Successful Integration of Contrast-enhanced US into Routine Abdominal Imaging

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Contrast material–enhanced US is recognized increasingly as a useful tool in a wide variety of hepatic and nonhepatic applications. The modality recently was approved for limited use for liver indications in adult and pediatric patients in the United States. Contrast-enhanced US uses microbubbles of gas injected intravenously as a contrast agent to demonstrate blood flow and tissue perfusion. The growing worldwide application of contrast-enhanced US in multiple organ systems is due largely to its advantages, including high contrast resolution (sensitivity to the contrast agent), real-time imaging, lack of nephrotoxicity, the purely intravascular property of microbubble contrast agents that allows the use of disruption-replenishment techniques, and repeatability during the same examination. Through illustrative cases, common useful clinical scenarios are discussed, including characterization of liver and renal masses, especially indeterminate lesions at CT or MRI; differentiation of neoplastic cysts from nonneoplastic cysts in various organs; differentiation of tumor thrombus from bland thrombus; and assessment after a renal transplant or local ablative therapy. Common applications in the biliary system, pancreas, spleen, and vasculature also are introduced. Successful routine use of contrast-enhanced US requires an efficient setup and workflow and a thorough understanding of appropriate clinical indications and its advantages that provide added value after CT and MRI. This article familiarizes radiologists with common abdominal applications of contrast-enhanced US and guides them to implement contrast-enhanced US successfully in their clinical practice.

Introduction

Since its introduction to clinical practice in the late 1990s, although only recently approved for liver application in the United States in 2016, contrast material–enhanced US has been added to the toolbox of diagnostic imaging around the world. Chief among the reasons for its increasing global use are its powerful performance characteristics when used for appropriate indications, applicability and practicality in busy clinical practices, and relatively low cost. Furthermore, it has the inherent benefits of US, which are real-time imaging, portability, and the relatively low cost of equipment and overhead. In critically ill or agitated patients, when there is a substantial language barrier, or when there is no access to CT or MRI, US is often the only viable cross-sectional imaging option, and contrast-enhanced US improves diagnostic ability when used with other modalities. Conversely, contrast-enhanced US may share the limitations of regular US, such as operator dependency, and therefore requires substantial hands-on training in addition to interpretative skills. In light of the recent approval of use of microbubble contrast material in the United States,
it is timely and essential for radiologists to have a systematic overview of contrast-enhanced US to guide its implementation into routine practice.

**Technical Essentials**

Contrast-enhanced US is performed with US imaging equipment with contrast material–specific modes, which allow imaging of nonlinear signals from microbubbles. A low mechanical index of 0.05–0.30 is used to minimize disruption of microbubbles. Currently, sulfur hexafluoride lipid type A microspheres (Lumason; Bracco Diagnostics, Monroe Township, NJ) and perflutren lipid microspheres (Definity; Lantheus Medical Imaging, North Billerica, Mass) are two of the most commonly used microbubble contrast agents. Bolus injection of the contrast agent (typical dose, 2.4 mL of Lumason or 0.2 mL of Definity) is immediately followed by a 5–10-mL normal saline solution flush. A dual screen simultaneously showing a contrast-only display and a B-mode display side by side is helpful to keep the liver lesion in the imaging plane. Imaging is performed continuously from the contrast material arrival on the screen until peak arterial phase enhancement of the target lesion or until 60 seconds after contrast material injection. After 60 seconds, imaging can be performed intermittently (typically every 30–60 seconds) until 4–6 minutes after injection.

**Why Use Contrast-enhanced US When CT and MRI Are Readily Available?**

In a typical clinical practice, contrast-enhanced US is useful in three broad categories of situations: (a) for characterization of indeterminate lesions detected at baseline US, (b) for characterization of indeterminate lesions found with other imaging modalities such as CT or MRI, and (c) when intravenous contrast material is necessary but iodine and/or gadolinium-based contrast agents are contraindicated, mostly in patients with renal failure.

Most contrast microbubbles are inert gas coated with lipid for stabilization. Adverse reactions are rare and mostly mild. The rate of serious adverse events in two large studies with a combined total of 103,571 injections was one in 10,000 patients, with no deaths. No renal excretion or toxicity is associated with contrast-enhanced US agents; therefore, no renal function test is needed.

The real-time nature of contrast-enhanced US and its high contrast resolution allow the modality to show arterial enhancement more consistently than does CT or MRI. The purely intravascular nature of contrast-enhanced US also allows for better determination of washout.

The key feature to differentiate malignant from benign lesions is washout (negative enhancement compared with the parenchyma). Because of its purely intravascular contrast, contrast-enhanced US shows the washout feature of malignancy more consistently than does CT or MRI, even in highly permeable tumors. Therefore, sustained enhancement on contrast-enhanced US images strongly suggests a benign lesion with no risk for HCC.

The most common renal indication for contrast-enhanced US is for differentiation of neoplastic from nonneoplastic complex cysts. Owing to its high sensitivity for detection of vascularity, contrast-enhanced US is a simple and useful tool to confirm the vascularity of a neoplastic cyst or to exclude malignancy with high confidence in the absence of vascularity in a complex-appearing cyst.
Contrast-enhanced US more consistently shows washout of contrast agent (negative enhancement relative to the surrounding parenchyma) (Fig 2). Contrast-enhanced US allows for repeated visualization of vascular patterns. The ability to clear the contrast agent immediately from the area of interest allows for use of the disruption-replenishment technique. US microbubbles are routinely visualized by using a low mechanical index setting to prevent their destruction by the sound waves. By

are another source of diminished effectiveness of CT and MRI in real-world applications.

