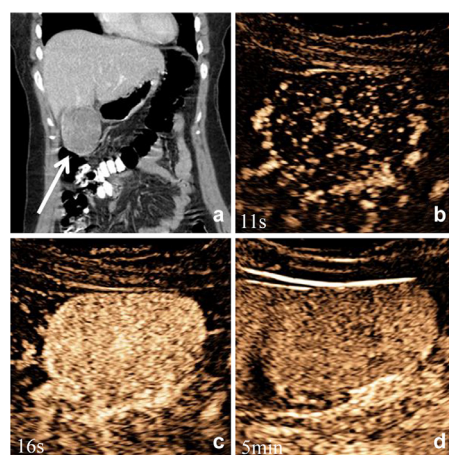


Fig. 8. Resolution of indeterminate mass on computed tomography (CT) and magnetic resonance imaging (MRI) scans. (a) Coronal CT image reveals an exophytic, hypo-attenuating mass arising from the tip of the right liver lobe (arrow). (b) On contrast-enhanced ultrasound at 11 s, there is enhancement of vessels predominantly at the periphery of the mass. (c) By 16 s, the mass is homogeneously enhanced because of the progressive, centripetal enhancement pattern typical of adenoma. (d) There is sustained enhancement of the lesion to 5 min. Hepatic adenoma is very rare in men. This large tumor is indeterminate on CT/MRI, but is easily confirmed on contrast-enhanced ultrasound. (See Supplementary Video 8, online only.)

centripetal filling for some adenomas (Fig. 8; Supplementary Video 8, online only). These patterns are reliably shown on CEUS because of the real-time dynamic nature of the image acquisition and display. By comparison, if these enhancement patterns are rapidly changing, they may not be appreciated on CT/MR scans, both of which obtain snapshots in time. This is especially important for the recognition of rapid, or “flash,” filling hemangiomas on CEUS, which may show only as a zone of arterial phase hyperenhancement on CT/MR scan (Fig. 6).

Principle 7

Unlike benign lesions, malignant tumors are not characterized as reliably by their arterial phase enhancement pattern, which may be highly variable, but instead by the identification of washout in the portal venous and late phases (Durot *et al.* 2018).

Principle 8

Discordance of imaging between CEUS and MRI/CT scan in the PVP is often related to differences in the mechanism of action of the contrast agents for each modality (Wilson *et al.* 2007). In Figure 9, CEUS reveals washout, and MR and CT scans may reveal instead sustained or increased enhancement. The purely intravascular microbubble contrast agents reliably reveal washout in malignant tumors. Contrast agents for CT and MR scans, by comparison, may diffuse through the hyper-

permeable endothelium of some non-hepatocellular malignancies, including ICC.

Principle 9

For dedicated imaging of those at high risk for HCC, inclusion of LI-RADS for US and for CEUS is recommended to allow for precise categorization of the CEUS observations. This standardizes diagnosis and management and allows communication between imagers and clinicians.

Principle 10

Agents such as Sonazoid that are taken up by the reticuloendothelial system (RES) of the hepatic sinusoids reveal somewhat different patterns of enhancement. In the normal liver, the bubbles begin to be retained from 4–6 min after injection, and can reveal enhancement for a further 30 min. This period is known as the post-vascular phase and is unique to such agents. Lesions in which the RES (including Kupffer cells) is depleted or absent appear hypo-echoic in this phase, typically imaged 10 min after injection, when the agent has washed out of the blood pool. Because of their lack of Kupffer cells, metastases are highly conspicuous in this phase, allowing very small lesions to be detected (Nakano *et al.* 2008).

Exceptions

The principles for interpretation of CEUS liver imaging are intended as guidelines. There are, of course, exceptions. Some with significant implications are as follows:

Cirrhotic nodules. A major exception related to the imaging of nodules from a cirrhotic liver includes features that may relate to nodules in different stages of hepatocarcinogenesis and also to the degree of differentiation of the tumor (Jang *et al.* 2007; Leoni *et al.* 2013). Confident diagnosis of HCC requires all of the following features: size >1 cm, arterial phase hyper-enhancement and late weak washout later than 1 min. Ultimately, it should be recognized that HCC and its precursors may have widely varied enhancement features in both the arterial and portal venous phases, including arterial phase iso- and hypo-enhancement and, in the portal venous phase, late or no washout (Jang *et al.* 2009; Wilson *et al.* 2018).

Hepatic adenoma. Although sustained enhancement in the PVP is generally associated with benignancy, hepatic adenomas exhibit weak washout in a substantial percentage of cases, raising concerns about malignancy. Although one may be reluctant to perform biopsy to clarify diagnosis, adenomas above a threshold size of about 5 cm will generally be subject to surgical removal, and therefore, definitive diagnosis is imperative (Kim *et al.* 2008; Tsimigras *et al.* 2019).

