Contrast-Enhanced Ultrasound of the Liver and Kidney

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INTRODUCTION

Over the last decade, the clinical applications of noncardiac contrast-enhanced ultrasound (CEUS) have been steadily increasing. The development of new second-generation contrast agents has allowed superior visualization of the microcirculation, once a domain restricted to angiography, contrast-enhanced computed tomography (CECT), and contrast-enhanced magnetic resonance imaging (CEMR). Ultrasound (US) contrast agents possess a good safety profile and, given their lack of nephrotoxicity, are indispensable in patients with critical renal function who may have contraindications to undergoing CECT or CEMR imaging. In addition, CEUS allows for real-time dynamic imaging of lesions and organs. This article provides a survey of the current clinical applications and potential future uses of CEUS in the liver and kidney.

CONTRAST AGENTS

US contrast agents, commonly referred to as microbubbles, are composed of tiny bubbles of a perfluorocarbon or nitrogen gas contained within a stabilizing shell made from a lipid or protein. The composition of the shell determines how long the agent remains in the circulation. These microbubbles avoid filtration in the lungs and heart because of their equivalent size to red blood cells. The highly echogenic microbubble gas core provides useful contrast from the background tissue.

LIVER

In the evaluation of focal liver masses, magnetic resonance imaging (MRI) signal, computed tomography (CT) attenuation, and echogenicity on conventional US taken alone are often nonspecific imaging characteristics. The distinguishing feature...
of many lesions remains their vascularity and hemodynamic parameters. CEUS has become increasingly accepted as an equally effective and sustainable alternative to multiphase CEMR or CECT while saving cost and avoiding potential nephrotoxicity and harmful radiation to the patient. The established recommended indications for CEUS in the liver include evaluation of lesions or a suspected lesion in a patient with a history of chronic liver disease or known malignancy, workup for incidental findings on routine US or inconclusive MRI/CT or biopsy results, and characterization of portal vein thrombosis (Box 1).

**Hemangioma**

Cavernous hemangiomas are the most common benign tumors of the liver, occurring in approximately 4% of the population. Most hemangiomas are small and asymptomatic, usually discovered incidentally, although large lesions can occasionally present with acute abdominal pain caused by hemorrhage or thrombosis.

The typical appearance of a hemangioma on conventional US is a well-circumscribed or lobulated mass that is homogeneously hyperechoic. This lesion may have posterior acoustic enhancement. Of note, echogenicity is relative to the background tissue; thus, in the setting of hepatic steatosis, a hemangioma may appear hypoechoic or isoechoic relative to the echogenic fatty liver parenchyma.1 Of note, echogenicity is relative to the background tissue; thus, in the setting of hepatic steatosis, a hemangioma may appear hypoechoic or isoechoic relative to the echogenic fatty liver parenchyma.2 On CEUS, hemangiomas will typically have peripheral globular-nodular enhancement in the arterial phase. This is followed by centripetal progression of the enhancement until the entire lesion is enhancing and hyperechoic compared with the background liver parenchyma (Fig. 1). This enhancement usually persists in the portal venous phase with equal or greater enhancement than the background liver tissue.1 Small flash hemangiomas typically show diffuse and immediate arterial enhancement, which will often persist on the later phases.3

**Focal Nodular Hyperplasia**

Focal nodular hyperplasia (FNH) is the second most common benign liver mass and histologically represents developmental hyperplastic lesions containing a mix of abnormally arranged nonneoplastic hepatocytes, Kupffer cells, biliary ducts, and components of portal triads.4 Similar to hemangioma, FNH is usually discovered incidentally and is asymptomatic.