The purely intravascular property of microbubble contrast agents provides unique contrast agent dynamics (9). Almost all CT and MRI contrast agents are smaller molecules that start to exit the intravascular space immediately after injection. In the equilibrium phase, most of the injected contrast material lies within the large extracellular fluid space, whereas with contrast-enhanced US, the microbubbles do not leave the vascular space because of their much larger size. When the vasculature in malignant tissue has increased permeability, CT and MRI contrast agents may leak into the tumor interstitium, causing prolonged or progressive enhancement, which can obscure washout. Contrast-enhanced US more consistently shows washout of contrast agent (negative enhancement relative to the surrounding parenchyma) (Fig 2).

Contrast-enhanced US allows for repeated visualization of vascular patterns. The ability to clear the contrast agent immediately from the area of interest allows for use of the disruption-replenishment technique. US microbubbles are routinely visualized by using a low mechanical index setting to prevent their destruction by the sound waves. By
briefly turning up the mechanical index to usual gray-scale levels, all microbubbles can be disrupted quickly and cleared in the insonated field.

The replenishment of the contrast agent can then be imaged dynamically in the field by using a low mechanical index setting. This allows repeated demonstration of a detailed vascular pattern and its quantification with a single injection (Movie 2). In the characterization of hypervascular lesions with a rapidly changing early arterial phase, repeating the sequence once is usually sufficient. The repeatability of contrast-enhanced US allows for multiple injections, and hence multiple examinations, during the same study. The half-life of most microbubbles is brief and the contrast agent is mostly cleared from the intravascular space in a few minutes (10). Therefore, multiple lesions or the same lesion can be studied during the same examination.

Safety Profile and Contraindications
Most contrast microbubbles are inert gas coated with lipid for stabilization. Adverse reactions are rare and mostly mild. The rate of serious adverse events in two large studies (11, 12) with a combined total of 101 571 injections was one in 10 000 patients, with no deaths. No renal excretion or toxicity is associated with contrast-enhanced US agents (13); therefore, no renal function test is needed. The commonly used contrast agents for contrast-enhanced US, such as perflutren lipid microspheres and sulfur hexafluoride microbubbles, are classified as risk category B for pregnancy, given the lack of studies in pregnant women.

The only current contraindication for contrast-enhanced US is a history of hypersensitivity reactions to the microsphere components or to any of the inactive ingredients in the US contrast agent. A study (14) of off-label use of contrast material in the pediatric population also showed relatively good safety, with only a 2% rate of adverse reactions such as altered taste, headache, and nausea, and only one in 500 patients showed anaphylactic shock related to contrast agent administration. Currently, the U.S. Food and Drug Administration–approved abdominal indications for contrast-enhanced US include characterization of focal liver lesions in both adult and pediatric patients and evaluation of vesicoureteral reflux in the pediatric population.

Limitations of Contrast-enhanced US
Different imaging modalities may provide different information and are not interchangeable; therefore, they are complementary to and not competitive with each other. The application of contrast-enhanced US for specific indications is the key to its successful integration with CT and MRI; a multimodality approach is the most effective for accurate diagnosis.
Contrast-enhanced US shares some common limitations with gray-scale US. The upper right subdiaphragmatic regions of the liver cannot be visualized in some patients through any acoustic window. If a nodule cannot be seen with gray-scale US because of its location, contrast-enhanced US will not be useful. This may be a real limitation in some patients with advanced cirrhosis and a shrunken liver in an upper subdiaphragmatic location. There is also a limit to how far ultrasound waves can penetrate at contrast-enhanced US. Nodules located deeper than 10 cm from the probe surface because of excess subcutaneous or hepatic fat are rarely well studied with contrast-enhanced US because of sound beam attenuation.

Assessment of washout in a severely fatty liver is a substantial challenge not only at CT and MRI but also at contrast-enhanced US. The highly echogenic background liver parenchyma may result in a false perception of washout in the delayed phase, especially when the nodule is markedly hypoechoic. CT tends to obscure the washout in a severely fatty liver because of the background low attenuation of the liver parenchyma.

Clinical Applications in Abdominal Imaging
Contrast-enhanced US may be used for a variety of hepatic and nonhepatic indications. Common clinically useful indications of contrast-enhanced US in nonhepatic organ systems are summarized in Table 1.

Contrast-enhanced US of the Liver
The liver is the most common organ in the abdomen to be examined with contrast-enhanced US (15–18). Because of its dual blood supply, contrast material dynamics, particularly arterial enhancement and washout, are critical in the assessment of hepatic lesions. The real-time nature of contrast-enhanced US and its high contrast resolution allow the modality to show arterial enhancement more consistently than does CT or MRI. The purely intravascular nature of contrast-enhanced US also allows for better determination of washout. The typical enhancement patterns for common liver focal lesions are illustrated in Figure 3 (19). The common clinical scenarios in which contrast-enhanced US can be applied in patients at high risk and at no risk for HCC are summarized in Table 2, and a brief overview of the most common useful indications is included. Further detailed discussion of each indication is beyond the scope of this article and can be found in the literature (20,21).