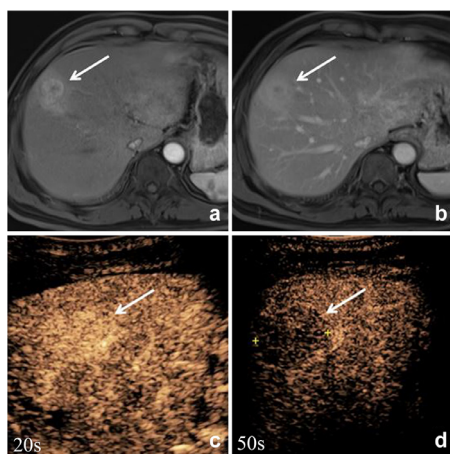


Fig. 9. Discordance of portal venous and late phase enhancement. (a) Arterial phase magnetic resonance image reveals an unusual lobulated mass with heterogeneous enhancement (arrow). (b) Delayed phase image reveals progressive enhancement over time (arrow). (c) Arterial phase contrast-enhanced ultrasound reveals hyper-enhancement (arrow), similar to that seen on magnetic resonance. (d) There is evidence of washout at 50 s, which appears quite marked with few bubbles remaining within. Washout on contrast-enhanced ultrasound is categorized as early (<1 min) and marked (arrow).

HCC AND LI-RADS

Although HCC is a highly lethal cancer with poor prognosis, early diagnosis can lead to cure by surgical resection, liver transplantation or ablation treatment. Imaging plays a pivotal role in HCC detection, diagnosis and follow-up post-treatment (Jang et al. 2015; Jo et al. 2017). For patients at risk for the development of HCC, international guidelines recommend surveillance US be performed at 6-monthly intervals. Once a nodule larger than 1 cm is identified, dynamic contrast imaging with CT, MRI or US is performed to establish diagnosis. Typically, cancer diagnosis requires biopsy. HCC is unique, as the majority are diagnosed by imaging without biopsy. Therefore, accurate imaging diagnosis is critical.

The cirrhotic liver consists of cirrhotic or regenerative nodules that are benign. Among those nodules, some will progress to low-grade dysplastic nodules, then to high-grade dysplastic nodules, to early HCC and, eventually, to progressed HCC (Fig. 10, top). During this multistep process of hepatocarcinogenesis, the blood flow to the nodules changes (Matsui et al. 2007). Cirrhotic nodules are supplied by both the portal vein and hepatic artery. Both portal venous and hepatic arterial flow begin to decrease, and at some point in this process, malignant angiogenesis initiates abnormal arterial flow, which eventually becomes the hyper-vascular arterial supply of a progressed HCC (Fig. 10, bottom). As the described vascular changes are occurring within the cirrhotic nodule, the

nodules also undergo histologic changes with increasing atypia and malignant transformation.

As liver nodules may be imaged at any point during the process of hepatocarcinogenesis, some cirrhotic nodules may appear isovascular or even hypovascular, making imaging diagnosis challenging. Additionally, these nodules may not be a classic HCC but reflect some lesser degree of malignant transformation. Therefore, there is a need for a classification system that recognizes these vascular changes as nodules change from benign regenerative nodules and convert over time to HCC. This need is met by LI-RADS, a system that standardizes terminology, technique, interpretation and reporting for liver imaging on those at high risk for HCC, endorsed by American College of Radiology (ACR) and by the guidelines of the American Association for the Study of Liver Disease (Marrero et al. 2018). Imaging diagnosis of HCC relies on identification of the features of the blood flow to the suspected nodule, with the classic description of HCC showing arterial phase hyper-enhancement and the unique and important feature of washout seen in later phases (Figs. 11 and 12; Supplementary Video 11).

CEUS can provide an accurate assessment of tumor blood flow, and has been reported to be as accurate as contrast-enhanced CT and/or MRI if not better (Hanna et al. 2016). LI-RADS was initially made for CT/MRI, and CEUS was added in 2016 (Wilson et al. 2018).

