

8-2018

## Advances in Modern Clinical Ultrasound

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### Recommended Citation

Gummadi, MD, Sriharsha; Eisenbrey, PhD, John R.; Li, MD, Jingzhi; Li, MD, Zhaojun; Forsberg, PhD, Flemming; Lyshchik, MD, Andrej; and Liu, MD, Ji-Bin, "Advances in Modern Clinical Ultrasound" (2018). *Department of Radiology Faculty Papers*. Paper 66.  
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# Advances in Modern Clinical Ultrasound

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Received June 1, 2018; revision requested September 1, 2018; revision received August 4; accepted August 6.

**Abstract:** Advances in modern clinical ultrasound include developments in ultrasound signal processing, imaging techniques and clinical applications. Improvements in ultrasound processing include contrast and high-fidelity ultrasound imaging to expand B-mode imaging and microvascular (or microluminal) discrimination. Similarly, volumetric sonography, automated or intelligent ultrasound, and fusion imaging developed from the innate limitations of planar ultrasound, including user-operator technical dependencies and complex anatomic spatial prerequisites. Additionally, ultrasound techniques and instrumentation have evolved towards expanding access amongst clinicians and patients. To that end, portability of ultrasound systems has become paramount. This has afforded growth into the point-of-care ultrasound and remote or tele-ultrasound arenas. In parallel, advanced applications of ultrasound imaging have arisen. These include high frequency superficial sonograms to diagnose dermatologic pathologies as well as various intra-cavitary or lesional interrogations by contrast-enhanced ultrasound. Properties such as real-time definition and ease-of-access have spurred procedural and interventional applications for vascular access. This narrative review provides an overview of these advances and potential future directions of ultrasound.

**Key words:** High resolution ultrasound; Point of care ultrasound; Contrast enhanced ultrasound

Advanced Ultrasound in Diagnosis and Therapy 2018;02:051–63

Major technologic developments in early ultrasound research came to a precipice in the 1950s with the clinical application of sonography [1]. The advent of commercially available real-time ultrasound by the 1960s reduced operator-dependency and increased interventional applications [1]. Rapid advances followed with domain expansion beyond obstetrics and cardiology to a wide range of fields including oncology and trauma [1].

This narrative review provides an overview of the momentum of clinical sonography in research and practice moving forward. Advances in ultrasound processing emerge at the forefront. A propensity towards field maturation has prompted developments in ultrasound technique and innovations in clinical application.

## Advances in ultrasound technology

Ultrasound imaging processing serves as the lead point for further advances in ultrasound. Major developments in depicting micro-perfusion and high-resolution sonography include contrast-enhanced ultrasound (CEUS), high-fidelity ultrasound and high frame rate imaging. Increasing morphological and interventional demands necessitates expansion into multi-dimensional and intelligent sonography. Together, fusion and multi-modality navigation represents a culmination of this development.

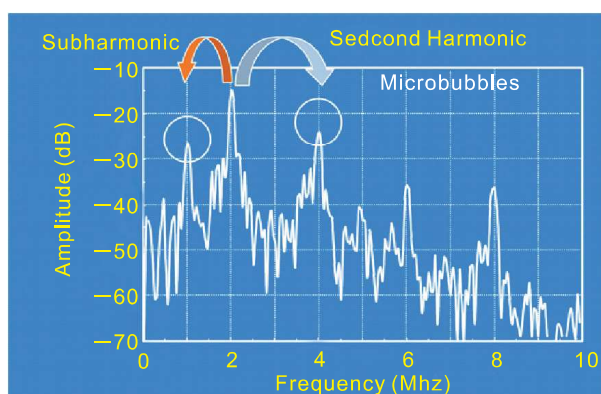
## Ultrasound contrast imaging processing

In CEUS, an ultrasound contrast agent (*i.e.*, billions of gas-filled, microbubbles) is administered (typically

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intravenously) and visualized on sonography. The insonation of ultrasound contrast agent results in non-linear scatter at the subharmonic ( $1/2 \times$  transmit frequency), harmonic, and superharmonic signal ( $n \times$  transmit frequency), as depicted in Fig. 1 [2]. Soft tissues typically display linear scatter instead. When paired with pulse inversion and other post-processing techniques, background tissue can be somewhat suppressed. This suppression can be further improved using nonlinear excitation pulse sequences and amplitude modulation [3].

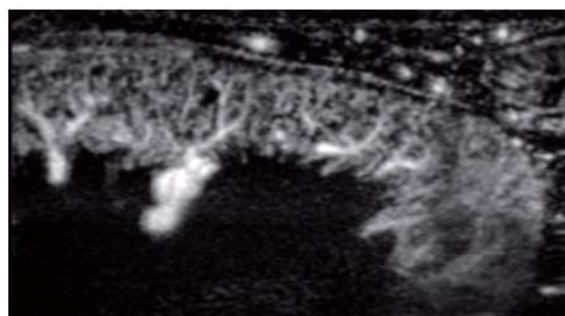


**Figure 1** Demonstration of the non-linear scatter of microbubbles into primarily the subharmonic ( $1/2 \times$  transmit frequency) and second harmonic ( $2 \times$  transmit frequency) signals with additional superharmonic ( $n \times$  transmit frequency) signals noted.

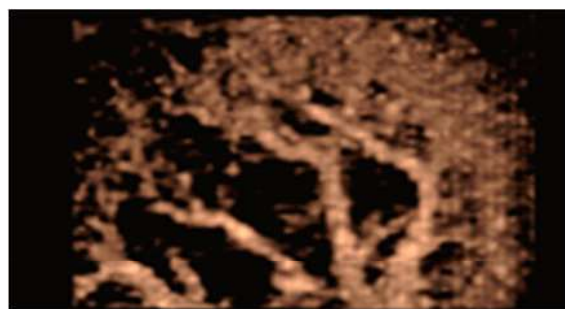
Early contrast agents included agitated saline and autologous blood, both of which resulted in the formation of compressible bubbles when infused at adequate rates [4]. First-generation commercial microbubble contrast agents utilize a stabilizing shell encapsulating a gas core of air [4]. However, owing to the high gas core solubility in blood, these agents could only maintain stability for a brief period of time. Second-generation commercial microbubble contrast agents utilized a variety of different outer shells (such as phospholipid, albumin, or surfactant) encapsulating a high density low blood solubility gas (such as sulfur hexafluoride or octafluoropropane) [4]. These agents maintain a longer period of stability in systemic circulation [4].