Benign versus Malignant Lesions
The key feature to differentiate malignant from benign lesions is washout (negative enhancement compared with the parenchyma). Because of its purely intravascular contrast, contrast-enhanced US shows the washout feature of malignancy more consistently than does CT or MRI, even in highly permeable tumors. Therefore, sustained enhancement on contrast-enhanced US images strongly suggests a benign lesion with no risk for HCC. Dynamic enhancement patterns of liver lesions are mostly concordant among contrast-enhanced US, CT, and MRI. However, infrequent discordant cases usually are seen in patients with cholangiocarcinoma, desmoplastic metastasis, or lymphoma, with sustained enhancement on CT or MR images (9). In such cases, contrast-enhanced US can lead to the correct diagnosis of malignancy by demonstrating washout (Fig 4).

Table 1: Common Indications for Application of Contrast-enhanced US in Nonhepatic Organ Systems

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Common Indications</th>
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</thead>
<tbody>
<tr>
<td>Renal and urinary tract</td>
<td>To distinguish neoplastic from nonneoplastic cysts</td>
</tr>
<tr>
<td></td>
<td>To identify a small indeterminate solid renal mass</td>
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<tr>
<td></td>
<td>To evaluate impaired graft function in a patient after renal transplant</td>
</tr>
<tr>
<td>Gallbladder and biliary system</td>
<td>To distinguish a gallbladder or intraductal biliary neoplasm from sludge</td>
</tr>
<tr>
<td>Pancreas</td>
<td>To verify an intraductal papillary mucinous neoplasm or cystic mass with inconclusive internal complexity</td>
</tr>
<tr>
<td>Vascular system</td>
<td>To evaluate an endoleak after endovascular aneurysm repair</td>
</tr>
<tr>
<td></td>
<td>To distinguish bland thrombosis from tumor thrombosis</td>
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</table>


HCC versus Non-HCC Malignancy

Because of its real-time capability, contrast-enhanced US can show arterial hypervascularity of varying duration in most malignant hepatic lesions, including tumors regarded as hypovascular on CT and MR images. Very early washout of metastases or cholangiocarcinoma in the arterial phase may explain their discordant arterial phase hypovascular appearance at CT and MRI (Fig 5). HCC has different washout features from those of non-HCC malignancies: The washout of non-HCC malignancies such as metastasis is rapid (30–50 seconds) and marked, whereas washout of HCC mostly occurs much later and is milder (22,23) (Fig 6). In a study (24) of 41 HCCs and 31 non-HCC malignancies, all metastases, cholangiocarcinomas, and lymphomas demonstrated rapid washout at 75 seconds after injection, 73% of which showed washout even earlier than 30 seconds. In a study of 97 HCCs, only 43% showed washout before 90 seconds, with the rest demonstrating washout at 91–300 seconds (48%) or no washout (9%) (23). This timing of washout is the key differential point between HCC and non-HCC malignancy (such as cholangiocarcinoma and metastasis) because both can demonstrate arterial hypervascularity at contrast-enhanced US. Such a distinctive difference in washout features between HCC and non-HCC malignancy is especially of great clinical value in patients at risk for HCC.

Characterization of Hypervascular Lesions

Contrast-enhanced US frequently is used to further characterize indeterminate hypervascular lesions seen on CT or MR images, such as flash-filling hemangiomas and FNH, because it can show a characteristic contrast material filling pattern in the early arterial phase owing to its real-time imaging with high temporal resolution (10–15 frames per second) (25). Even in flash-filling hemangiomas that are indeterminate at CT or MRI, contrast-enhanced US can show their characteristic initial peripheral nodular
enhancement with a progressive centripetal filling pattern.

Classic FNH manifests as a spoke-wheel vascular pattern or central stellate arteries, with centrifugal progression and sustained enhancement in the portal phase (Fig 3, Movie 2). Central scarring can be seen as a hypoechoic region during the portal venous phase. On the other hand, adenoma usually shows peritumoral arteries with centripetal or diffuse filling, progressing to homogeneous arterial enhancement (26). Differentiating FNH from adenoma is a common clinical dilemma because both often manifest as an indeterminate hypervascular mass in a young woman.

Contrast-enhanced US is a great problem solver because it allows the specific diagnosis of FNH to be made on the basis of a characteristic arterial vascular pattern. Repetitive demonstration of the enhancing profile by means of a disruption-replenishment technique can be helpful for accurate differential diagnosis, especially for a lesion with rapidly changing arterial vascularity (Movie 2). The sensitivity of contrast-enhanced US for diagnosis of FNH in hypervascular lesions during the arterial phase is approximately 90%, with a specificity of approximately 77% (26).

