The place of ultrasonography in knee joint osteoarthritis: an update

Ultrasound is gaining ground over conventional imaging methods in the assessment of musculoskeletal changes in osteoarthritis. Systematic ultrasound scanning following established guidelines enables the detection of even minimal and early abnormalities of cartilage, synovial tissue and subchondral bone. Thus far, ultrasound has shown to be extremely sensitive in the detection of soft tissue changes in knee osteoarthritis, including synovial proliferation and synovial fluid. Such abnormalities are correlated with symptomatic flares and have associated prognostic implications. Although there has been some progression, there is still a lack of standardization and validation over the definition and scoring of ultrasound signs that are thought to reflect structural damage affecting different joint structures. Meanwhile, exciting developments are expanding the applications of ultrasound in the musculoskeletal field; the application of technologies such as sonoelastography, imaging coupling, 3D ultrasound and ultrasound contrast agents in the field of osteoarthritis is expected to improve not only healthcare-related aspects but also our current understanding of the pathophysiology of the disease.

KEYWORDS: cartilage ■ contrast-enhanced ultrasound ■ knee joint ■ menisci ■ osteoarthritis ■ osteophytes ■ sonoelastography ■ subchondral bone ■ synovitis ■ ultrasound

Carlos Pineda*[1], Cristina Hernández-Díaz[1], Angelica Pena[2] & Pablo Villaseñor-Ovies[1]

[1]Musculoskeletal Ultrasound Department, Instituto Nacional de Rehabilitacion, Avenida Mexico-Xochimilco No. 289, Arenal de Guadalupe, Tlalpan, Mexico City 14389, Mexico
[2]Rheumatology Department, Instituto Nacional de Rehabilitacion, Mexico City, Mexico
**Author for correspondence: Tel.: +52 559 991 000 ext. 13227 carpineda@yahoo.com*

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of chronic disability, in large part due to lower extremity involvement. The knee is one of the most common joints involved in OA. The prevalence of symptomatic knee OA (KOA) is reported to be as high as 16% in the elderly population [1,2].

Notwithstanding that the diagnosis of KOA is based on symptoms and clinical findings, most cases require the assessment of structural damage through an imaging technique [3]. As in other joints, conventional radiography (CR), hitherto the primary imaging tool in OA, shows late and indirect findings related to joint damage; what's more, it has been long recognized that clinical symptoms do not correlate with CR changes in OA [4]. Joint space narrowing used in CR as a surrogate of cartilage thickness, probably reveals little about cartilage health in early stages of the disease. More to the point, cartilage is not the only anatomic structure involved in the disease: the capsule, ligaments, synovial membrane and bursae may show structural abnormalities that are invisible in CR. Thus, CR is far from an ideal assessment tool of disease status and outcome measure in OA [5].

Ultrasound (US), on the other hand, offers the possibility to depict different structures within the knee in their finest details, including the synovium, synovial fluid, menisci, joint capsule, cartilage and bone cortex [6]. This endows US with exciting possibilities in KOA, from outcome assessment and monitoring therapeutic response, to understanding pathogenesis and the role of inflammation. Notwithstanding this, there is still a long way to go. The recent systematic review in which Keen *et al.* analyzed the overall usefulness of US as an assessment tool in OA, arrived at two important conclusions [7]. First, the lack of accepted definitions of US pathology in OA results in considerable heterogeneity between studies and suboptimal quality regarding reports of the abnormal findings, their definitions and scoring. Also, data on validity of US as a tool for assessment in OA is scarce. This is particularly true in the structural assessment of bone and cartilage components of OA pathology. **Box 1** shows the current indications, advantages and disadvantages of US as an assessment device in KOA. The main purpose of this special report is to provide updated information about the value and current place of US in the assessment of OA of the knee. To accomplish this, pertinent literature published in the last 5 years was reviewed.

Scanning technique

The US scan should follow a systematic technique [8]. However, variations in the acquisition

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Box 1. Utility, advantages and limitations of ultrasound evaluation in knee osteoarthritis.