Modern microbubbles (in addition to first generation agents) are produced at standard sizes (between 1 to 10  $\mu\text{m}$ )—at or smaller than the size of circulating red blood cells [4]. Compared with iodinated contrast or gadolinium (used in computed tomography CT or magnetic resonance imaging MRT, respectively), ultrasound contrast agents administered intravascularly pool within the vessels with limited or no extravasation of contrast [4]. This property allows for greater vascular definition, improving their characterization of soft tissue and parenchymal tumors (Fig. 2 and Fig. 3) [5, 6]. Additionally, there are no concerns with renal toxicity or hepatotoxicity with these agents [5].

There are three ultrasound contrast agents approved by the Food and Drug Administration for use in the United States. Definity (Lantheus Medical Imaging, N. Billerica, MA) and Optison (GE Healthcare, Marlborough, MA) are approved for echocardiography; while Lumason (Bracco Diagnostics, Monroe Township, NJ) is approved for echocardiography, characterization of focal liver lesions, and evaluation of vesicoureteral reflux in the pediatric population [7, 8].



**Figure 2** Harmonic contrast enhanced ultrasound of the kidney by MicroFlow Imaging (Canon Medical Systems, Tustin, CA) demonstrates the renal cortical vasculature.



**Figure 3** Subharmonic contrast enhanced ultrasound of the kidney details macro- and micro-circulation of the renal parenchyma in a three-dimensional rendering display.

### High fidelity ultrasound imaging

High fidelity ultrasound imaging represents the culmination of improved spatial resolution and sensitivity of B-mode and Doppler ultrasound. Taken together, high fidelity ultrasound has the potential to broaden the scope of diagnostic sonography. Advancements in ultrasound spatial resolution are appreciated in both high resolution ultrasound (HRU) and Doppler technology. Additionally, high sensitivity Doppler (HSD) may provide a more sensitive interrogation of microperfusion associated with target pathologies. These sophisticated technologies have been implanted in several high-end ultrasound systems.

HRU and Advanced Dynamic Flow (ADF, Canon Medical Systems, Tustin, CA) both represent significant developments in ultrasound spatial resolution. HRU relies on ultrasound bandwidths higher than 15 MHz [9].

This is much higher than typically used in abdominal (2.5–3.5 MHz) and vascular ultrasound (5.0–10.0 MHz). This allows for discrimination as small as 100  $\mu\text{m}$  [9]. Novel clinical applications of HRU include dermatologic and ophthalmologic sonography [9]. ADF couples high resolution sonography to standard Doppler imaging with the utilization of a broadband transmission frequency, selective filtering approaches and high frame rate, bringing resolution and lateral discrimination comparable to B-mode (Fig. 4) [10].



**Figure 4** High resolution ultrasound (A) and advanced dynamic flow (B) are demonstrated with the examination of the distal end of an index finger. Image provided by Cannon Medical Systems.

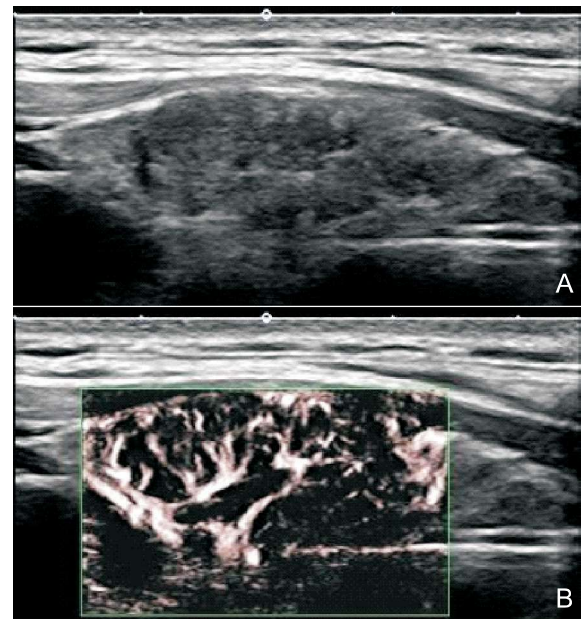
In contrast, HSD techniques rely on suppressing the standard wall-filter elimination of low-flow vasculature [11,12]. Specifically, Superb Microvascular Imaging (SMI, Canon Medical Systems, Tustin, CA) utilizes a proprietary adaptive algorithm to suppress background motion artifact without eliminating low-flow signals [11]. This technique maintains the high resolution and frame rates of ADF and B-mode ultrasound [11]. SMI may provide an evaluation of microperfusion without the administration of ultrasound contrast agents [11]. This can allow for improved tumor characterization, identification of ischemia, and gradation of inflammation or neovascularization (Fig. 5) [11,12]. As demonstrated earlier in Fig. 2, Microflow Imaging (Canon Medical Systems, Tustin, CA) represents an amalgam of HSD and ultrasound contrast processing techniques.

### Volumetric ultrasound

Volumetric ultrasound or three-dimensional (3D) ultrasound was developed in response to challenges inherent to standard two-dimensional (2D) ultrasound. Specifically, planar ultrasound suffers from concerns of non-representative or non-continuous image sections requiring a subjective user extrapolation to define extent of pathology with notable operator dependence.

Consequently, variation in technique and complex anatomy can make quantitative assessments more difficult (especially for inexperienced users) [13].

Using volumetric ultrasound, a single systematic pass through target pathology can be performed and measurements can be methodically calculated—even in cases of complex geometry [13]. Images can be acquiring through 2D array transducers, transducers with mechanical motors, or through a freehand technique in which images are “spliced” together with 3D localization. When images are obtained continuously over a time interval, these are termed four-dimensional ultrasound [13].



**Figure 5** B-mode (A) and SMI (B) evaluation of a thyroid tumor is demonstrated. Notable tumor vascularity is appreciated. Image provided by Cannon Medical Systems.