**Table 2: Common Clinical Scenarios for Use of Contrast-enhanced US in Patients at Risk and Not at Risk for HCC**

<table>
<thead>
<tr>
<th>Advantages of Contrast-enhanced US</th>
<th>In Patients Not at Risk for HCC</th>
<th>In Patients at Risk for HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitive depiction of arterial hypervascularity</td>
<td>To differentiate neoplastic cysts from benign complex cysts</td>
<td>To noninvasively diagnose indeterminate lesions seen at CT or MRI as HCC</td>
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<tr>
<td></td>
<td>To distinguish bland thrombosis from tumor thrombosis</td>
<td></td>
</tr>
<tr>
<td>Visualization of characteristic arterial phase filling pattern</td>
<td>To differentiate small indeterminate hyperenhancing lesions, such as hypervascular metastasis, FNH, and hemangioma</td>
<td>To distinguish a flash-filling hemangioma from a small HCC</td>
</tr>
<tr>
<td></td>
<td>To distinguish FNH from adenoma</td>
<td></td>
</tr>
<tr>
<td>Demonstration of rapid and marked washout</td>
<td>To differentiate benign from metastatic small indeterminate hypoattenuating lesions</td>
<td>To distinguish HCC from non-HCC malignancy</td>
</tr>
<tr>
<td>Nonnephrotoxicity</td>
<td>To characterize a focal lesion in severe renal failure</td>
<td>To characterize a focal lesion in severe renal failure</td>
</tr>
<tr>
<td>“One-stop” characterization of lesions seen at conventional US</td>
<td>Incidental lesion</td>
<td>Lesion seen at surveillance US</td>
</tr>
<tr>
<td></td>
<td>Immediate benign diagnosis to save further workup and relieve the patient’s anxiety</td>
<td>Immediate benign diagnosis so that the patient can continue routine surveillance</td>
</tr>
<tr>
<td></td>
<td>Immediate diagnosis of malignancy to prompt further treatment</td>
<td>No miscorrelation between modalities</td>
</tr>
<tr>
<td>Differentiation of a real nodule from a perfusion abnormality</td>
<td>NA</td>
<td>Clarification of indeterminate arterial phase enhancing foci at CT or MRI</td>
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</table>

Note.— FNH = focal nodular hyperplasia, NA = not applicable.

**Differentiation of Small Indeterminate Lesions Seen at CT and/or MRI**

Small hypoattenuating lesions detected at CT or MRI in oncology patients can present diagnostic challenges in differentiating malignant from benign lesions (27). Given their small size, these lesions are often considered indeterminate on the basis of the CT and MRI results. Contrast-enhanced US frequently helps to resolve these indeterminate small lesions seen at CT or MRI and allows confident diagnosis (28). Metastasis shows brief arterial phase hypervascularity followed by rapid marked washout (Fig 7, Movie 3). A benign lesion shows a typical enhancement pattern such as a slowly enhancing hemangioma (Fig 8) or a lesion with no vascularity or no washout. Owing to the consistent marked washout of metastasis, a portal venous phase liver sweep at maximal liver enhancement allows very sensitive detection of small additional metastases (Movies 4, 5).

For a small hyperattenuating lesion in a patient with a risk of hypervascular malignancy, a combination of high contrast resolution in the early arterial phase and the rapid marked washout of metastasis often enables differentiation of hypervascular metastasis from a benign hypervascular...
nodule such as a flash-filling hemangioma or FNH at contrast-enhanced US (Fig 9).

**Patients at High Risk for HCC**

Contrast-enhanced US has two important roles in the evaluation of liver nodules in patients at high risk for HCC. The first is in the evaluation of nodules detected at gray-scale surveillance US (29). The benefits of contrast-enhanced US in this setting include (a) “one-stop” assessment of false-positive results such as hemangiomas and (b) avoidance of miscorrelation of a nodule at surveillance and subsequent diagnostic imaging that may lead to diminished performance of subsequent workup imaging. Because shunts and pseudolesions are not visible at gray-scale surveillance US, contrast-enhanced US evaluation of detected nodules precludes pseudolesions and hence decreases the false-positive findings detected at CT or MRI (Fig 10) (20).

Arterial phase hypervascularity alone, even without washout, in a US-detected real nodule without hemangioma features is highly specific for HCC, whereas 70%–90% of small arterial phase enhancing foci without washout at CT or MRI are not HCCs (30). The specificity and sensitivity for diagnosing HCC in small nodules of 1–2 cm in a cirrhotic liver with contrast-enhanced US were found to be 87% and 100%, respectively (28).

The second role of contrast-enhanced US in patients at risk for HCC is for the evaluation of indeterminate nodules detected at CT and/or MRI and is, in fact, the most frequent indication for contrast-enhanced US in our institution. The reasons why contrast-enhanced US may add to already performed CT or MRI are the sensitive depiction of the arterial hypervascularity of HCC and the improved demonstration of early washout for non-HCC malignancies and late

![Figure 4](https://example.com/f4.png)

**Figure 4.** Incidental liver mass with a discordant washout pattern in a 23-year-old woman. (a, b) Axial gadolinium-enhanced MR images show hypoenhancement of a hepatic lesion (arrow) in the arterial phase (a), progressive enhancement with 1-, 2-, and 3-minute delays (not shown), and prolonged enhancement with a 5-minute delay (b). (c–e) Contrast-enhanced US images with 10-second (c), 16-second (d), and 3-minute (e) delays show brief early enhancement (c) and rapid washout of contrast material (d, e) in the liver mass (arrow), findings highly suggestive of malignancy. Biopsy results confirmed the diagnosis of Hodgkin lymphoma.
washout in some HCCs (21). The visualization of vascular filling patterns for benign hypervascular lesions such as flash-filling hemangiomas or FNH in a noncirrhotic liver is of high value.

Contrast-enhanced US after CT or MRI for evaluation of hepatic nodules in patients at risk for HCC is of definite incremental value. However, we do not advocate replacing CT and/or MRI evaluation with contrast-enhanced US but rather suggest using contrast-enhanced US as a problem-solving tool.