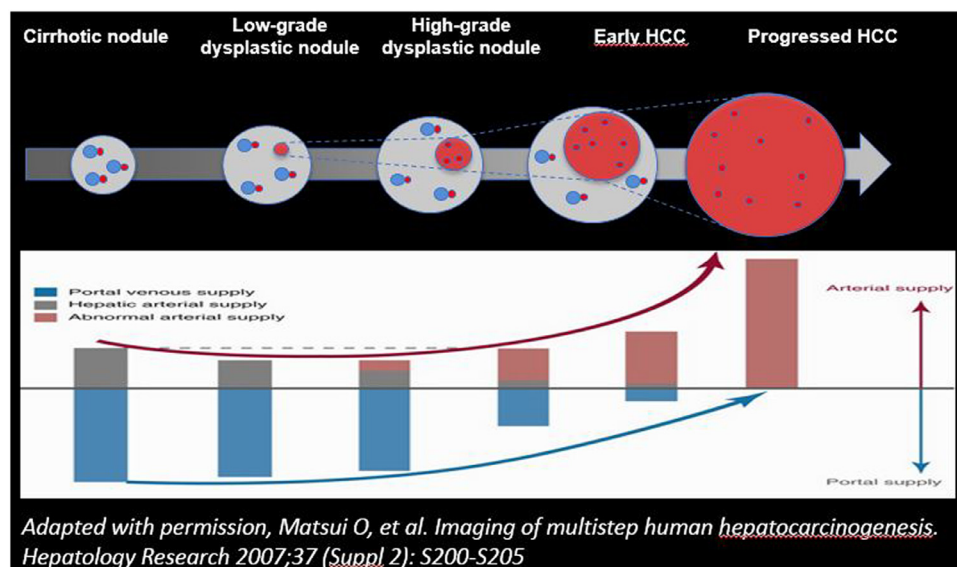


Fig. 10. Multistep hepatocarcinogenesis. Top: The schematic illustrates the evolution of a cirrhotic nodule to a low-grade and then a high-grade dysplastic nodule, with increasing size and cellular atypia, before being replaced fully by a progressed hepatocellular carcinoma (HCC). Bottom: Associated vascular changes that occur with reduction of the normal hepatic arterial and portal venous blood flow and their replacement with abnormal arterial flow through the process of neo-angiogenesis. This progression explains the wide variety of enhancement features that may occur on contrast-enhanced imaging of cirrhotic nodules found on surveillance scans. Reprinted with permission, from Matsui et al. (2007).

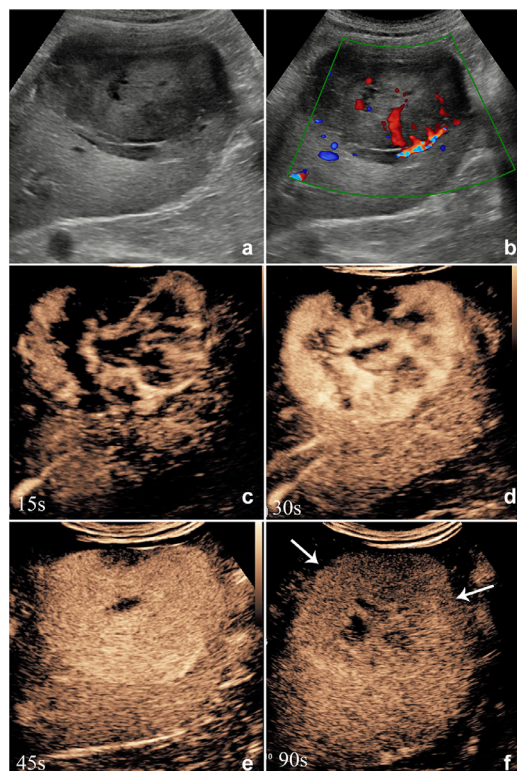


Fig. 11. Value of real-time dynamic imaging with vessel-tracking techniques. (a) Large liver mass. (b) Color Doppler reveals peri- and intra-lesional vessels. (c) At 15 s in the early arterial phase with a bubble-tracking technique, there is evidence of dysmorphic vascularity. (See Supplementary Video 11 online only.) (d) At 30 s the vascularity has increased. (e) At 45 s, the peak of arterial phase enhancement, the mass is homogeneously enhanced with a central avascular scar-like area. (See Supplementary Video 11, online only.) (f) At 90 s, there is very weak washout of the lesion. Washout is categorized as late (>1 min) weak. This is a biopsy-confirmed hepatocellular carcinoma. (Reproduced with permission, Specialty Imaging Fundamentals of CEUS. Elsevier 2019).

LI-RADS includes eight different categories with various probability for HCC. LI-RADS 1 (LR-1) is a confidently assessed benign tumor, such as hemangioma or focal fat deposition, and with logical progression, LR-5 is a definite HCC, with probability close to 100% (Terzi *et al.* 2018; Makoyeva *et al.* 2019), which allows imaging diagnosis of HCC without histologic examination. High specificity of LR-5 is the key importance of LI-RADS as treatments such as surgical resection, liver transplant, locoregional treatment and systemic therapy would be applied. Between LR-1 and LR-5 are the cirrhotic nodules with different probabilities of being HCC, including those nodules undergoing hepatocarcinogenesis.