Sonographically, FNH can be subtle and difficult to detect in large part because histologically FNH is essentially hyperplastic normal liver tissue. When seen, FNH typically becomes apparent because of displacement of the normal surrounding vasculature and subtle contour abnormalities rather than an inherent difference in the echogenicity of the lesion compared with the surrounding liver parenchyma. The linear or stellar central scar seen in FNH is usually hypoechoic although occasionally hyperechoic.5 After contrast administration, FNHs will enhance (predominately within the central scar) and a large feeding vessel can often be seen on the arterial phase. This is followed by a centrifugal filling direction in the portal venous phase (in contrast to the centripetal filling seen in hemangiomas). Enhancement is sustained in the portal venous phase with equal or greater enhancement than the background liver tissue (Fig. 2). Occasionally, an unenhanced scar may be seen in both the arterial and portal venous phases.

**Adenoma**

Adenomas consist of normal to slightly atypical hepatocytes that occasionally contain bile ducts, Kupffer cells, calcification, and fat, thus, making their appearance highly variable on all imaging modalities. They are associated with women using oral contraceptives and, although typically asymptomatic, can present with severe pain in the setting of hemorrhage or infarction. The risk of rupture, hemothorax, and shock makes the management of these lesions more complicated than, for instance, hemangiomas. Thus, small adenomas are often managed conservatively, whereas large or growing adenomas are considered for resection.

The gray-scale US appearance of adenomas is extremely variable. With regard to their vascularity, adenomas may have well-defined intraluminal blood vessels (usually venous) and can, therefore, be difficult to distinguish from FNH based on their nonspecific conventional US and Doppler appearance.6 CEUS can aid in distinguishing between adenomas and FNHs. Adenomas will typically be hypervascular on the arterial phase just as FNH,
although usually to a lesser extent. The distinguishing factor, however, is the centripetal filling pattern seen on the subsequent phases with adenomas. This is in contrast to the centrifugal filling pattern of FNH.

Fig. 1. A 42-year-old man with a hepatic hemangioma. Three sequential CEUS images of a liver mass (arrows). (A) Early peripheral nodular enhancement. (B) Progressive centripetal contrast enhancement. (C) Near-complete enhancement of the hemangioma.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) commonly occurs in the setting of chronic liver disease and cirrhosis (alcoholic and viral) and is the most common primary visceral malignancy in the world, accounting for 80% to 90% of all primary liver malignancies. Of note, the liver does not necessarily have to have a cirrhotic appearance on imaging to be predisposed to increased risk of HCC, as in the setting of hepatitis B virus. Although usually solitary tumors, HCCs may be multifocal or infiltrative in nature.

Sonographically, HCC is variable in appearance. When larger in size, HCCs often have mixed echogenicity because of tumor necrosis and hypervascularity, whereas smaller lesions are usually solid and appear hypoechoic. HCCs may also be hyperechoic if fatty metamorphosis or sinusoidal dilation is present. Small hyperechoic HCCs can, therefore, simulate hemangiomas, hypervascular metastases, or lipomas. On color Doppler, HCCs usually show hypervascularity and tumor shunting.
On CEUS, HCCs show classic and characteristic arterial enhancement owing to arterial neo-vascularity. This is followed by decreased portal venous flow (washout), findings similar to those seen on 4-phase CEMRIs and CECTs (Fig. 4). Of note, several atypical variations of enhancement patterns of HCCs have been described, including arterial-phase hypovascularity with delayed or no enhancement and arterial enhancement without washout.8

HCC tumor thrombus within the portal and hepatic veins can be diagnosed with CEUS. The enhancement patterns should be similar to those of the tumor from which it originated and will have a different appearance than a normally enhancing vessel (ie, an arterial tumor blush rather than discrete vessels), secondary to malignant neovascularity (Fig. 5).9 A marked wash out in the portal and late phases may occur in metastatic portal vein thrombosis. A bland thrombus, however, will show no arterial enhancement (Fig. 6).