**Bland Thrombosis versus Tumor Thrombosis**

Portal venous thrombosis can be seen in various underlying abnormalities, such as cirrhosis, HCC, and other gastrointestinal malignancies, and even sometimes as the first sign of underlying HCC (31). Early accurate differentiation of tumor thrombosis from bland thrombus in patients with HCC is of paramount importance because tumor thrombosis is one of the most critical determinants of staging and treatment options and has a dismal prognosis if left untreated (31,32).

The strength of contrast-enhanced US is in real-time direct visualization of arterial neovascularity in the tumor thrombus in addition to morphologic ancillary features, which are easily distinguished from portal venous phase enhancement of a patent lumen and a persistently nonenhancing bland thrombus (33). Along with consistently high intrinsic sensitivity to contrast material, contrast-enhanced US has been shown in many studies (4,33–35) to provide high sensitivity for both detection and correct differentiation of a tumor thrombus from a bland thrombus. Contrast-enhanced US showed sensitivity of 88%–95% for

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**Figure 5.** Non-HCC malignancy in a 42-year-old man with chronic hepatitis B who was at risk for HCC. (a, b) Axial contrast-enhanced CT images show a hypointense indeterminate lesion (arrows) in the arterial (a) and 3-minute delay (b) phases. (c, d) Contrast-enhanced US images show hypervascularity of the lesion (arrows) at 16 seconds (c), with early marked washout at 26 seconds (d). These contrast-enhanced US findings are characteristic of a non-HCC malignancy. Final pathologic evaluation results confirmed the diagnosis of cholangiocarcinoma.
detection of tumor thrombosis, which is much higher than that with color Doppler and fine needle biopsy, at 22% and 76%, respectively (35).

A comparison study with CT showed superior performance of contrast-enhanced US in detection (100% detection rate, \( P < .0001 \)) and characterization (\( P = .0001 \)) of tumor thrombosis (4). More recently, Raza et al (33) reported 100% sensitivity, negative predictive value, 82%–92% specificity, and 97% positive predictive value with excellent interreader agreement for differentiation of a tumor from bland thrombosis at contrast-enhanced US (Figs 11, 12). At our institution, contrast-enhanced US serves as a final step to confirm or exclude tumor thrombosis when it is indeterminate at CT or MRI, especially in candidates for liver transplant.

**Postablation Follow-up**

CT and MRI are currently the standard modalities for comprehensive evaluation of the liver and abdomen. Detection of HCC recurrence after radiofrequency ablation (RFA) can be challenging because of the perfusion changes related to the ablation procedure. These perfusion abnormalities often are caused by arterioporal shunting and manifest as hypervascular areas, which could mimic or obscure residual or recurrent HCC (36–38). Contrast-enhanced US can assist in reliable detection of the hypervascularity and subsequent washout of contrast material, which allows for further clarification of lesions that are indeterminant at surveillance CT or MRI after ablation (37,38) (Fig 13).

At our institution, an inconclusive result after CT and MRI is the most common indication for contrast-enhanced US. A recent meta-analysis (39) of 933 post-RFA hepatic lesions in 772 patients showed a contrast-enhanced US–evaluated success rate of RFA for HCC of 91%, which was similar to that with CT or MRI. Increasing evidence also points to the comparable performance of contrast-enhanced US to that of CT and MRI for detection of recurrence at follow-up examination of patients after RFA (40,41).

Hypovascular recurrence may be difficult to assess with CT because of its similar hypoattenuation to that in the ablation zone. Most non-HCC malignancies, even those that are hypovascular at CT, demonstrate brief arterial vascularity and invariable fast washout at contrast-enhanced US; therefore, contrast-enhanced US provides great added value to resolving inconclusive recurrence or residual disease at CT in these hypovascular lesions after ablation.

Contrast-enhanced US also can assist in the pre-RFA localization of an invisible tumor target or an indistinguishable recurrence in the previously treated zone at baseline US. During the RFA procedure, contrast-enhanced US allows immediate detection of residual tumor and an increased completion rate, with higher cost-effectiveness. Detailed discussion about preprocedural and in-session application of contrast-enhanced US at RFA is beyond the scope of this review.

**Contrast-enhanced US of the Kidney**

**Complex Renal Cysts**

The most common renal indication for contrast-enhanced US is for differentiation of
neoplastic from nonneoplastic complex cysts. Owing to its high sensitivity for detection of vascularity, contrast-enhanced US is a simple and useful tool to confirm the vascularity of a neoplastic cyst or to exclude malignancy with high confidence in the absence of vascularity in a complex-appearing cyst (42,43) (Fig 14). A recent study (44) of 47 patients with Bosniak 2F or 3 complex cysts showed superior sensitivity and specificity with contrast-enhanced US for identification of malignancies when compared with MRI and CT (44). In multiple other studies (42,45,46), contrast-enhanced US showed accuracy at least comparable to that of CT. In a study (47) of 721 patients with indeterminate renal masses, contrast-enhanced US was found to have 100% sensitivity and 95% specificity for identification of malignancy. Contrast-enhanced US also was found to help identify septa and solid components in a cyst, with higher sensitivity and no significant increase in the rate of false-positive results (43) (Fig 15, Movie 6).