Although the integration of CEUS into the imaging for HCC continues, CEUS has strong competitive attributes, including high temporal and spatial resolution,

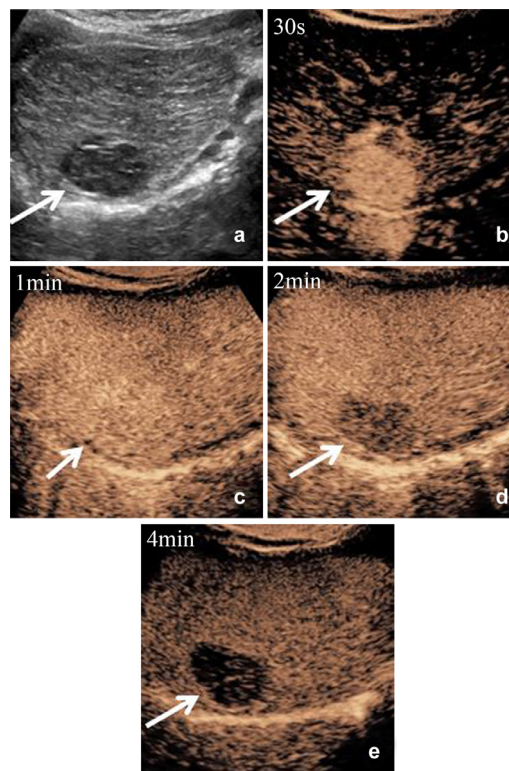


Fig. 12. Liver Imaging Reporting and Data System (LI-RADS) 5: confident hepatocellular carcinoma diagnosis. (a) Gray-scale image reveals a foal liver mass in an at-risk patient (arrow). (b) There is arterial phase hyper-enhancement at 30 s (arrow). (c) Isovascularity at 1 min (arrow). (d) At 2 min, there are very early signs of weak washout (arrow). (e) Washout is unequivocal at 4 min (arrow).

dynamic real-time scanning and the use of a purely intravascular microbubble, which make CEUS results highly contributory to patient management. Additionally, CEUS resolves well-described indeterminate results from CT and MR scans (Hu *et al.* 2020).

CEUS in ablative therapy

CEUS can play a vital role in ablative therapy for malignant liver tumors including patient selection, intra-procedural guidance and immediate post-procedural assessment. The inherent value of US for performance of interventional procedures is now shared with CEUS for guidance of ablative procedures. Performance of immediate CEUS monitoring allows for reduction of residual tumor on secondary surveillance. Though not widely used, during our experience with CEUS in secondary surveillance, we have found that it can accurately detect residual/recurrent tumor, characterize the geographic pattern of recurrence (intralesional, extralesional, segmental, or remote) and assess for tumor in vein (Bansal *et al.* 2019).

Some common artifacts and pitfalls

Dosing artifacts. Too little or too much contrast has a dramatic effect on the examination. Too low a dose not only produces inadequate enhancement of perfused structures, but enhancement that is both depth dependent (with deeper-lying structures being lost to attenuation) and time dependent (with inadequate enhancement in the portal or late phase). Too high a dose, on the other hand, produces attenuation in the parenchyma of the liver, both shadowing distal structures and exacerbating the non-linear propagation artifact (below) (Fig. 13; Supplementary Video 13, online only).

Microbubble destruction. At high MIs, comparable with those used in non-contrast imaging, bubbles are disrupted by the US beam (Kono et al. 1997). But