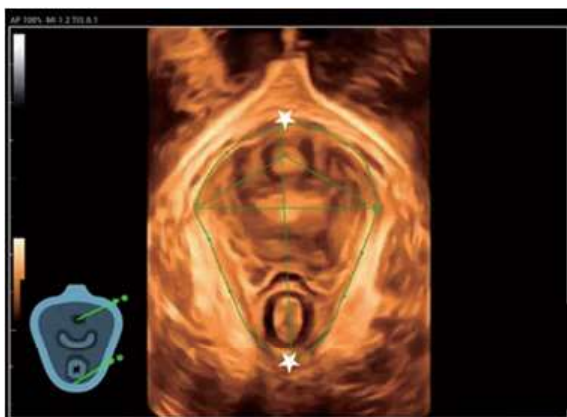
Early applications of volumetric ultrasound were focused on obstetrics for the diagnosis of anatomic congenital abnormalities *in utero* (Fig. 6) [14,15]. However, volumetric ultrasound may also be used in intraabdominal lesion characterization and superficial structure assessment, such as in breast and thyroid [16]. Volumetric ultrasound may be superior in defining the anatomy of the lower genitourinary tract because of the complex geometric anatomy present [14]. This is particularly true in cases with concern for bladder or prostate cancer [14]. Additionally, volumetric ultrasound may improve cardiovascular imaging [14]. 3D reconstruction of the cardiac chambers may provide a better structural understanding of ventricular anatomy [14]. 3D reconstruction of aorta by ultrasound can be used in the assessment of endoleaks after stent graft placement [14].



**Figure 6** Volumetric obstetric ultrasound performed of an in-utero fetus with three-dimensional facial rendering detailing topographic and developmental anatomy.

### Automatic and intelligent imaging function

Intelligent ultrasound imaging provides a reproducible measurement and quantification analysis of select pathologies and organ systems. As in 3D ultrasound, intelligent ultrasound imaging will allow for rapid volumetric measurements with minimal user input [17]. Applications include echocardiography, abdominal imaging, pelvic floor imaging (Fig. 7), breast imaging, and interventional applications with multi-modality fusion



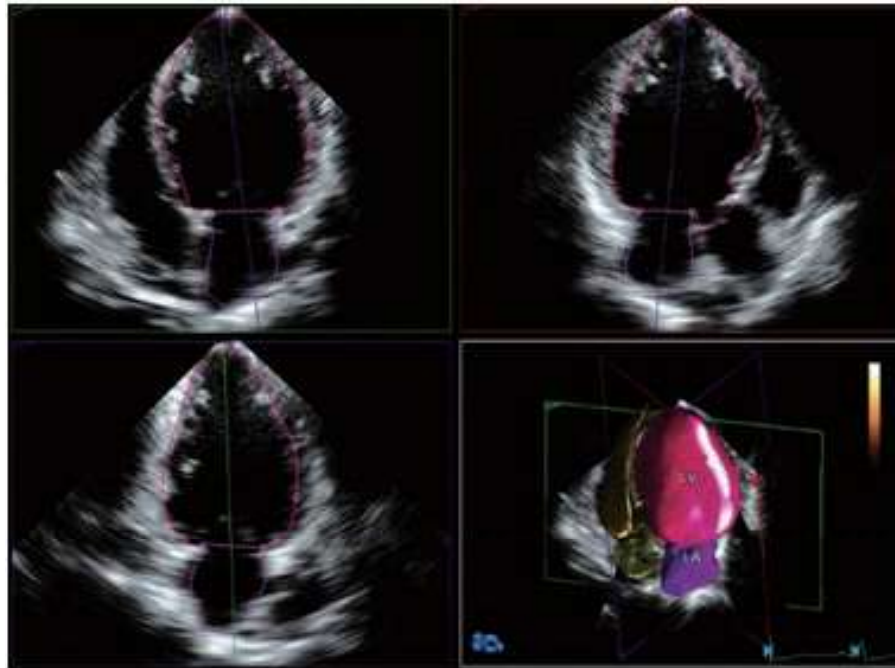
**Figure 7** A volumetric ultrasound of the pelvic floor is depicted with the automated annotation and measurement of key standardized perimeters using intelligent post-processing software via the Mindray Resona 7 system. Image provided by MindRay.

imaging.

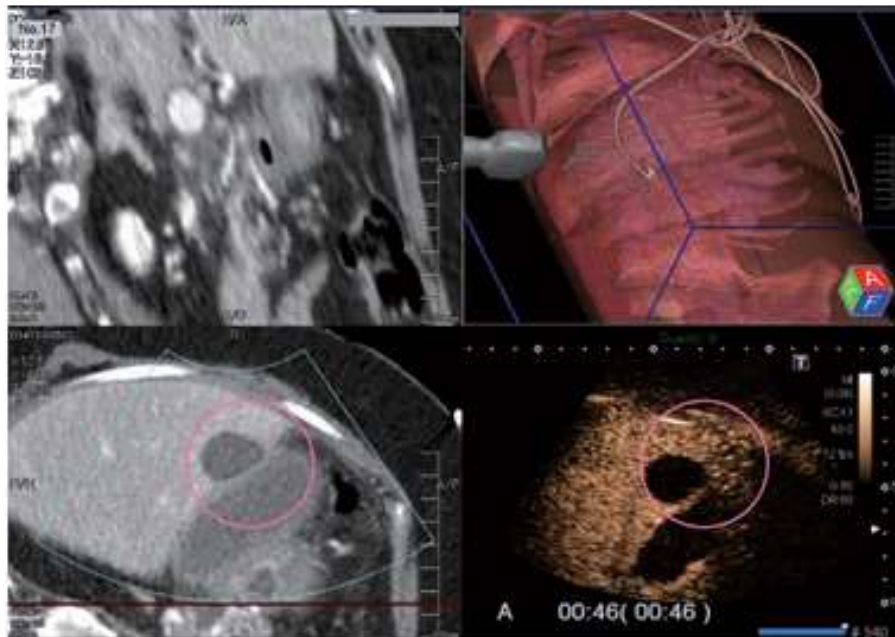
Anatomical Intelligence (Philips, Amsterdam, Netherlands) functions by coupling key known or stable landmarks in the patient’s anatomy to a virtual representation established within the software [17]. Using adaptive system intelligence, this virtual representation is then fit to the actual clinical image. Automated measurements are then taken using the virtual representation as the reference [17]. When paired with volumetric ultrasound, modern technologies such as HeartModel (Philips, Amsterdam, Netherlands) provide immediate and reproducible left ventricle and left atrial volumes (Fig. 8) [9]. Similarly, solutions exist for immediate diagnosis and visualization of a wide range of structural heart diseases [9,17].

### Imaging fusion and interventional navigation

Advances in fusion technology allow increased confidence in diagnosis and interventional navigation by exploiting the advantages brought by each of the fused imaging modalities. Specifically, co-registration of MRI or CT data with real-time ultrasound can provide additional spatial reasoning, aiding in lesion identification (Fig. 9) and needle tracking. Additionally, ultrasound fusion may have a role in trainee education, providing a more robust three-dimensional correlate [18,19].