The advantages of high contrast sensitivity at contrast-enhanced US also apply to indeterminate lesions with questionable vascularity in various organs, including indeterminate complex cysts in the liver, pancreas, or any other sites and tumor versus sludge or clots in the gallbladder or biliary or urinary tracts.
Small Renal Mass

Of all solid renal masses smaller than 1 cm that are excised, 46% are pathologically proven to be benign (48). It can be challenging to differentiate benign from malignant small incidental renal lesions reliably with CT and MRI. The integration of contrast-enhanced US could be of added benefit in these small indeterminate renal masses. In a prospective study (49) of 94 solid renal masses (<4 cm) in which lipid-rich angio- myolipomas were excluded, two independent readers determined that arterial hypovascularity relative to the renal cortex was highly specific for malignancy (100% specificity) (Fig 16), with sensitivity of 31%–35%; 75% of these malignancies were papillary renal cell carcinomas.

Avoiding invasive biopsy for these patients with a hypovascular solid mass, who comprise one-third of patients with a malignant mass, is of clinical value, given the risk of complications and the possibility that a diagnosis of a small renal mass cannot be made on the basis of biopsy results. Hypervascularity can be seen in both benign masses, such as oncocytoma and lipid-poor angiomyolipomas, and malignant masses such as clear cell renal cell carcinoma.

In a study by Li et al (50), malignancies tended to show early washout. In their series of 91 solid renal lesions, 85% of malignant lesions showed hyperenhancement during the cortical phase and hypoenhancement in the late phase. In another study (51) of 84 renal cell carcinomas, 88% showed hyperenhancement in the cortical phase, and 73% of them showed hypoenhancement during the renal parenchymal phase.
In a recent review (52) of CT enhancement of renal masses smaller than 4 cm, 20.7% of renal cell carcinomas did not reach the 20-HU threshold for diagnosis of a solid mass in the corticomedullary phase, and 11.9% did not meet the threshold in the nephrographic phase. In a series of renal masses smaller than 4 cm, Atri et al (49) used contrast-enhanced US, and all renal cell carcinomas showed vascularity. Therefore, one of the indications for contrast-enhanced US for evaluation of a renal mass is when enhancement at CT does not reach the threshold to confirm a solid mass.

**Urinary Tract Tumor versus Clot**

The microbubble contrast material is not excreted by the kidneys; therefore, any enhancement of intravenously injected microbubble contrast material in the collecting system is a true vascular enhancing lesion. This property allows us to distinguish true tumors from clots or debris in the urinary collecting system more clearly and with more confidence than with CT or MRI. Along with the high sensitivity of US to microbubble contrast material, a small tumor focus obscured within the large clot can be detected, whereas no contrast enhancement in a urinary tract lesion reliably excludes a soft-tissue tumor such as a transitional cell carcinoma (Fig 17).

**Vascular Evaluation of a Posttransplant Kidney**

Contrast-enhanced US often provides an urgent diagnostic solution for patients after renal transplant, especially in those with impaired graft function, because of nonnephrotoxicity, easy repeatability, portability, and high sensitivity to microbubbles (53). In the absence of flow signal at conventional Doppler US, contrast-enhanced US can allow reliable differentiation of a true

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**Figure 9.** FHN in a 27-year-old woman with a history of a neuroendocrine tumor. (a) Axial nonenhanced MR image shows a mass (arrows) with moderate T2 hyperintensity. (b, c) Axial gadobenate dimeglumine–enhanced MR images show arterial phase hypervascularity (b) and a large area of central hypointensity with thin peripheral retention in the hepatobiliary phase with a 2-hour delay (c). The overall pattern is not entirely diagnostic of FHN, given the patient’s risk of hypervascular metastasis. (d–f) Sequential dynamic contrast-enhanced US images of the same hepatic lesion (short arrows) with 12- (d), 13- (e), and 15-second (f) delays show a central stellate artery (long arrow in d), with centrifugal progression of enhancement in only 15 seconds (f), which is characteristic for FHN.
infarcted transplant, with estimation of the extent from slow or low flow undetected at conventional Doppler US (54) (Fig 18, Movie 7).

**Post-RFA Surveillance**

Contrast-enhanced US also can be applied after ablation of kidney lesions, with the ablation zone showing a complete lack of contrast material enhancement. In patients with renal dysfunction or a transplanted kidney, and those with a low risk of recurrence, we use contrast-enhanced US as a surveillance modality after RFA because a survey of the entire kidney can be achieved with high confidence.

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**Figure 10.** True HCC nodule in a 68-year-old man with hepatitis B cirrhosis. (a, b) Axial CT images (b obtained at a different level than a) show numerous arterial phase hyperenhancing lesions (arrows; arrowheads in b), with no corresponding washout. MR images showed the same findings. (c) Baseline conventional US image shows that only one hyperenhancing lesion in segment 6 from the CT images (arrowheads in b) corresponds to a real nodule (arrows in c), and the rest of the foci are not seen. (d, e) Contrast-enhanced US images focused on the real nodule (arrows) show arterial phase hypervascularity (d) and mild washout at 2 minutes (e), which are typical findings of HCC. The rest of the innumerable arterial phase hyperenhancing foci seen at CT and MRI were not seen on contrast-enhanced US images. These were confirmed at surgery and follow-up imaging to be pseudolesions from arterioportal shunting.
Contrast-enhanced US of the Gallbladder, Biliary System, and Pancreas

Differentiation of a Neoplasm from Inflammation or Sludge

Chronic inflammation of the gallbladder can cause irregular thickening of the gallbladder wall that can mimic gallbladder cancer on images acquired with any imaging modality. Contrast-enhanced US can be helpful in the differentiation of chronic cholecystitis from gallbladder malignancy (55,56) (Fig 19). In a comparison study with conventional US, contrast-enhanced US showed superior sensitivity for diagnosis of gallbladder malignancy; wall disruption, hyperenhancement, and rapid washout are considered highly suspicious for gallbladder malignancy (56).