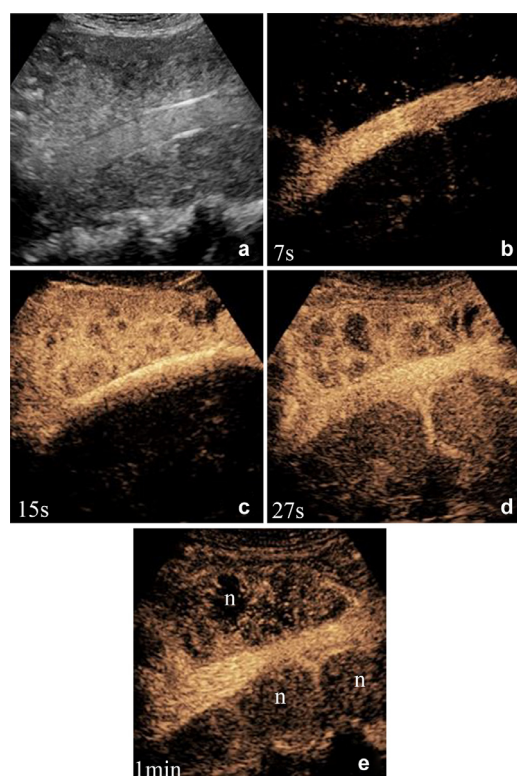


Fig. 13. Attenuation caused by too much microbubble contrast agent. (a) This sagittal gray-scale image reveals the aorta filled with contrast. (b) The contrast-enhanced ultrasound image at 7 s reveals enhancement of the aorta. (c) At 15 s, the tissue anterior to the aorta is enhanced. The entire area deep to the aorta appears black as if the aorta attenuates all of the ultrasound beam. (d) By 27 s, the region deep to the aorta starts to reveal enhancement and outlines extensive lymphadenopathy. (e) As microbubble contrast agent volume declines over time, enhancement of the tissues posterior to the aorta can be observed, with a mass of hyper-enhancing nodes (N) elevating the aorta from the spine. (See Supplementary Video 13, online only.)

acoustic pressure experienced by bubbles in the US beam varies with transducer characteristics and is typically higher closer to the transducer face. This can lead to selective disruption of bubbles in an image. If the flow in the lesion is particularly slow, continuous insonation, even at low MI, can selectively destroy those bubbles that dwell for a long period and are thus subject to many pulses of sound. The result is that continuous scanning of a lesion such as a hemangioma can make it appear to lose contrast enhancement and “wash out”; intermittent scanning is therefore preferred (Dietrich et al. 2007).

Inadequate tissue suppression. Bubble-specific imaging modes are designed to suppress echoes from tissue and reveal only echoes from bubbles. But if the echo from tissue is too strong, or if the tissue structure is causing aberration of the beam, tissue may appear enhanced in a bubble-specific mode without contrast. A liver with fatty infiltration, for example, may exhibit enhancement without the injection of bubbles. Lowering the gain reduces such pseudo-enhancement, at the expense of sensitivity to the bubbles.

Non-linear propagation artifact. A particular form of pseudo-enhancement is produced by the propagation of the US beam through a non-linear medium, such as a liver containing bubbles (Fig. 14). A distal structure that is echogenic but not enhancing (such as the diaphragm) will appear enhanced because the system detects non-linear backscatter from the object even though it does not contain bubbles (Tang and Eckersley 2006). Using a high-MI “flash,” as described above, will make both the enhancement and the pseudo-enhancement disappear, as it destroys the bubbles in the beam’s path. Thus, this particular artifact can be hard to identify. It is seen in echoes from the post-ablation zone in hepatic tumors, for example (Yu et al. 2010).

CONTROVERSIES

A persistent belief that CEUS is unable to diagnose ICC and distinguish it from HCC has delayed—and in some cases prevented—the inclusion of CEUS in the imaging guidelines of major liver associations (Rimola et al. 2009; Vilana et al. 2010). We believe that implementation of the LR-M criteria described here and the discordance in principle 7 will accurately allow for the identification and differentiation of ICC and HCC.

Washout is a somewhat mysterious phenomenon, without clear hemodynamic explanation, but known to be the most important feature to differentiate malignant from benign lesions in all imaging modalities. It is also very important that HCC typically washes out very late (>1 min after contrast administration) and to a mild

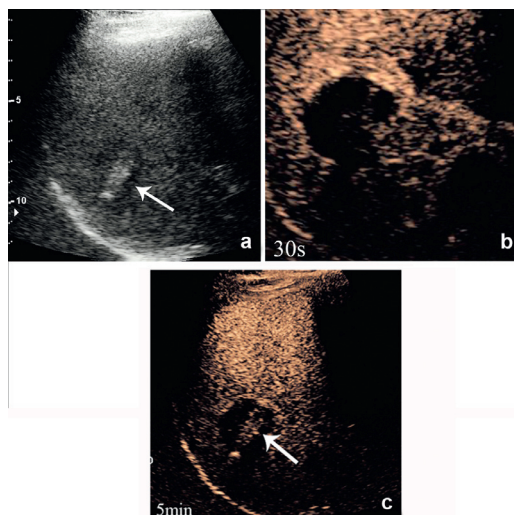


Fig. 14. Non-linear artifact. (a) Gray-scale image reveals a recent microwave ablation treatment site of a hepatocellular carcinoma. The mass is dark with an echogenic linear region centrally, representing artifact from the treatment probe. (b) Arterial phase contrast-enhanced ultrasound image reveals that the treatment site is black and avascular at 30 s, suggestive of successful ablation. However, after the liver has filled at 2 min, centrally within the treated tumor, there is a zone of apparent enhancement which can be seen to correlate precisely with the artifact created by the ultrasound probe (arrows). This is pseudo-enhancement, which occurs later than the normal wash-in time for contrast-enhanced ultrasound. (c) At 5 minutes the central region is still enhanced. It also does not reveal washout as would be expected if this were a tumor recurrence. The non-linear artifact occurs deep to enhanced tissues in targets containing a brightly echogenic component.