Indications
- To corroborate clinical diagnosis
- Detection of cartilage lesions
- Detection of osteophytes, erosions and other cortical abnormalities
- Identification of other typical structural abnormalities
- To identify alternative sources of pain in a patient with or without an established diagnosis (i.e., anserine bursitis or iliotibial band syndrome)
- To monitor structural damage progression
- To evaluate pain exacerbation, especially related to inflammatory flares
- Detection of joint effusion
- Detection of synovial hypertrophy
- To execute US-guided procedures

Advantages
- Safe, no contraindications
- No ionizing radiation exposure
- Noninvasive
- Can be performed with prosthetic devices
- Broadly available
- Low running cost
- Portable equipments (bedside procedure)
- Well accepted by patients
- Only mildly time consuming
- Studies may be repeated several times
- Multiregional and multistructural assessment
- Dynamic assessment
- Furthers the precision and understanding of clinical maneuvers
- Contralateral assessment easily done

Disadvantages
- Operator dependant
- Long learning curve
- Limited acoustic windows
- Partial evaluation of the meniscus
- Partial evaluation of the femoral cartilage
- Limited evaluation of the cruciate ligaments
- Unable to visualize the patelofemoral joint
- Not fully validated for KOA
- Lack of standardized definitions of OA pathology

KOA: Knee osteoarthritis; OA: Osteoarthritis; US: Ultrasound.

technique such as voluntary quadriceps contraction with extended knee and varying degrees of flexion of the joint have been suggested to increase sensitivity to detect joint effusion [9]. The most sensitive position to detect fluid in knee joints is at 30° flexion. A comprehensive joint evaluation including dynamic examination of the anatomic recesses will provide information about the presence and distribution of both, synovial hypertrophy and joint effusion, providing targets for accurate interventional procedures [10].

OA pathology & US abnormalities

OA arises from a chain of events that lead to abnormal remodeling affecting different components of the joint anatomy (Table 1).

Cartilage

KOA results from both mechanical and biological events that destabilize the normal coupling of degradation and synthesis of chondrocytes and extracellular matrix; progressive degeneration with loss of cartilage and hypertrophy of the subchondral bone are the most representative findings of the disease [11]. The US appearance of cartilage in the knee affected by OA is initially characterized by a loss of the sharp contour and variations in the echogenicity of the cartilage matrix; these may be observed at the lateral femoral condyle, medial condyle and interchondylar notch. Initially, the chondrosynovial margin becomes blurred and the clarity of the cartilage layer is decreased. Later, an asymmetric narrowing of the cartilage layer takes place;

Table 1. Joint elements and ultrasound findings in knee osteoarthritis.

Component	Main ultrasound findings
Structural damage	
Cartilage	Loss of normal sharpness Heterogeneous structure Irregularities in thickness
Subchondral bone	Cortical irregularities Bone erosions†: an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes Osteophytes: characteristic bone step-ups of the bone profile, located at the edges of the joint surfaces, with or without acoustic shadow
Meniscus	Extrusion or subluxation, with or without displacement of collateral ligaments
Tendons and ligaments	Coexistence of soft tissue abnormalities Early loss of thickness of quadriceps tendon
Inflammatory markers	
Synovial hypertrophy†	Abnormal hypoechoic intra-articular tissue that is nondisplaceable and poorly compressible that may exhibit Doppler signal
Synovial fluid†	Fluid collection within the joint, defined as abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible but does not exhibit Doppler signal

†These definitions were generated by the OMERACT trial by consensus for common pathological lesions seen in patients with inflammatory arthritis, mainly rheumatoid arthritis [43]. *Their use has extended to include conditions that are not of a pure inflammatory nature, such as osteoarthritis.*

nearly complete loss of articular cartilage can be observed in patients with most advanced OA [12]. Studied *ex vivo* in a group of patients with KOA programmed for arthroplasty, these US findings showed good correlation with OA histological scores and individual findings included: cartilage flaking and fibrillation, chondrocyte enlargement, hyalinization, pitting and cartilage loss [13]. Furthermore, Naredo *et al.* studying cadavers demonstrated that US measurement of the femoral condylar thickness is highly reproducible and accurate when compared with direct measurements of the cartilage thickness [14].