Sludge in the gallbladder can manifest as echogenic nonmobile masses and therefore can mimic gallbladder tumors. Because of its high contrast sensitivity and real-time nature, contrast-enhanced US helps in the reliable confirmation or exclusion of vascularity in the tissue, therefore allowing tumors to be differentiated from sludge or blood clots (Fig 20, Movie 8).

The sensitive and reliable detection of vascularity in a tumor also can apply to many other...
Figure 13. Recurrence of HCC in a 69-year-old man after RFA. A small hypoechoic lesion adjacent to the RFA zone was found at 16-month post-RFA US. (a) Axial arterial phase CT image and delayed phase images (not shown) did not show the suspected lesion because it was obscured by the overlying area of arterioporal shunting (long arrow), which was the expected location of recurrence. Short arrow = RFA zone. (b) Contrast-enhanced US image focused on the same region clearly shows arterial phase hypervascularity (black arrow) of the hypoechoic lesion and a wedge-shaped area of arterioporal shunting (c) surrounding the nonenhancing RFA zone (white arrow). (c, d) Oblique contrast-enhanced US images slightly cranial to b show the full extent of the hypoechoic lesion (arrow), with arterial phase hypervascularity (c) and washout with a 2-minute delay (d), which are findings diagnostic for HCC recurrence.

Figure 14. Complex renal cyst in a 68-year-old man. (a) US image shows a complex renal cyst (arrows) with echogenic mural nodules that was found incidentally. Doppler US showed no vascular flow. (b) Contrast-enhanced US image shows the lesion (arrows) to be completely avascular (the enhancing area is the renal parenchyma), which allowed for immediate diagnosis of a benign nonneoplastic complex cyst. The diagnosis was confirmed at a follow-up examination.
indicators in the biliary tract and pancreas (eg, a small incidental pancreatic tumor [Movie 9], an intraductal pancreatic mucinous neoplasm, or an intraductal biliary neoplasm with equivocal vascularity or inconclusive internal complexity at CT or MRI). Contrast-enhanced US is often used to further characterize focal pancreatic lesions detected with conventional US (57), and there is good evidence that contrast-enhanced US can allow reliable differentiation of cysts from cyst-like tumors in the pancreas (58–60).

**Contrast-enhanced US of the Spleen**

Splenic focal lesions are relatively rare and often are nonspecific and indeterminate at imaging. Biopsy should be performed only when absolutely necessary, given the high risk of bleeding. A meta-analysis (61) of 859 splenic biopsies showed a complication rate of 5.4%, with 20% of them being major complications related to hemorrhage. The most common and well-recognized application of contrast-enhanced US in the spleen is for further characterization of suspicious splenic lesions detected at conventional US (57), CT, or MRI (62).

Malignant splenic lesions such as lymphoma and metastases almost invariably show washout at contrast-enhanced US during the late phase, with hypoenhancement in 50% of lesions even during the arterial phase; whereas most benign lesions such as hemangiomas and hamartomas are hyper- or isovascular during the arterial phase and show sustained enhancement (Fig 21) (63–66). Therefore, contrast-enhanced US can help to avoid unnecessary invasive biopsy of those nonwashout lesions. Contrast-enhanced US also can be useful
in an acute trauma setting for sensitive detection or ruling out of splenic infarcts and lacerations (62), specifically in children and in patients with stable low-energy isolated trauma (62).

**Vascular Contrast-enhanced US**

Imaging follow-up after endovascular aneurysm repair for abdominal aortic aneurysm is essential to detect an endoleak, which, when found, can complicate the procedure in 26% of cases (67). Although CT angiography has been the most commonly used imaging modality for this purpose, results of recent studies (67–70) have shown comparable sensitivity and specificity between contrast-enhanced US and CT angiography for detection of endoleaks, at 90%–100%. Sensitive detection and accurate localization of endoleaks (Fig 22; Movies 10, 11), and nonnephrotoxicity make contrast-enhanced US an ideal modality for surveillance after endovascular aneurysm repair and especially valuable in patients with renal issues (Fig 23).