degree, while non-hepatocellular malignancy such as cholangiocarcinoma and metastasis washes out early (<1 min after contrast administration) and to a more marked degree, as explained above.

CONCLUSIONS

CEUS makes unique contributions to contrast-enhanced liver imaging including excellent spatial and temporal resolution, superior detection of arterial phase hyper-enhancement and the most accurate demonstration of washout in malignant tumors. These features are accomplished routinely with low-MI contrast-specific modes on state-of-the-art US systems (Fig. 13). CEUS studies are performed in dynamic real time, using a purely intravascular agent, which is shown with such exquisite sensitivity that even a single bubble can be seen within the field of view. CEUS has an excellent safety profile, relies on no ionizing radiation and has no nephrotoxicity. It has the additional benefit of relative insensitivity to cardiac and respiratory motion, making it a robust and versatile imaging technique.

Recent decades have witnessed a growing devotion of radiologists to pursue excellence in imaging of liver tumors, motivated largely by the growing significance of liver cancer throughout the world. As a condition that is often best treated after non-invasive diagnosis with imaging and that incorporates radiology into a multidisciplinary team of specialists who devote expertise to the management of this growing international health crisis, CEUS with the additional benefits of LI-RADS should be an essential component of this modern multidisciplinary approach. Although US alone did not compete with the performance of contrast-enhanced CT and MR scans for the evaluation of the liver and its tumors, CEUS surely does.

Conflict of interest disclosure—The authors declare no competing interests.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.ultrasmedbio.2019.12.021](https://doi.org/10.1016/j.ultrasmedbio.2019.12.021).

REFERENCES

- Albrecht T, Blomley MJ, Burns PN, Wilson S, Harvey CJ, Leen E, Claudon M, Calliada F, Correas JM, LaFortune M, Campani R, Hoffmann CW, Cosgrove DO, LeFevre F. Improved detection of hepatic metastases with pulse-inversion US during the liver-specific phase of SHU 508A: Multicenter study. *Radiology* 2003;227:361–370.
- Bansal S, Gui J, Merrill C, Wong JK, Burak KW, Wilson SW. Contrast-enhanced US in local ablative therapy and secondary surveillance for hepatocellular carcinoma. *RadioGraphics* 2019;39:1302–1322.
- Bhayana D, Kim TK, Jang HJ, Burns PN, Wilson SR. Hypervascular liver masses on contrast-enhanced ultrasound: The importance of washout. *AJR Am J Roentgenol* 2010;194:977–983.
- Burns PN, Wilson SR. Microbubble contrast for radiological imaging: 1. Principles. *Ultrasound Q* 2006;22:5–13.
- Burns PN, Wilson SR. Focal liver masses: Enhancement patterns on contrast-enhanced images—Concordance of US scans with CT scans and MR images. *Radiology* 2007;242:162–174.
- Burns PN, Wilson SR, Hope Simpson D, Chin CT, Lai X. Harmonic interval delay imaging: A new ultrasound contrast method for imaging the blood pool volume in the liver. *Radiology* 1998;209:189.
- Burns PN, Wilson SR, Simpson DH. Pulse inversion imaging of liver blood flow: Improved method for characterizing focal masses with microbubble contrast. *Invest Radiol* 2000;35:58–71.
- Burrowes DP, Medellin A, Harris AC, Milot L, Wilson SR. Contrast-enhanced US approach to the diagnosis of focal liver masses. *Radiographics* 2017;37:1388–1400.
- Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsoe CP, Piscaglia F, Wilson SR, Barr RG, Chammas MC, Chaubal NG, Chen MH, Clevert DA, Correas JM, Ding H, Forsberg F, Fowlkes JB, Gibson RN, Goldberg BB, Lassau N, Leen EL, Mattrey RF, Moriyasu F, Solbiati L, Weskott HP, Xu HX. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver—Update 2012: A WFUMB—EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultraschall Med* 2013;34:11–29.
- Cosgrove D. Ultrasound contrast enhancement of tumours. *Clin Radiol* 1996;51:44–49.
- Dietrich CF, Mertens JC, Braden B, Schuessler G, Ott M, Ignee A. Contrast-enhanced ultrasound of histologically proven liver hemangiomas. *Hepatology* 2007;45:1139–1145.