**Figure 8** HeartModel provides a robust, reproducible ejection fraction and offers automated multi-dimensional views and reproducible quantification with one-button simplicity. The image provided by Philips Healthcare. LV, left ventricular; LA, left atrium.



**Figure 9** Computed tomography to contrast ultrasound fusion is depicted demonstrating the hepatic lesion to navigate real-time targeted biopsy. Image provided by Cannon Medical Systems.

Co-registration of ultrasound data is reliant on accurate tracking. Techniques include electromagnetic, optical, and internal image tracking [18,20]. In electromagnetic tracking, a magnetic field generator is positioned near the patient. As the ultrasound probe is moved across the patient's body, the electrical current experienced by a sensor on the probe changes,

establishing probe position in 3D space [20]. In optical tracking, a nearby camera tracks the ultrasound probe position by the detection of a laser or infrared light emitter on the probe. Internal image tracking attempts to correlate designated anatomic landmarks between modalities [20]. Of note, automatic co-registration of previously acquired cross-sectional imaging is at

the forefront of interventional navigation, combining intelligent imaging function with volumetric ultrasound to alleviate concerns of technical difficulty and time-investment in ultrasound imaging fusion [21]. While workflow challenges exist when using these technologies, multi-modality imaging has the potential for significant value, particularly within the interventional space.

### Developments in ultrasound technique

Modern developments in ultrasound imaging techniques have revolved around the expediency of problem-solving afforded by sonography. Specifically, point-of-care ultrasound, made possible by portable ultrasound systems, has grown tremendously with cross-discipline support. To that end, tele-ultrasound leverages the expertise of radiologists with the portability of sonography.

### Point-of-care ultrasound (POC)

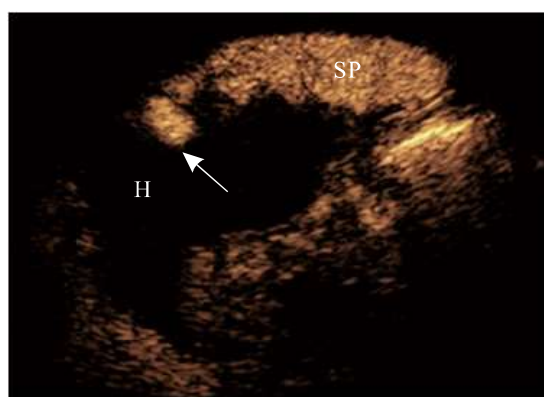
Over last two decades, POC ultrasound has grown tremendously, contributing to the concept of the “ultrasound stethoscope” [22]. That is, ultrasound should be accessible as well as easy to use, provide rapid feedback regarding the patient’s status, and have minimal morbidity. Consequently, POC ultrasound is well positioned in the critical care and emergency setting [23]. Ultrasound is being advocated for part of the core curriculum for physician training in non-radiologic specialties including emergency medicine and surgery [24].

Moore et al. [23] differentiates POC ultrasound into three broad applications: Procedural, diagnostic, and screening. Procedural applications of POC ultrasound include all advanced needle-guidance techniques such as vascular access and pericardiocentesis. These are discussed later (see Image-Guided Therapy). Diagnostic POC ultrasound serves as a “goal-directed” interrogation of a known pathologic endpoint [23]. Specifically, the focused assessment with sonography for trauma may be used in trauma patients for the rapid assessment of hemodynamically significant intraabdominal hemorrhage or pericardial effusion (Fig. 10) [23]. Echocardiography and inferior vena cava compressibility may be used to evaluate the left or right heart systems and volume status [23]. Pulmonary ultrasound may be used to exclude pneumothorax, identify pleural effusions, and follow the progress of pulmonary edema. Finally, POC ultrasound may be used for screening applications such as in the identification of abdominal aortic aneurysms in high risk patients in a primary care provider’s office [23].

### Portable ultrasound systems

Portable ultrasound systems developed out of

a recognized role for POC ultrasound in urgent or emergent but remote environments [11]. Modern portable ultrasound machines include narrow profile mobile devices (Fig. 11) or free-standing ultrasound probes that utilize a connected mobile phone for post-processing and display (Fig. 12) [11,25]. Little additional infrastructure is necessary for the implementation of portable ultrasound—making it a particularly valuable tool in resource-limited clinical scenarios [11]. This includes disaster management and imaging in rural areas [11].



**Figure 10** Contrast-enhanced examination of a patient after abdominal trauma is depicted. An area of extravasation (arrow) is demonstrated from the spleen (SP) into an anechoic early hematoma (H). Image provided by Dr. Faqin Lv.



**Figure 11** Narrow profile laptop-based ultrasound machines can facilitate portable ultrasound examinations (X5 model, SonoScape Medical Corp, Shenzhen, China).

While there is a paucity of data on the relative efficacy of portable ultrasound devices compared with standard ultrasound machines, existing literature suggests comparable test statistics [11]. However, lower quality B-mode imaging and diminutive screen sizes can make advanced diagnostic techniques such as lesion



characterization and quantification less reliable [15]. Portable ultrasound devices are likely most valuable for answering specific emergency questions such as the presence of abdominal ascites, pleural effusions, or gallstones [15].



**Figure 12** Handheld ultrasound unit is depicted (Sonostar Technologies Co., Ltd, Guangzhou, China). A wireless connection to a nearby smartphone is maintained for image visualization.

### Tele-ultrasound

Tele-radiology has evolved to become a major resource for hospitals wishing to provide continuous coverage by an experienced radiologist [16]. Additionally, tele-radiology may be utilized in regions and countries with limited access to advanced radiology [16]. This may even include outer space—ultrasound is the only medical imaging modality available on the International Space Station [26]. To this extent, tele-ultrasound provides unique challenges and opportunities.

Tele-ultrasound may be performed in a synchronous or asynchronous fashion [16]. That is, the tele-radiologist may read and interpret ultrasound images in real-time or after the entire examination is complete and transmitted [16]. Synchronous tele-ultrasound allows for early detection of problems associated with the examination [16]. Additionally, it proves the interpreting radiologist additional anatomic-clinical context by affording real-time physiologic and spatial context (Fig. 13) [16].

Early on, limitations of synchronous tele-ultrasound existed with adequate data compression and bandwidth [16]. Advances in broadband internet access and compression techniques have alleviated telecommunication concerns [16]. However, synchronous tele-ultrasound requires constant supervision of the medical personnel performing the examination [16]. Robotic arm-assisted sonography, still early in development, provides the radiologist with the ability to remotely control the ultrasound probe and direct the actual examination (Fig. 14 and Fig. 15) [16].