Subchondral bone

Although it remains unknown whether the changes observed in the subchondral bone precede or follow the onset of OA, several studies point towards an active role of the subchondral bone in the pathogenic pathways that take place in OA. Its partaking probably occurs through various mechanisms including defects in its shock absorbent properties, osteocyte dysfunction and the production of soluble substances that regulate both bone and cartilage turnover and immune function. In addition, a crucial role is believed to be played by the vascular invasion of bone marrow tissue into this region, contributing to the degradation of adjacent hyaline cartilage [15]. This may explain the strong association between bone marrow abnormalities outlined in MRI and subchondral cystic changes in the joint [16]. In any case, chronic damage to subchondral bone results in new bone formation. The early bone changes in KOA are detected as hyperechoic signals in the area of the attachment of the joint capsule to the osteocartilaginous margin, where osteophytes as step-ups of bony prominences at the end of the normal bone contour, with or without posterior shadow, are often depicted [12]. Nevertheless, it is important to acknowledge that the validity of US-detected cortical changes in OA, including osteophytes, enthesophytes, cortical irregularities and erosions, needs further investigation. For example, studies addressing the performance and validity of US in detecting knee osteophytes, one of the cardinal features of the disease, did not appear in our review of the literature. Our group has recently proposed a simple scoring system to assess severity of KOA, which is essentially based on sonographic characteristics of cortical abnormalities, particularly osteophytes (Figure 1) [17].

Meniscus

The menisci of the knee are crescent-shaped fibrocartilage wedges that lie between the condyles of the femur and the tibia. The menisci act to disperse the weight of the body and reduce friction during movement. In KOA, US often shows protrusion of the meniscus as a rounded hyperechoic structure that projects out of the tibia plateau and femoral condyle habitually displacing the collateral ligaments. This sign needs

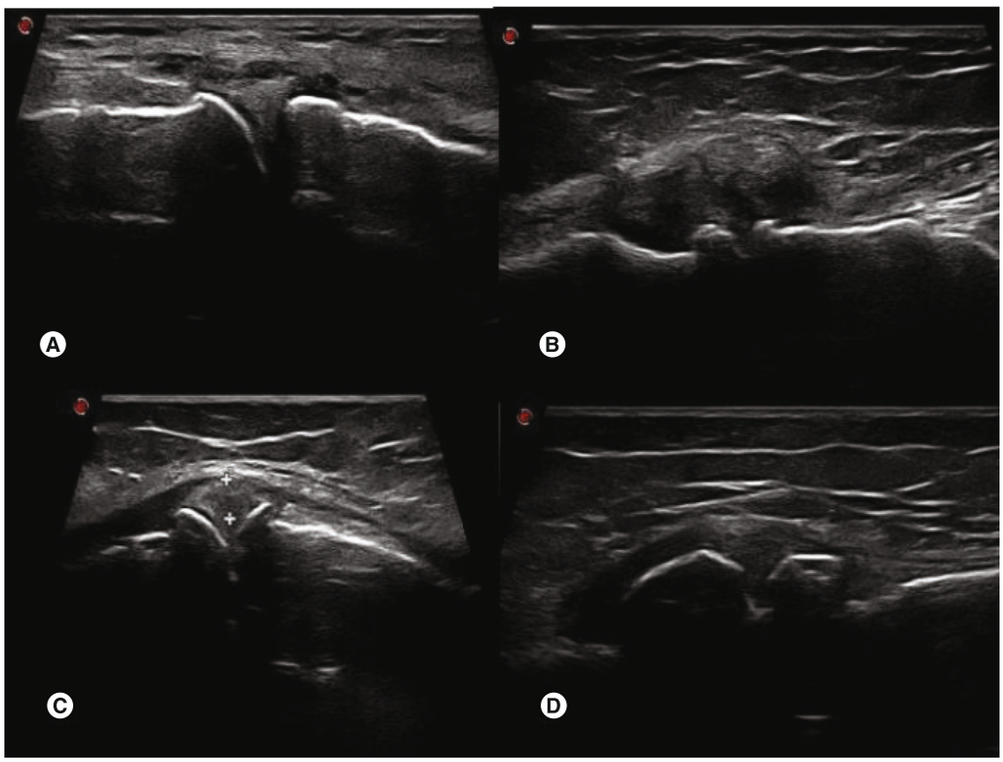

Figure 1. Osteophytes defined as a bony prominence at the end of the normal bone contour or at the margin of the joint seen in two perpendicular planes, with or without acoustic shadow. A semi-quantitative scale according to the size of the outgrowth was used: **(A)** minimum, **(B)** mild, **(C)** moderate and **(D)** severe.

further standardization and validation, however it has been described in 40–58% of patients with KOA [18,19] and it seems to be correlated with joint space narrowing and pain [20,21].