- Dietrich CF, Ignee A, Greis C, Cui XW, Schreiber-Dietrich DG, Hocke M. Artifacts and pitfalls in contrast-enhanced ultrasound of the liver. *Ultraschall Med* 2014;35:108–125 quiz 26–27.
- Durot I, Wilson SR, Willmann JK. Contrast-enhanced ultrasound of malignant liver lesions. *Abdom Radiol (NY)* 2018;43:819–847.
- Faccioli N, D'Onofrio M, Comai A, Cugini C. Contrast-enhanced ultrasonography in the characterization of benign focal liver lesions: Activity-based cost analysis. *Radiol Med* 2007;112:810–820.
- Friedrich-Rust M, Klopffleisch T, Nierhoff J, Herrmann E, Vermehren J, Schneider MD, Zeuzem S, Bojunga J. Contrast-enhanced ultrasound for the differentiation of benign and malignant focal liver lesions: A meta-analysis. *Liver Int* 2013;33:739–755.
- Hanna RF, Miloushev VZ, Tang A, Finklestone LA, Brejt SZ, Sandhu RS, Santillan CS, Wolfson T, Gamst A, Sirlin CB. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. *Abdom Radiol (NY)* 2016;41:71–90.
- Hope Simpson D, Chin CT, Burns PN. Pulse Inversion Doppler: A new method for detecting nonlinear echoes from microbubble contrast agents. *IEEE Trans Ultrason Ferroelectr Freq Control* 1999;46:372–382.
- Hu J, Bhayana D, Burak K, Wilson S. Resolution of indeterminate MRI with CEUS in patients at high risk for hepatocellular carcinoma. *Abdom Radiol* 2020;45:123–133.
- Jang HJ, Kim TK, Burns PN, Wilson SR. Enhancement patterns of hepatocellular carcinoma at contrast-enhanced US: Comparison with histologic differentiation. *Radiology* 2007;244:898–906.
- Jang HJ, Kim TK, Wilson SR. Small nodules (1–2 cm) in liver cirrhosis: Characterization with contrast-enhanced ultrasound. *Eur J Radiol* 2009;72:418–424.
- Jang HJ, Kim TK, Burns PN, Wilson SR. CEUS: An essential component in a multimodality approach to small nodules in patients at high-risk for hepatocellular carcinoma. *Eur J Radiol* 2015;84:1623–1635.
- Jo PC, Jang HJ, Burns PN, Burak KW, Kim TK, Wilson SR. Integration of contrast-enhanced US into a multimodality approach to imaging of nodules in a cirrhotic liver: How I do it. *Radiology* 2017;282:317–331.
- Kim TK, Jang HJ, Burns PN, Murphy-Lavallee J, Wilson SR. Focal nodular hyperplasia and hepatic adenoma: Differentiation with low-mechanical-index contrast-enhanced sonography. *AJR Am J Roentgenol* 2008;190:58–66.
- Kong WT, Wang BJ, Huang BJ, Mao F. Value of wash-in and wash-out time in the diagnosis between hepatocellular carcinoma and other hepatic nodules with similar vascular pattern on contrast enhanced ultrasound. *Gastroenterol Hepatol* 2014;29:576–580.
- Kono Y, Moriyasu F, Mine Y, Nada T, Kamiyama N, Suginoishi Y, Matsumura T, Kobayashi K, Chiba T. Gray-scale second harmonic imaging of the liver with galactose-based microbubbles. *Invest Radiol* 1997;32:120–125.
- Laumonier H, Cailliez H, Balabaud C, Possenti L, Zucman-Rossi J, Bioulac-Sage P, Trillaud H. Role of contrast-enhanced sonography in differentiation of subtypes of hepatocellular adenoma: Correlation with MRI findings. *AJR Am J Roentgenol* 2012;199:341–348.
- Leoni S, Piscaglia F, Granito A, Borghi A, Galassi M, Marinelli S, Terzi E, Bolondi L. Characterization of primary and recurrent nodules in liver cirrhosis using contrast-enhanced ultrasound: Which vascular criteria should be adopted? *Ultraschall Med* 2013;34:280–287.
- Makoyeva A, Kim T, Jang H, Medellin A, Wilson S. CEUS LI-RADS: A validation study. *Radiology: Imaging Cancer* 2019; in press.
- Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018;68:723–750.
- Matsui O, Gabata T, Kobayashi S, Terayama N, Sanada J, Kouda W, Kawashima H. Imaging of multistep human hepatocarcinogenesis. *Hepatol Res* 2007;37(Suppl. 2):S200–S205.