**Figure 13** A portable ultrasound system (Shenzhen Wisonic Medical Technology Co., Ltd., Shenzhen, China) is depicted. The system utilizes a built-in telecommunication capability for real-time consultation for both domestic and international applications.



**Figure 14** A light-weight six-axis robot system (Kuka, Augsburg, Germany) is depicted with the capability to maneuver and stabilize an ultrasound probe (arrow).



**Figure 15** A robotic tele-ultrasound system (MGIUS-R3, MGI Tech Co., LTD., Shenzhen, China) can be used to remotely scan patients and communicate with doctors for diagnosis and consultation. Image provided by MGI Tech.

### Innovations in clinical ultrasound application

Advances in ultrasound processing and sonographic technique have lent themselves to major innovations

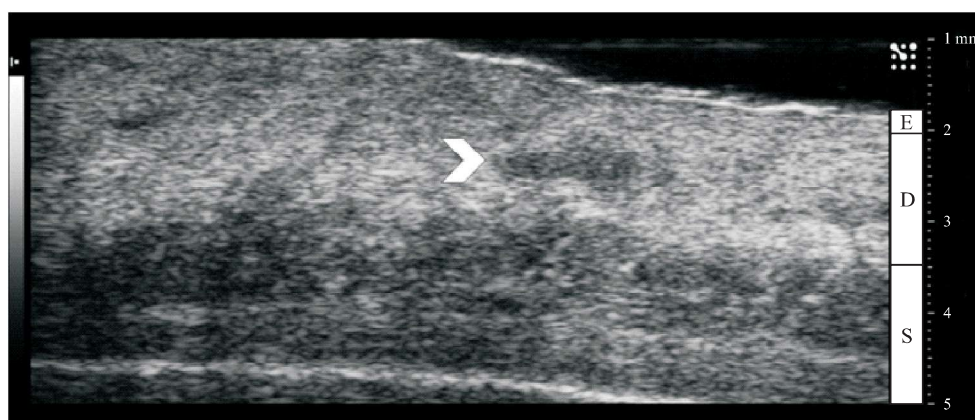
in clinical ultrasound applications. These innovations are fundamental to clinical translation of industrial and academic ultrasound research. Emerging applications include superficial structure imaging, CEUS, and image-guided therapies.

### Superficial structure imaging

Superficial structure imaging by ultrasound relies on HRU to delineate cutaneous lesions and pathologies (Fig. 16). Frequencies between 13.5–15 MHz allow for penetration of up to 3 cm and high resolution visualization of the epidermis and dermis [27]. However, frequencies between 50–100 MHz may be used to visualize the epidermis alone [27].

Dermatologic ultrasound was first used in the

detection of skin cancers in the 1990s [27]. Cutaneous malignancies (malignant melanoma, basal cell carcinoma, or squamous cell carcinoma) are typically appreciated as a poorly defined hypoechoic lesion with evidence of lesion vascularization which is differentiated from benign epidermal cysts typified by well-defined hypoechoic lesions and minimal vascularization [27]. While malignancy differentiation frequently requires histology, the presence of hyperechoic dots within the lesion (representing calcifications or necrotic nests of cells) may signify basal cell carcinoma [27]. HRU may also help to establish tumor margins and depth of extent. However, significant hyperkeratosis, inflammation and reticular dermal extension may make delineation of subcuticular extension difficult [27].

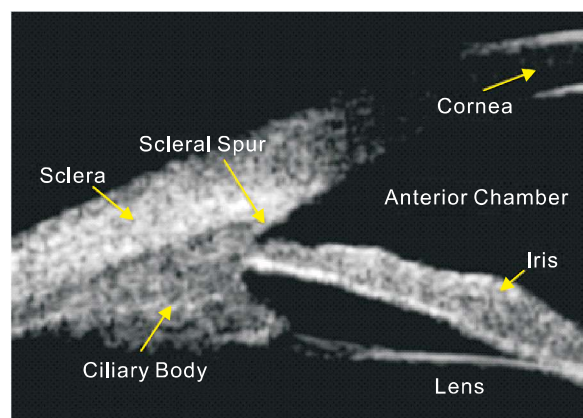


**Figure 16** High resolution ultrasound performed at 70 MHz details the layers of the skin. From superficial to deep, the epidermis (E), dermis (D), and subcutaneous layer (S) is appreciated. An unnamed compressible vein within the dermis is indicated by an arrowhead.

More recently, HRU has been used in the characterization of benign cutaneous lesions and the identification of inflammatory or infectious diseases. Ultrasound discrimination of common skin disorders such as keloids, lichen planus, eczema, psoriasis and seborrheic keratosis has been described [27]. Additionally, lipomas may be differentiated from epidermoid cysts, hemangiomas, and metastatic malignant nodules. Inflammatory disease activity in systemic sclerosis may be monitored by HRU. Finally, early evidence of cellulitis (as indicated by a subcutaneous increase in echogenicity representing edema) may be identified [27].

Ultrasound frequencies much higher than 25 MHz have been used in limited but evolving clinical applications [27]. Targeted sonography of the epidermis alone may be performed [27]. Additionally, ultrasound biomicroscopy (UBM) utilizes frequencies of at least 50 MHz [28,29]. UBM is valuable in the sonographic examination of the anterior segment or peripheral posterior segment of the eye (Fig. 17) [29]. Additional

applications include the diagnosis of acute angle glaucoma, ciliary body pathology and quantitative analysis of the anterior chamber angle [29].