Fibrolamellar HCC is a histologic subtype of HCC often seen in younger individuals and is not associated with chronic liver disease. These tumors are usually solitary and well encapsulated. Similar to HCC, fibrolamellar HCC can have a variable sonographic appearance. Common findings include punctate calcifications and a hyperechoic central scar. On CEUS, fibrolamellar HCC will
typically show heterogeneous arterial enhancement secondary to necrosis with washout during the portal venous phase.¹⁰

**Cholangiocarcinoma**

Cholangiocarcinomas are the second most common primary hepatic tumor after HCC. Histologically, cholangiocarcinomas are usually adenocarcinomas arising from the bile duct epithelium and are highly malignant, occurring primarily in the sixth and seventh decades of life. They can arise peripherally or centrally in the liver, with the hilar variant known as a Klatskin tumor. Given their biliary origin, both variants may cause more proximal biliary ductal dilation secondary to luminal obstruction.

Sonographically, cholangiocarcinomas usually appear as mixed echogenicity masses with associated biliary ductal dilatation. On CEUS, most cholangiocarcinomas show peripheral irregular rimlike enhancement with heterogeneous central hypoenhancement during the arterial phase followed by characteristic wash out on portal and late phases.¹⁰

**Cystadenoma/Cystadenocarcinoma**

Biliary cystadenomas and cystadenocarcinomas are rare cystic tumors that likely arise from ectopic

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**Fig. 3.** A 63-year-old woman with a hepatic adenoma. Two sequential CEUS images of a liver lesion (arrows). (A) Hypervascular early central enhancement on the arterial phase, typically less intense than FNH. (B) Centripetal filling pattern seen on more delayed phase.

**Fig. 4.** A 61-year-old woman with HCC. Two sequential CEUS images. (A) Intense early arterial enhancement (arrow). (B) Contrast washout of HCC (arrow) on later phase (approximately 4-minute delay).
nests of primitive biliary tissue. Unfortunately, on imaging, benign cystadenomas cannot be reliably differentiated from malignant cystadenocarcinomas. Sonographically, they appear as large, well-defined multiloculated anechoic masses with highly echogenic septa. Nodular components may be present. Because they are largely avascular, minimal enhancement is seen with CEUS; however, abnormal enhancing vessels may be seen peripherally or within the septa.11

Metastasis

Metastatic lesions to the liver most commonly originate from primary tumors of the gallbladder, colon, stomach, pancreas, breast, and lung. Metastases are the most common liver tumor in the United States, up to 20 times more common than HCC.5

Patients with metastatic liver disease usually present with multifocal disease and less commonly with a solitary lesion or as an infiltrative process. Sonographically, they may be hypoechoic, isoechoic, or hyperechoic depending on vascularity, hemorrhage, and mucin content. The so-called target appearance of a hepatic parenchymal mass with a hypoechoic halo is a common sonographic pattern for liver metastases. Many metastatic lesions are similar in echogenicity to the background liver, making their detection...
difficult or impossible. CEUS can help combat this problem by improving the conspicuity of metastasis. After contrast administration, the appearance of metastatic disease on the arterial phase is variable depending on the vascularity of the lesion. During the arterial phase, hypovascular metastases (ie, gastrointestinal tumors, ovarian, pancreatic) are hypoenhancing, whereas hypervascular metastases (ie, neuroendocrine tumors, melanoma, renal) are hyperenhancing. The portal venous phase is often more useful in detecting and characterizing metastases, as they almost always washout (Fig. 7). When detected initially on US, the diagnosis can be confirmed with biopsy.\textsuperscript{12}

**Infection**

Hepatic abscesses (whether pyogenic, parasitic, or fungal in etiology) may have a rimlike enhancement pattern, which may persist or fade to background on the delayed phases. If the abscess center is liquefied, it will not enhance and will appear as a persistent hypoechoic defect on delayed phases. Occasionally, enhancing septae may be seen within the central defect.\textsuperscript{3}