- Murphy-Lavallee J, Jang HJ, Kim TK, Burns PN, Wilson SR. Are metastases really hypovascular in the arterial phase? The perspective based on contrast-enhanced ultrasonography. *J Ultrasound Med* 2007;26:1545–1556.
- Nakano H, Ishida Y, Hatakeyama T, Sakuraba K, Hayashi M, Sakurai O, Hataya K. Contrast-enhanced intraoperative ultrasonography equipped with late Kupffer-phase image obtained by sonazoid in patients with colorectal liver metastases. *World J Gastroenterol* 2008;14:3207–3211.
- Rimola J, Forner A, Reig M, Vilana R, de Lope CR, Ayuso C, Bruix J. Cholangiocarcinoma in cirrhosis: Absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. *Hepatology* 2009;50:791–798.
- Seitz K, Strobel D, Bernatik T, Blank W, Friedrich-Rust M, Herbay A, Dietrich CF, Strunk H, Kratzer W, Schuler A. Contrast-enhanced ultrasound (CEUS) for the characterization of focal liver lesions—Prospective comparison in clinical practice: CEUS vs. CT (DEGUM multicenter trial). *Ultraschall Med* 2009;30:383–389.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5–29.
- Sporea I, Martie A, Bota S, Sirlin R, Popescu A, Danila M. Characterization of focal liver lesions using contrast enhanced ultrasound as a first line method: A large monocentric experience. *J Gastrointest Liver Dis* 2014;23:57–63.
- Tang MX, Eckersley RJ. Nonlinear propagation of ultrasound through microbubble contrast agents and implications for imaging. *IEEE Trans Ultrason Ferroelectr Freq Control* 2006;53:2406–2415.
- Terzi E, Iavarone M, Pompili M, Veronese L, Cabibbo G, Fraquelli M, Fraquelli M, Riccardi L, De Bonis L, Sangiovanni A, Leoni S, Zocco MA, Rossi S, Alessi N, Wilson SR, Piscaglia F. Contrast ultrasound LI-RADS LR-5 identifies hepatocellular carcinoma in cirrhosis in a multicenter retrospective study of 1,006 nodules. *J Hepatol* 2018;68:485–492.
- Tsilimigras DI, Rahnamai-Azar AA, Ntanasis-Stathopoulos I, Gaviatopoulou M, Moris D, Spartalis E, Cloyd JM, Weber SM, Pawlik TM. Current approaches in the management of hepatic adenomas. *J Gastrointest Surg* 2019;23:199–209.
- Vilana R, Forner A, Bianchi L, Garcia-Criado A, Rimola J, de Lope CR, Reig M, Ayuso C, Brú C, Bruix J. Intrahepatic peripheral cholangiocarcinoma in cirrhosis patients may display a vascular pattern similar to hepatocellular carcinoma on contrast-enhanced ultrasound. *Hepatology* 2010;51:2020–2029.
- Villanueva A. Hepatocellular carcinoma. *N Engl J Med* 2019;380:1450–1462.
- Wilson SR, Burns PN. An algorithm for the diagnosis of focal liver masses using microbubble contrast-enhanced pulse-inversion sonography. *AJR Am J Roentgenol* 2006;186:1401–1412.
- Wilson SR, Kim TK, Jang HJ, Burns PN. Enhancement patterns of focal liver masses: Discordance between contrast-enhanced sonography and contrast-enhanced CT and MRI. *AJR Am J Roentgenol* 2007;189:W7–W12.
- Wilson SR, Jang HJ, Kim TK, Iijima H, Kamiyama N, Burns PN. Real-time temporal maximum-intensity-projection imaging of hepatic lesions with contrast-enhanced sonography. *AJR Am J Roentgenol* 2008;190:691–695.
- Wilson SR, Lyschik A, Piscaglia F, Cosgrove D, Jang HJ, Sirlin C, Dietrich CF, Kim TK, Willmann JK, Kono Y. CEUS LI-RADS: Algorithm, implementation, and key differences from CT/MRI. *Abdom Radiol (NY)* 2018;43:127–142.
- Younossi ZM. Non-alcoholic fatty liver disease—A global public health perspective. *J Hepatol* 2019;70:531–544.
- Yu H, Jang HJ, Kim TK, Khalili K, Williams R, Lueck G, Hudson J, Burns PN. Pseudoenhancement within the local ablation zone of hepatic tumors due to a nonlinear artifact on contrast-enhanced ultrasound. *AJR Am J Roentgenol* 2010;194:653–659.