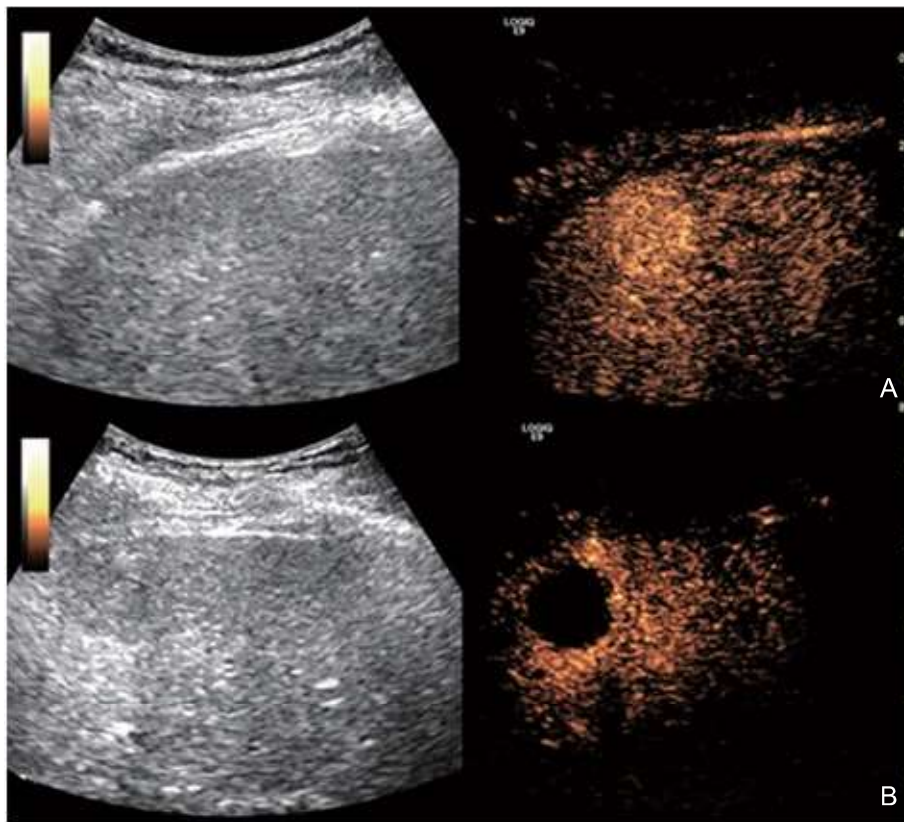
**Figure 17** Ultrahigh frequency ultrasound biomicroscopic imaging (50 MHz, Quantel Aviso, France) demonstrates the normal structures of a superficial eye with detailed anatomic visualization. Image provided by Dr. Wenli Yang.

### Contrast-enhanced ultrasound

As noted earlier, ultrasound contrast agents have been FDA approved for left ventricular opacification, characterization of focal liver lesions, and diagnosis of uretero-vesicular reflux [7,8]. However, CEUS is particularly well-positioned for the detection of any pathology differentiated by microperfusion (intravenous injection) or the variable distribution of any luminal structures (intracavitary injection) [5].

CEUS has shown significant value in oncology and interventional oncology based on its ability to detect

changes in lesion perfusion and microperfusion [30]. CEUS has promise in the early detection of locoregional therapy failure after trans-arterial chemo-embolization of hepatocellular carcinoma (Fig. 18) [31]. CEUS may also serve as a valuable diagnostic tool in the evaluation of indeterminate renal lesions (Fig. 19) and breast lesions [5,32]. Additionally, CEUS may aid in biopsy guidance, particularly in lesions with significant necrotic components or with poor differentiation from surrounding normal tissues (such as in prostate cancer) [32].



**Figure 18** Contrast-enhanced ultrasound examination of a patient with hepatocellular carcinoma prior to trans-arterial chemoembolization (TACE) (A) and 2 weeks after TACE (B). The tumor was confirmed as completely treated by routine MRI performed at 6 months.

Other novel applications of CEUS include endoleak detection, biliary imaging, and lymphosonography [5]. Ultrasound contrast agents injected intravascularly can be used to dynamically detect and quantify flow into excluded aneurysmal sacs that might be missed by CT or MRI [33]. Biliary injection of ultrasound contrast agent may be used to visualize the biliary tree (Fig. 20) and localize luminal appliances and lesions [5]. Finally, subdermal or subcutaneous injection of UCA may be used to trace lymphatic drainage [34]. When injected peri-tumorally, UCA may serve as a novel agent in the

identification of sentinel lymph nodes (Fig. 21) [35].

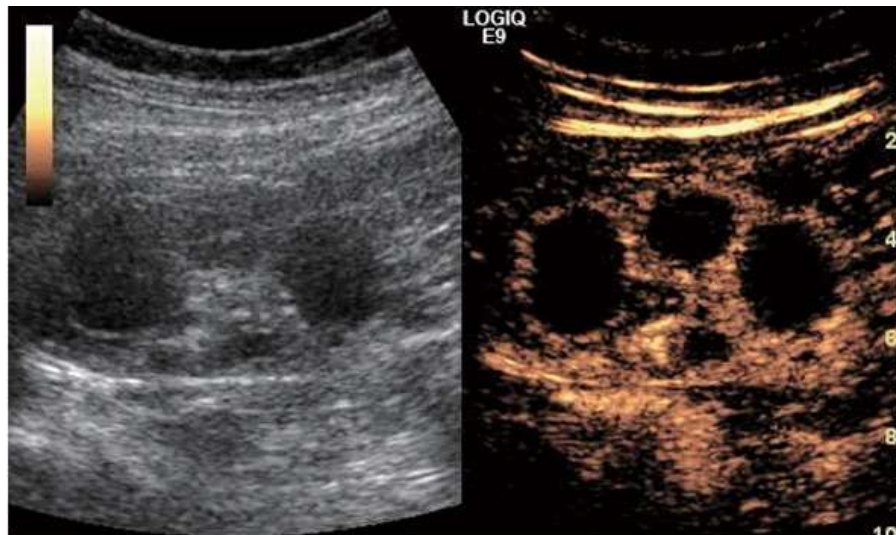
### Image-guided therapy

Ultrasound is particularly well-positioned for improving image-guided therapy as it provides the practitioner real-time feedback and is easily portable. As a result, interventionalists have long found value in ultrasound-guided procedures. Increasingly, additional procedural specialties are expanding the role of ultrasound in targeted therapies. Two major fields of technical advancement include locoregional anesthetic

blocks and vascular access.

Ultrasound guided peripheral nerve blocks provide a newer and potentially safer alternative to central neuraxial (such as epidural) and paravertebral regional anesthesia techniques [36]. Ultrasound guidance affords increased rates of success, decreased operative pain, and

reduced vascular puncture [37]. Certainly, concerns with increased cost and training barriers exist compared with landmark and nerve stimulation techniques. Nonetheless, patients with known difficult anatomy may specifically benefit from ultrasound-guided nerve localization and real-time needle tracking (Fig. 22) [37].

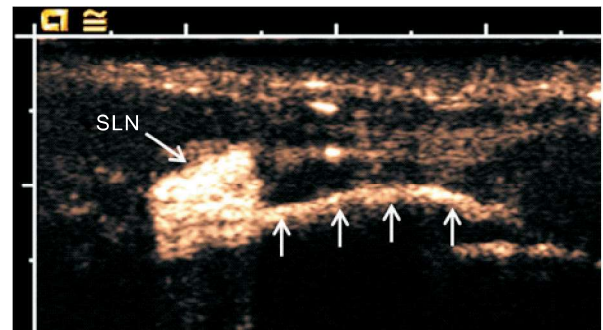


**Figure 19** Contrast enhanced ultrasound performed of a kidney with previously indeterminate lesions demonstrates multiple benign renal cysts. These are characterized by thin-walls and no internal enhancement or vascularity.



