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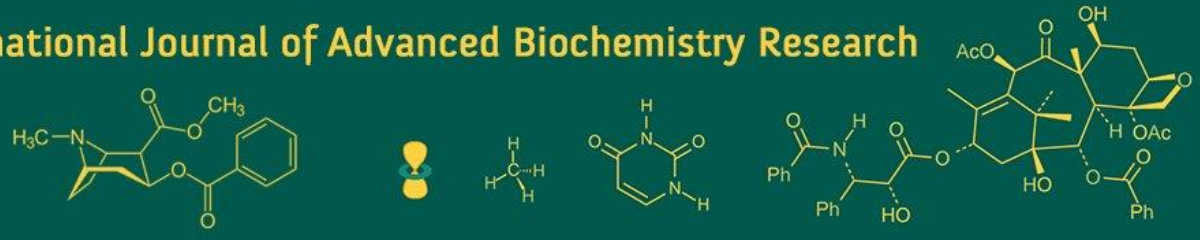

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Advancements in ultrasound elastography: A comprehensive review of principles and applications

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Abstract
A relatively recent noninvasive imaging technique that map elastic characteristics of soft tissues is called elastography. The application of ultrasound elastography for imaging tissues was first described in 1987 by Krouskop. Elastography has recently became available in a number of commercial ultrasound systems and is beginning to show promise in a variety of clinical settings. Elastography, which examines tissue elasticity, measures a tissue's capacity to withstand deformation when a force is applied or to return to its former shape when force is removed. assuming that a material's deformation doesn't depend on time and that it's entirely elastic. Hooke's Law can be used to characterize elasticity. There are several ultrasound-based elastographic techniques. Strain imaging, SWI (Shear wave imaging) are 2 primary types of ultrasonic elastography. There are 2 main forms of SWE: point SWE (pSWE), that samples a very short linear segment of tissue (few millimeter), and 2D-SWE (bi-dimensional SWE), which samples large square regions of 1-4 cm2. By utilizing altered elasticity of soft tissues brought on by particular pathological or physiological processes, clinical applications involving differentiation of malignant and benign tumors, evaluation of liver and renal fibrosis, quantification of portal hypertension, breast, prostate, thyroid, and lymph node imaging, among others.

Keywords: Elastography, imaging techniques, ultrasound

Introduction
Clinicians understand how crucial it is to make the right diagnosis. A diagnostic error could lead to the patient receiving potentially harmful, wrong medication or being denied timely access to effective therapy. A misdiagnosis can have disastrous results, even though a timely course of treatment could have restored a individuals complete health. For individual, getting correct diagnosis is important. Timeliness as well as accuracy are main concerns. For acute conditions, timing may be minutes; for subacute illnesses, it may be weeks.
Palpation has been utilized since beginning of medicine to find variations in tissue consistency that might point to existence of disease. Because mechanical characteristics of sick tissue are usually different from those of nearby healthy tissue, this method works. Moreover, palpation is not very effective at finding masses that are deeply buried relative to the skin's surface (Konofagou, 2004) [20].
Elastography has recently become available in number of commercial ultrasound systems and is beginning to show promise in a variety of clinical settings. It is a new dynamic approach that uses ultrasound (US) to quantify tissue stiffness and analyzes degree of deformation under the application of external force. Hence, its also called 'palpation by imaging'.

Principles and techniques of ultrasound elastography
Elastography evaluates a tissue's capacity to either revert to its initial shape after resisting a force or to remove distortion when a force is applied. If a material is totally elastic and its deformation (i.e., viscosity) is time-independent, then Hooke's Law can be used to explain elasticity:
$\sigma=\Gamma. \varepsilon$
σ=stress (force/area, top row)

ε=strain (expansion/length)
Γ= elastic modulus (stress divided by strain)
Here is a summary of the general idea behind harmonic, quasi-static, transient elastography:

1) Disturb tissue utilising a harmonic, quasi-static, transient mechanical force
2) Calculate the mechanical response that results (either strain, displacement, or vibration's phase and amplitude).
3) Apply a simplified or continuum mechanical model to recorded mechanical response to approximate biomechanical features of underlying tissue.

Types of elastography

Ultrasound is used in several elastographic techniques. The primary subfields of ultrasonic elastography include transient elastography, quasistatic elastography/strain imaging, acoustic radiation force impulse imaging (ARFI), SWEI (shear wave elasticity imaging), and SSI (supersonic shear imaging). Over the past ten years, there has been a consistent rise in elastography-related activities, indicating technology's effective use in a number of medical diagnostic and therapy monitoring applications (Sarvazyan *et al.*, 2011) [33].