**Postprocedure Monitoring (Local Ablative and Transarterial Chemoembolization Treatment)**

Percutaneous ablation and trans-arterial chemoembolization have become viable alternatives for the management of selected patients with liver malignancies. It is essential to follow up with these treated lesions to exclude residual or nontreated disease, and to assess for recurrence and CEUS is a useful modality with the ultimate goal being complete devascularization of the mass. Live scanning through the entire treated lesion is necessary to detect focal areas of persistently enhancing tissue within or surrounding the treated lesion. For hypovascular malignancies, the completeness of treatment can be assessed by comparing the pretreatment lesion appearance with that of the posttreatment necrotic region (Fig. 8). For this reason, obtaining a pretreatment CEUS of the lesion to be ablated or embolized is of high utility. Of note, normal peripheral uniform enhancement can be seen in the postablative setting for up to 30 days, and careful consideration should be made before misinterpreting this hyperemic halo as residual disease. A treated lesion with nodular or irregular enhancement should raise the suspicion for residual disease (Fig. 9). If residual malignancy is suspected, the patient may be referred for retreatment of the tumor.\textsuperscript{3}

**RENAL**

The use of CEUS in evaluating renal pathology is maturing and evolving. Current uses include evaluation of the general vascular perfusion of the kidney and its most publicized use—the evaluation of focal renal masses (Box 2).\textsuperscript{1,13}

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**Fig. 7.** A 66-year-old woman with RCC metastasis to the liver. (A) Arterial phase contrast-enhanced image shows rapid enhancement (11 seconds) of a small liver mass (arrow). (B) Rapid early washout (arrow) is also present (19 seconds).
Normal Appearance

In the arterial phase, the renal cortex enhances rapidly. This phase is followed by successive perfusion of the medulla and then a more homogeneous appearance corresponding to the nephrographic phase as seen on CECT or CEMRI. As contrast is reduced within the circulation, enhancement gradually fades. Although there is thought to be a fair amount of potential in the evaluation of renal perfusion and blood flow quantification, this has not yet translated into routine clinical use (Fig. 10).\textsuperscript{14,15}

Renal Cell Carcinoma

Renal cell carcinomas (RCCs) are the eighth most common malignancy affecting adults and the most common malignant renal neoplasm. On conventional US, these masses are typically heterogeneously hypoechoic or isoechoic, although small masses (<2 cm) may be echogenic. On CEUS, RCCs typically are heterogeneously hypervascular with early washout on the delayed phase. A pseudocapsule may be present (Fig. 11).\textsuperscript{16}

Complex Renal Cysts

Complex cystic masses have variable malignant potential depending on the existence of certain

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**Box 2**

Uses of contrast US in the kidney

1. Characterization of renal masses
   a. Evaluation and characterization of renal pseudotumors versus true mass lesions
   b. Characterization of complex mass lesions
   c. Characterization of renal cysts
2. Renal ischemia and perfusion
3. Abdominal/renal trauma
4. Guidance of renal biopsy and ablative procedures
characteristics such as septations and wall thickness, the presence or absence of mural nodules, and septal enhancement. The role of CEUS in delineating these features has been studied with good results. CEUS can also be used to classify cysts through Bosniak grading. The presence of contrast-enhanced septations and nodular protuberances can help differentiate a benign cyst from an indeterminate or neoplastic cyst (Fig. 12).

**Angiomyolipoma**

Angiomyolipomas (AMls) are benign mesenchymal tumors of the kidney that are usually asymptomatic, but larger (>4 cm) lesions can hemorrhage. On conventional US, AMLs are commonly hyperechoic. On CEUS, AMLs tends to enhance peripherally and enhance less than the normal cortex centrally.

**Oncocytoma**

Oncocytoma is the most common benign solid renal tumor but unfortunately, it shares many of the imaging features also found in RCC. Conventional US may show a well-defined, homogeneous, and hyperechoic to isoechoic solid mass, with or without an echogenic central scar. CEUS features of oncocytoma include early enhancement, enhancement greater than adjacent cortex and rapid washout (Fig. 13). The well described avascular scar depicted on CT and MR has also been reported.