Tendons & ligaments

Soft tissue involvement often coexists with KOA. US examination is often useful in revealing disruption of the periarticular tissue that contributes to symptoms and disability in various stages of the disease (i.e., anserine bursitis). Nevertheless, US examination may also be important in early KOA providing information about soft tissue involvement. Monteforte *et al.* demonstrated diminution of thickness in quadriceps tendons in patients with early KOA as compared with healthy controls [22].

Synovium & synovial fluid

Inflammation is frequently ascertained in KOA particularly during flares of knee pain. Approximately 50% of patients with these characteristics show US evidence of synovitis and/or effusion as a possible explanation for their pain exacerbation [23]. Accordingly, de Miguel-Mendieta *et al.* showed that patients with KOA and recent onset pain had higher prevalence of Baker's cyst and joint effusion, as compared with painless OA knees [18]. In agreement with this, both suprapatellar pouch effusion and synovitis correlate with pain and functionality [24]. On the other hand, sonographic inflammation markers have also been observed in an important proportion of patients not selected by their pain-flare status [25]. Joint effusion as a proxy for inflammation is fairly common in KOA and can occur with or without synovitis [26]. Fluid in the knee appears as an anechoic intra-articular signal, with variable distribution and often presents in multiple compartments, with the most common site being the suprapatellar pouch (Figure 2) [27]. New high frequency probes are able to detect even minimal amounts of fluid [28]. In a large prospective study of painful KOA [29], the predictive potential of different disease variables was analyzed using joint replacement as the outcome measure. Among the two sonographic variables that were studied, effusion and synovitis, only the first was a predictor of joint replacement, even after adjustment for other characteristics of the disease. This study established that a feature of synovial inflammation in KOA is an independent predictor of joint replacement. The fact that US-detected effusion but not clinically detected effusion was a predictive variable shows that the greater sensitivity that US has over clinical

examination in the detection of joint effusion [30] has important predictive consequences.

Popliteal cysts appear as hypoechoic or anechoic masses arising between the semimembranous and medial head of gastrocnemius muscles with the knee in full extension [31]. Popliteal cysts appear in 15–36% of patients with KOA and seem to be more prevalent in symptomatic OA [18].

Technological innovations

Technological progress takes the form of useful applications that may add considerable value to US assessment of KOA and is currently represented by the development of new software, volumetric probes and intraoperating arthroscopic transducers. It is additionally represented by the application of sonoelastography, fusion imaging and 3D US techniques.

Sonoelastography

Sonoelastography is an ultrasonographic imaging technique that allows a noninvasive estimation of tissue stiffness [32]. It is based on the fact that soft tissues have greater displacement than hard tissue when externally compressed. Sonoelastography allows calculation and comparison of tissue displacement before and after tissue compression. It is performed with conventional US equipment but using additional software [33]. The feasibility of US elastography of articular cartilage employing instantaneous static compression, using high-resolution (55 MHz) US elastography *in vitro* as a potential arthroscopic technique has been developed by Ginat *et al.* [34].

Hybrid imaging modalities

The role of new hybrid imaging techniques integrated within the US equipment, enable the fusion of real-time MRI and US images. This technique has been used to study the small joints in patients with OA and rheumatoid arthritis, concluding that fusion imaging offers a composite set of information with accurate anatomical correlations [35]. The application of fusion techniques in large joints remains to be evaluated.