**How to Implement a Successful Contrast-enhanced US Program in Clinical Practice**

It is important to minimize extra time for radiologists and maximize efficiency per contrast-enhanced US examination in busy daily practice. At our institution, we delegate regular time slots for contrast-enhanced US and use a designated room with a US scanner and supplies readily available. All requests are prescreened by the radiologists who perform contrast-enhanced US to ensure proper indications and priorities. It is essential to have the right personnel to assist in contrast-enhanced US. We have several sonographers who are trained in intravenous cannulation and US contrast material injection and have essential knowledge of the modality. They perform baseline US before the radiologists arrive. We also try to ensure that one of them is available daily for unscheduled contrast-enhanced US studies needed for inpatient or emergency cases or when unexpected findings are noted at routine nonenhanced US.
Figure 19. Chronic cholecystitis in a 71-year-old woman who had no fever or right upper quadrant pain but was unwell for 2 months. (a) Axial CT image shows marked asymmetric thickening with heterogeneous enhancement of the gallbladder wall (arrows) during the arterial phase, a finding suspicious for gallbladder cancer. (b) US image shows heterogeneous internal echogenicity contiguous with the ill-defined hypoechoic area (arrows) in the adjacent liver through disruption of the thickened gallbladder wall. (c) Arterial phase contrast-enhanced US image shows a smooth mucosal outline with homogeneous wall enhancement; there is no vascularity from internal irregular echogenicity, in comparison with hyperemia in the adjacent liver (arrows) without portal phase washout (not shown). The findings at contrast-enhanced US are suggestive of cholecystitis with an adjacent hepatic inflammatory lesion, likely from previous intrahepatic rupture. Biopsy results showed chronic inflammation of the gallbladder.

Figure 20. Incidental gallbladder abnormality found at CT in a 76-year-old woman who presented with gastrointestinal bleeding and diabetic nephropathy. (a) Axial nonenhanced CT image shows a mildly distended gallbladder with internal heterogeneous attenuation (arrows), which could be sludge or a tumor. (b) US image shows the smooth outline of the gallbladder (short arrows), with a large heterogeneous internal echogenicity in addition to stones (long arrow), which could be sludge or a tumor. (c) Contrast-enhanced US image (see also Movie 8) shows a definite enhancing irregular intraluminal soft-tissue mass (arrows), which is consistent with gallbladder cancer. Surgical pathologic results revealed papillary adenocarcinoma of the gallbladder, predominantly intraluminal.

The immediate confirmation of benign incidental lesions seen at regular US is an invaluable contribution to best patient care because it relieves patient anxiety and helps to avoid unnecessary further workup. Immediately before the contrast-enhanced US examination, the radiologist reviews
Figure 21. Benign splenic lesion in a 35-year-old man with a history of leukemia who presented with vague abdominal pain. (a) Nonenhanced US image shows a large isoechogenic mass (arrows) in the spleen. (b, c) Same-day contrast-enhanced US images show homogeneous hyperenhancement of the splenic lesion (arrows) in the arterial phase (b) and persistent mild hyperenhancement with a 4-minute delay (c), findings that are suggestive of a benign lesion. Sulfur-colloid nuclear imaging showed splenic tissue in the lesion, in keeping with a benign splenic hamartoma.

...all relevant prior imaging, including CT, MRI, and baseline US images, to plan ahead and achieve optimal use of imaging time.

Informing both radiologists and clinicians about proper indications and safety is an essential component of successful integration of contrast-enhanced US. Training a radiologist already adept at US to use contrast-enhanced US does not take much time. For the liver, we suggest supervised training with 20–30 patients, and for other organs one or two additional supervised sessions should suffice.

It does take somewhat longer for technologists or assistants with no prior training to master intravenous cannulation. Hospitals and radiology departments usually have training programs for allied health professionals whose jobs require obtaining intravenous access, such as CT technologists and nurses. Such programs can be used to train staff in US departments who are delegated to assist with contrast-enhanced US.

Abdominal radiologists should understand when to recommend contrast-enhanced US for the best outcome in a multimodality approach. Likewise, clinicians need to know when to request contrast-enhanced US, and providing educational rounds or reference literature specifying the indications is useful. As always, close communication with practitioners to explain results, especially early on, helps with effective implementation.

Conclusion

Contrast-enhanced US offers advantages that provide added value to imaging practice in various organ systems and has an essential role in multimodality imaging. These advantages include extremely high sensitivity to the microbubble contrast agent, real-time imaging, the purely intravascular property of contrast agents, lack of nephrotoxicity, easy repeatability, portability, and relatively low cost.

It is important to note that contrast-enhanced US requires substantial hands-on training in addition to interpretative skills and that each imaging modality is complementary to rather than competitive with each other. Therefore,
Figure 22. Endoleak in a 79-year-old man after endovascular aortic repair of an abdominal aortic aneurysm. (a) Angiogram shows a leak (arrow) that appears to be contiguous with the right iliac limb. Balloon intervention was performed in the right iliac artery; however, a persistent leak at the same location was detected after balloon angiography. (b) Contrast-enhanced US image shows a small leak (arrow) contiguous with the left iliac limb (*). (Movie 10). Another contrast agent injection and an oblique view (Movie 11) showed the leak from the left iliac limb, jetting toward the right limb. The leak was successfully treated with balloon intervention to the left iliac artery.

Figure 23. Type II endoleak in an 80-year-old man with a high creatinine level after endovascular aortic repair. (a) Contrast-enhanced US image of the first transverse aortic sweep with an 11-second delay shows bilateral iliac arterial enhancement with no leak into the aneurysmal sac (arrows). (b) With a 30-second delay, a transverse sweep shows a small delayed leak (arrow). (c) Sagittal sweep with a 1-minute delay shows the delayed leak into the posterior aspect of the aneurysmal sac (arrow), likely from the lumbar artery, a finding consistent with a type II endoleak.

A thorough understanding of the appropriate indications with clinically relevant application of contrast-enhanced US is key to its successful integration into routine practice and maximization of its added value.

References