**Figure 20** A contrast-enhanced intra-biliary ultrasound examination is depicted in a patient with known cholangiocarcinoma. Diluted ultrasound contrast agent is injected through a left percutaneous transhepatic biliary drainage catheter. The sonogram depicts enhancement of the left intrahepatic bile duct while the left hepatic duct is cut off. The right intrahepatic bile duct and the common bile duct are not displayed. Image provided by Dr. Rongqin Zheng.

Ultrasound guided vascular access has evolved tremendously. Both internal jugular and femoral vein cannulation have been traditionally performed by a landmark technique [38]. However, ultrasound guidance has been shown to reduce the number of failed attempts, increase the chance of success, and decrease procedural

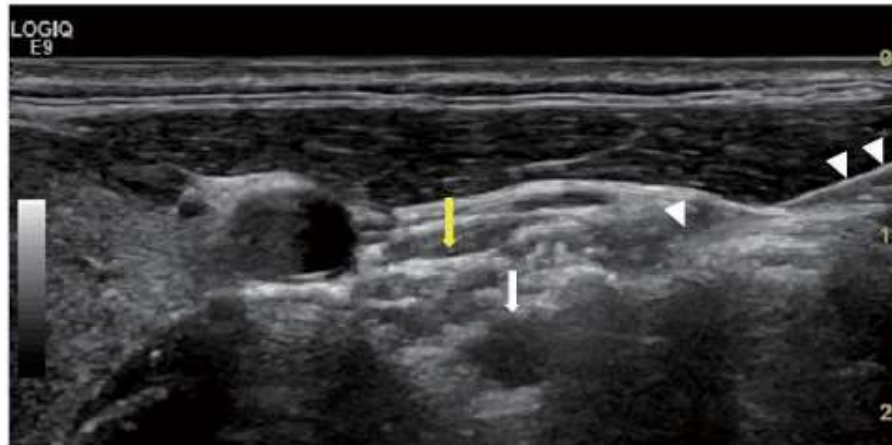


**Figure 21** Contrast-enhanced ultrasound imaging shows a sentinel lymph node (SLN) and drainage lymphatic channel (arrows) after subcutaneous injection of around a melanoma tumor in a swine model.

complications (Fig 23) [38]. New ultrasound systems focus on needle guidance. Needle guidance may be provided via bracket systems or free-hand position-based systems. In the former, the needle and the probe are physically coupled and the needle is inserted at a static angle and distance from the probe [39]. In the latter, a variety of external guidance position systems are utilized to localize the needle and the probe within three-dimensional space (such as electromagnetic emitters and sensors) [40]. This provides more flexibility in angle and approach at the expense of complexity.

Of course, the above advances can be expanded to any needle-based techniques. Biliary access procedures (such as percutaneous cholecystostomy or percutaneous transhepatic cholangiography) are frequently performed under ultrasound guidance [41]. As noted earlier, ultrasound and CEUS may be used to direct

soft tissue or trans-abdominal needle biopsy or access [32]. Percutaneous techniques such as direct abdominal aortic sac puncture and lymphangiography may be performed at advanced centers under ultrasound guidance as well [42,43].



**Figure 22** Ultrasound-guided cervical nerve block is depicted. The needle tip and track are visualized (arrowhead). The 5th cervical nerve root (white arrow) is targeted with close anatomic relationship to the anterior scalene muscle (yellow arrow). Image provided by Dr. Dingzhang Chen.



**Figure 23** Under real-time ultrasound guidance, a 24-gauge angiocatheter (arrow) is inserted into the left radial artery (RA-LEFT).

## Conclusion

The field of medical ultrasound has expanded greatly since the early 1950s. Advances in ultrasound signal and image processing serve as a cornerstone of ultrasound research. Significant developments in diagnostic ultrasound include contrast agents, automated/intelligent or multi-dimensional imaging, and high-fidelity sonography. Moving forward, research and clinical growth in interventional and therapeutic applications of ultrasound is expected.

## Conflicts of interest

The authors report non-financial and grant support from GE Healthcare, Cannon Medical Systems (formerly Toshiba Medical Systems), Mindray, SonoScape Medical Corp, and Shenzhen Wisonic Medical Technology outside the submitted work.

## References

- [1] Newman PG, Rozycki GS. The history of ultrasound. *Surg Clin North Am* 1998;78:179–95.
- [2] Eisenbrey JR, Sridharan A, Liu JB, Forsberg F. Recent experiences and advances in contrast-enhanced subharmonic ultrasound. *Biomed Res Int* 2015;2015:640397.