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**Fig. 10.** Appearance of renal cortex and medulla after ultrasound contrast injection. (A) Early arterial phase after contrast injection: normal renal cortex enhances early with renal pyramids well seen as relative areas hypoperfusion at this stage. (B) Nephrographic phase equivalent: there is a more homogenous appearance to the entire kidney. (C) Late phase: appearance of the kidney is similar to normal gray-scale US images. (D) Gray-scale image of normal kidney.
**Fig. 11.** A 65-year-old woman with a left-sided renal mass. (A) Gray-scale image shows a solid left renal mass (arrow). (B) Early phase CEUS image shows very early enhancement centrally (arrow). Surgical pathology showed RCC.

**Fig. 12.** A 56-year-old man with a complex renal cyst. (A) Gray-scale imaging shows a nodular thickened complex septation along the margin of the larger cyst (arrow). (B) After contrast injection, there is marked enhancement of the septation (arrow). This classifies the cyst as a Bosniak III lesion. On resection, this was a cystic clear cell renal carcinoma.
A renal pseudotumor is a mass that simulates a tumor on imaging but is composed of nonneoplastic tissue. CEUS can aid in differentiating a true mass from a pseudotumor. Examples include a congenital hypertrophied column of Bertin and a postprocedural surgical bed mass as those seen in patients undergoing minimally invasive treatment of renal tumors (ie, laparoscopic/robotic-assisted nephron-sparing surgery, cryoablation, and radiofrequency ablation). There is an established role of CEUS in the evaluation of renal masses during and after minimally invasive treatments to monitor completeness of therapy and for the detection of disease recurrence. Specifically, postoperative renal pseudotumors should not have any internal enhancement, as they often represent surgical gelatin sponge material or hematoma and usually resolve or decrease in size over time (Fig. 14).²⁰⁻²²

**Metastasis**

Metastasis to the kidney is uncommon. The main diagnostic dilemma is to distinguish a renal metastasis from a primary renal tumor. Renal metastases do not have a characteristic enhancement pattern on CEUS but tend to be hypovascular compared with normal cortical enhancement (Fig. 15).

**Ischemia/Infarction**

Renal ischemia/infarction results from reduced or a complete lack of perfusion to the kidney. Underlying etiologies include thromboembolism (most common), aortic or renal artery dissection, vasculitis, and iatrogenic. CEUS aids in evaluating the presence and extent of renal parenchymal ischemia and, therefore, can be used in the evaluation of suspected infarction. Renal infarcts will appear as wedge-shaped areas of nonperfusion.
In addition, CEUS can help detect a nonperfused or hypoperfused organ such as a failing transplanted kidney.\textsuperscript{23,24}

**Infection**

An abnormal finding on conventional US is seen in only around 20\% of patients with bacterial pyelonephritis. When positive findings of pyelonephritis are discovered on sonography, they may include renal enlargement, hydronephrosis, increased renal cortical echogenicity, and abscess formation. Gas identified in the renal parenchyma aids in diagnosing emphysematous pyelonephritis. CEUS can assist in differentiating focal pyelonephritis from mass lesions and aids in delineating abscesses, either parenchymal or perinephric (Fig. 16).\textsuperscript{23}

**Fig. 14.** A 60-year-old man after resection of a left RCC. (A) Postoperative gray-scale US shows a complex septated mass (arrow) measuring 4.6 cm within the surgical bed. Differential of tumor recurrence versus postoperative pseudotumor was given. (B) CEUS of the mass (arrow) shows no enhancement, findings consistent with benign pseudotumor.

**Fig. 15.** A 78-year-old man with metastatic melanoma to the kidney. (A) CEUS image shows a poorly defined relatively hypovascular focal lesion (arrow). Incidental note is made of a Bosniak I simple cyst (arrowhead). (B) Corresponding gray-scale images unable to reliably identify the focal lesion.
CEUS is a safe and effective imaging technique with a growing number of clinical applications. Targeted CEUS can greatly aid in the characterization and diagnosis of perfusion defects and focal lesions of several visceral organs, including the liver and kidney.

REFERENCES