3D US techniques

The presence of an elementary OA lesion, synovial hypertrophy, was evaluated by means of 3D US along with synovial fluid analysis including concentrations of vascular endothelial growth factor, TGF-β and serum inflammatory markers in 22 KOA patients. Stereoscopic views of proliferative synovium ranged from simple proliferations to shrubby structures. Growth factors were significantly higher in patients with complex synovial proliferation. 3D technology was useful in delineating the synovium shape. This advanced imaging technique may have a possible impact on future imaging in rheumatology [36]. However, as stated by Chao and Jalunian, 3D power Doppler US is yet to be formally studied

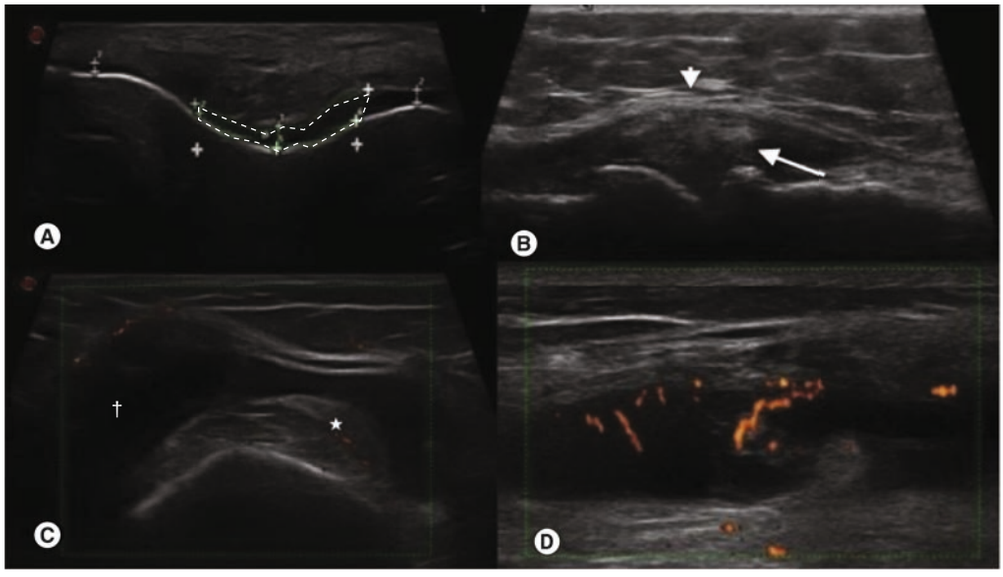

Figure 2. Spectrum of soft tissue and structural joint damage in knee osteoarthritis.
(A) Asymmetric narrowing of the cartilage layer (marked by the dotted line). **(B)** Meniscal protrusion (arrow) with displacement of medial collateral ligament (arrowhead). **(C)** Short axis view of the suprapatellar pouch showing synovitis (synovial hypertrophy [★] and effusion [†]). **(D)** Power Doppler image of the suprapatellar pouch demonstrating synovial hypervascularity.

in OA. The ability to image the synovial vascular tree may improve our understanding of the role of angiogenesis in OA, allowing us to compare its nature and extent with those of the inflammatory arthritides [28].

Biomarkers & US findings

Little is known about the relationship between US findings and metabolism of bone and cartilage. Jung *et al.* studied 51 patients with established KOA exploring the relationship between US changes and synovial-cartilage biomarkers. They observed that serum levels of hyaluronic acid were significantly higher in patients with a greater degree of effusion and/or synovial proliferation, longer medial ostephytosis and capsular distension, as compared with patients with less severe changes. Medial osteophytes and knee joint distension also correlated with levels of cartilage oligomeric matrix protein. In addition, the serum osteocalcin levels did not show any association with US findings [37]. Recently, Kumm *et al.* investigated the association between US findings in early-stage, symptomatic KOA and biomarkers of bone and cartilage metabolism in 106 individuals. Six different assays were used for the assessment of bone/cartilage metabolism. Typical US signs of inflammation, including joint effusion, synovial hypertrophy, and Baker's cysts were metabolically mirrored by biomarker levels (urinary level of the C-telopeptide fragments of type II collagen, serum concentration of type II A procollagen amino–terminal propeptide and cartilage oligomeric matrix protein) among women. Synovitis was correlated with an increased synthesis of type I collagen and decreased expression of type II collagen in premenopausal women. The authors confirmed that US findings in soft tissue played a major role in the variability of biomarkers of bone and cartilage metabolism in patients with early-stage KOA [38]. In a different study that aimed to examine the relationship between three different parameters: phonoarthrography (a measurement system based on analysis of high frequency acoustic emission signals for assessing the dynamic integrity of knee joints), US and biochemical markers and the severity of KOA, Bassiouni *et al.* studied 100 osteoarthritic knees together with 50 normal knees. Results showed that phonoarthrography values were inversely correlated with cartilage thickness. Mean levels of matrix metalloproteinase-3 and tissue inhibitor of proteinase were significantly elevated in advanced KOA. The authors suggested that phonoarthrography and US can be used as parameters for following up cartilage in KOA [39].