- [3] Eckersley RJ, Chin CT, Burns PN. Optimising phase and amplitude modulation schemes for imaging microbubble contrast agents at low acoustic power. *Ultrasound Med Biol* 2005;31:213–9.
- [4] Paefgen V, Doleschel D, Kiessling F. Evolution of contrast agents for ultrasound imaging and ultrasound-mediated drug delivery. *Front Pharmacol* 2015;6:197.
- [5] Piscaglia F, Nolsøe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, et al., The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med* 2012;33:33–59.
- [6] Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsøe CP, et al. 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. *Ultrasound Med Biol* 2013;39:187–210.
- [7] Lyschchik A, Kono Y, Dietrich CF, Jang HJ, Kim TK, Piscaglia F, et al., Contrast-enhanced ultrasound of the liver: technical and lexicon recommendations from the ACR CEUS LI-RADS working group. *Abdom Radiol (NY)* 2018;43:861–79.
- [8] Muskula PR, Main ML. Safety With Echocardiographic Contrast Agents. *Circ Cardiovasc Imaging* 2017;10:e005459.
- [9] Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26:1–133.
- [10] Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, et al., Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine - Needle Aspiration State of the Science Conference. *Diagn Cytopathol* 2008;36:425–37.
- [11] Hotta N, Tagaya T, Maeno T, Ayada M, Sato K, Ishikawa T, et al. Advanced dynamic flow imaging with contrast-enhanced ultrasonography for the evaluation of tumor vascularity in liver tumors. *Clin Imaging* 2005;29(1):34–41.
- [12] Machado P, Segal S, Lyschchik A, Forsberg F. A Novel Microvascular Flow Technique: Initial Results in Thyroids. *Ultrasound Q* 2016;32:67–74.
- [13] Singaporewalla RM, Hwee J, Lang TU, Desai V. Clinico-pathological correlation of thyroid nodule ultrasound and cytology using the TIRADS and Bethesda classifications. *World J Surg* 2017;41:1807–11.
- [14] Lazebnik RS, Desser TS. Clinical 3D ultrasound imaging: beyond obstetrical applications. *Diagn Imaging* 2007;1:1–6.
- [15] Artul S, Nseir W, Armaly Z, Soudack M. Superb microvascular imaging: Added value and novel applications. *J Clin Imaging Sci* 2017;7:45.
- [16] Fenster A, Downey DB, Cardinal HN. Three-dimensional ultrasound imaging. *Phys Med Biol* 2001;46:R67–99.
- [17] Prager RW, Ijaz UZ, Gee AH, Treece GM. Three-dimensional ultrasound imaging. *Proc Inst Mech Eng H* 2010;224:193–223.
- [18] Palmentieri B, de Sio I, La Mura V, Masarone M, Vecchione R, Bruno S, et al. The role of bright liver echo pattern on ultrasound B-mode examination in the diagnosis of liver steatosis. *Dig Liver Dis* 2006;38:485–9.
- [19] Medvedofsky D, et al. Automatic transthoracic three-dimensional echocardiographic quantification of the heart chambers. *Philips Ultrasound*, 2016.
- [20] Younossi ZM, Stepanova M, Afendy M, Fang Y, Younossi Y, Mir H, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol* 2011;9:524–530.
- [21] Prater D, Cardinale M, Schneider R. AutoEF using a 2DQ featuring Anatomical Intelligence. *Philips Ultrasound*, 2014.
- [22] Narula J, Chandrashekhar Y, Braunwald E. Time to add a fifth pillar to bedside physical examination: inspection, palpation, percussion, auscultation, and insonation. *JAMA Cardiol* 2018;3:346–50.
- [23] Moore CL, Copel JA. Point-of-care ultrasonography. *N Engl J Med* 2011;364:749–57.
- [24] Beal EW, Sigmond BR, Sage-Silski L, Lahey S, Nguyen V, Bahner DP. Point-of-Care Ultrasound in general surgery residency training: A proposal for milestones in graduate medical education ultrasound. *J Ultrasound Med* 2017;36:2577–84.
- [25] Nelson BP, Melnick ER, Li J. Portable ultrasound for remote environments, Part I: Feasibility of field deployment. *J Emerg Med* 2011;40:190–7.
- [26] Martin DS, South DA, Garcia KM, Arbeille P. Ultrasound in space. *Ultrasound Med Biol* 2003;29:1–12.
- [27] Kleinerman R, Whang TB, Bard RL, Marmor ES. Ultrasound in dermatology: principles and applications. *J Am Acad Dermatol* 2012;67:478–87.
- [28] Sadaka A, Prager T, Beaver H, Malik A. A novel use of ultrasound biomicroscopy. *Eye (Lond)* 2018;32:474–475.
- [29] Pavlin CJ, Foster FS. Ultrasound biomicroscopy of the eye. 2012: Springer Science & Business Media.
- [30] Eisenbrey JR, Forsberg F. Contrast-enhanced ultrasound for molecular imaging of angiogenesis. *Eur J Nucl Med Mol Imaging* 2010;37 Suppl 1:S138–46.
- [31] Shaw CM, Eisenbrey JR, Lyschchik A, O'Kane PL, Merton DA, Machado P, et al. Contrast-enhanced ultrasound evaluation of residual blood flow to hepatocellular carcinoma after treatment with transarterial chemoembolization using drug-eluting beads. *J Ultrasound Med* 2015;34:859–67.
- [32] Gummadi S, Eisenbrey JR, Lyschchik A. Contrast-enhanced ultrasonography in interventional oncology. *Abdom Radiol (NY)* 2018. doi: 10.1007/s00261-018-1581-5. [Epub ahead of print]
- [33] Gummadi S, Eisenbrey JR, Lyschchik A. A Narrative Review on Contrast-Enhanced Ultrasound in Aortic Endograft Endoleak Surveillance. *Ultrasound Q* 2018. doi: 10.1097/RUQ.0000000000000353. [Epub ahead of print]
- [34] Goldberg BB, Merton DA, Liu JB, Murphy G, Forsberg F. Contrast - Enhanced Sonographic Imaging of Lymphatic Channels and Sentinel Lymph Nodes. *J Ultrasound Med* 2005;24:953–65.
- [35] Goldberg BB, Merton DA, Liu JB, Thakur M, Murphy GF, Needleman L, et al. Sentinel lymph nodes in a swine model with melanoma: contrast-enhanced lymphatic US. *Radiology* 2004;230:727–34.
- [36] Lin E, Choi J, Hadzic A. Peripheral nerve blocks for outpatient surgery: evidence-based indications. *Curr Opin Anaesthesiol* 2013;26:467–74.
- [37] Jeng CL, Rosenblatt MA. Overview of Peripheral Nerve Blocks, in UpToDate, R. Maniker, Editor. 2018, UpToDate: Waltham, MA.
- [38] Sabado JJ. Principles of Ultrasound-Guided Venous Access, in UpToDate, D.L. Cull, A.B. Wolfson, and A.M. Stack, Editors. 2018, UpToDate: Waltham, MA.
- [39] Turan A, Babazade R, Elsharkawy H, Esa WA, Maheshwari K, Farag E, et al. Novel needle guide reduces time to perform ultrasound-guided femoral nerve catheter placement: A randomised controlled trial. *Eur J Anaesthesiol* 2017;34:135–140.
- [40] Li X, Long Q, Chen X, He D, He H. Real-time ultrasound-guided PCNL using a novel SonixGPS needle tracking system. *Urolithiasis*

2014;42:341-6.

- [41] Bakkaloglu H, Yanar H, Guloglu R, Taviloglu K, Tunca F, Aksoy M, et al. Ultrasound guided percutaneous cholecystostomy in high-risk patients for surgical intervention. *World J Gastroenterol* 2006;12:7179–82.
- [42] Nadolski GJ, Itkin M. Feasibility of ultrasound-guided intranodal

lymphangiogram for thoracic duct embolization. *J Vasc Interv Radiol* 2012;23:613–6.

- [43] Boks SS, Andhyiswara T, de Smet AA, Vroegindeweyj D. Ultrasound-guided percutaneous transabdominal treatment of a type 2 endoleak. *Cardiovasc Intervent Radiol* 2005;28:526–9.