Contrast-enhanced US

US contrast agents enhance blood scattering reflection and increase the sensitivity of Doppler signals. Microbubble contrast agents improve detection of low-volume blood flow in small vessels by increasing the signal-to-noise ratio and thereby facilitating detection of angiogenetic vessels in inflammatory conditions. Recently, contrast-enhanced US (CE-US) was studied in 41 patients with painful KOA. Compared with B-mode gray scale US, power Doppler US showed greater capability to detect inflammation (64 vs 58%) at the suprapatellar pouch. Still, when a contrast agent was used, inflammation was detected in 95% of patients. Interestingly, inflammation was detected in a lower proportion of patients (82%) when contrast-enhanced MRI (CE-MRI) was used. While this could imply that CE-US has greater sensitivity than CE-MRI to detect inflammation in OA, it may have also been the result of a higher rate of false positive results and therefore less specificity; further studies using different reference standards are required to solve this issue [40].

The degenerative process of OA may be accompanied by nondestructive synovitis that has been confirmed in KOA by arthroscopy histology and US [41]. The mechanism of painful KOA is not clearly established. Among the pain mediators are bradykinins. Icatibant, a bradykinin receptor-2 antagonist has been reported to have an analgesic effect in KOA, however, its role in the inflammatory process is not clear. A randomized, double-blind, placebo-controlled study comparing CE-US using sulfur hexafluoride microbubbles (SonoVue®) to CE-MRI in assessing the anti-inflammatory and analgesic effects of icatibant was performed. Good agreement was observed between the two imaging techniques in the assessment of inflammatory changes in KOA. The analgesic effect of the study drug was clearly shown. However, the authors could not find an antiinflammatory effect by CE-US. Only CE-MRI of the lateral recess demonstrated a statistically significant improvement in the icatibant group, but this might have been an incidental finding [42].

Exciting developments are expanding the applications of US in the musculoskeletal field, offering the advantages of real-time performance, high tissue resolution and relative speed at a reasonable cost.

Conclusion & future perspective

US is a safe, low-cost, useful tool that provides an extensive evaluation of the different structures within the knee and their involvement in the degenerative process that prominently affects this joint. US enables rheumatologists a straightforward detection of structural damage such as cartilage degeneration and new bone formation. Yet, scientific studies that submit US through the different components of the OMERACT filters in OA are expected to appear in the next few years. Standardization of US findings will enable the generation of damage scoring systems in KOA which will in turn provide the grounds of much needed disease monitoring and therapy evaluation.

On the other hand, US is an excellent and inexpensive imaging technique to detect synovitis, and this has offered the grounds to establish its association with symptom flares and in the long term with negative disease outcomes (joint replacement). It is fair to anticipate upcoming US studies that will show the relevance of the inflammatory flares in the disease process, classification, progression and response to therapy.

Newer modalities in US enhance spatial resolution and the ability to detect subtle inflammation with exciting possibilities in OA from disease monitoring to understanding pathogenesis. Unfortunately, new technologies will come with higher costs and increased complexity to the issue of standardization.

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Executive summary

Background

- Imaging is mandatory in the evaluation of knee osteoarthritis (KOA).
- Conventional radiography is far from an ideal assessment method of osteoarthritis.
- Ultrasound (US) is being increasingly recognized as a powerful tool in the diagnosis, evaluation of extent and follow-up of patients with KOA.

Technique

- The use of a methodical technique is necessary for accurate and global evaluation of the knee joint.

US findings, value & meaning

- US shows knee joint changes both in early and late disease KOA.
- US has great value in demonstrating inflammatory signs in KOA.
- US has still to show it is an accurate and reproducible method to identify structural abnormalities. Once this is accomplished, rheumatologists will have a powerful tool for monitoring of disease progression and response to therapy.

Technological innovations

- Technological developments may add significant value to US assessment of KOA in the near future. Some of the most promising ones are: imaging fusion, sonoelastography and 3D US.

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