Imaging technique called as USE (ultrasound elastography), that is sensitive to tissue stiffness, has been initially introduced in the 1990s (Gennisson *et al.*, 2013) [17]. It has been improved and developed further in recent yrs to allow quantitative assessments of tissue stiffness. According to Shiina *et al*. (2015) [34], elastography methods take advantage of changes in soft tissue elasticity caused by specific physiological or pathological processes. Therefore, elastography techniques can be utilised to differentiate between healthy and injured tissue for diagnostic purposes.

Ultrasound elastography techniques

These principles allow several USE approaches currently in usage to be grouped based on physical quantity being measured.

1) Strain imaging
2) SWI

Strain Imaging

Strain imaging has been first USE method to be introduced (Ophir *et al.*, 1991) [28]. There are 2 methods for performing US strain imaging:
SE (Strain elastography) as well as Acoustic radiation force impulse (ARFI) strain imaging.

Strain Elastography

Excitation method additionally divides strain elastography into:

1) Using the ultrasonic transducer, operator manually compresses tissue in first way (Ophir *et al.*, 1991) [28]. For superficial organs like the thyroid and breast, manual compression is quite effective; however, it is tough to assess suppleness of deeper organs including liver(Morikawa *et al.*, 2011) [25].
2) In 2nd excitation approach, internal physiologic motion (example; respiratory, cardiovascular) creates tissue displacement while the ultrasonic transducer is held stationary. This technique can be employed to evaluate deeper-located organs because it doesn't rely on compression that is administered superficially (Gennisson *et al.*, 2013) [17].

B-mode image is superimposed with an elastogram, semitransparent color map that shows strain readings. Low strain or stiff tissue is typically represented by blue, whereas high strain or soft tissue is indicated by red, though color scale may differ based on US vendor (Bhatia *et al.*, 2013) [3]. One pseudo-quantitative metric that can be used is the strain ratio, that is ratio of strain determined in a nearby (often normal) reference tissue ROI to strain recorded in target lesion ROI. When strain ratio is >1, target lesion compresses < normal reference tissue, indicating reduced strain as well as enhanced stiffness (Choi *et al.*, 2015) [5].

Acoustic radiation force impulse (ARFI):

This is an alternative method for measuring strain. This method uses short-duration (0.1 to 0.5 ms) high-intensity (spatial peak temporal average=0.7 W per cm^2, spatial peak pulse mean =1400 W per centimeter^2) acoustic "pushing pulse" or acoustic radiation force to displace tissue (by roughly ten to twenty micrometre) in a normal direction, or perpendicular to surface (Nightingale, 2011) [27]. Displacement inside designated ROI is then calculated using techniques similar to those utilized in strain elastography.

Shear wave imaging (SWI)

Using a dynamic stress, SWI generates shear waves in perpendicular or parallel dimensions, as opposed to strain imaging, which examines actual tissue displacement parallel to applied normal stress. By measuring shear wave speed, tissue elasticity can be evaluated quantitatively and qualitatively. For SWI, there are presently three technical methods:

a) 1D-TE (1-dimensional transient elastography),
b) pSWE (Point shear wave elastography)
c) 2D-SWE (2-dimensional shear wave elastography)

A) One Dimensional Transient Elastography

1D-TE system called FibroScan™ (Paris, Echosens, France) was first SWI system to be made commercially available for liver evaluation (Garra, 2015) [16]. Clinicians frequently employ it since it is most common and valid method for evaluating liver fibrosis. Fibroscan™ probe is single device which combines a mechanical vibrating mechanism with an US transducer. Even though 1D-TE is a US-based method, direct B-mode image guidance is not used. Operator selects imaging area by utilizing time-motion US, which finds liver portion 2.5 to 6.5 centimetres below skin's surface as well as clear of major vascular structures. To produce a low-quality image, many A-mode lines are assembled in time at various proximal positions.
Mechanical vibrating device then applies controlled vibrating external "punch" to body surface, producing shear waves that pass into tissue. Same probe then utilises A-mode US to measure shear wave speed, as well as Young's modulus *E* is calculated. According to Friedrich *et al.* (2012) [15], a tissue volume measuring around 1centimetres in width and 4 centimetres in length is measured; this is more than 100 times the volume of a conventional biopsy sample.
The following criteria are used by the examiner to validate repeated measurements: (1) at least 10 valid measurements; (2) IQR (interquartile range), which represents measurement variability, is < 30 percent of median value of liver stiffness measures; and (3) ratio of valid calculations to total measurements is greater than and equal to 60 percent

(Castera *et al.,* 2008). It takes about five mins to complete the exam (Friedrich *et al.,* 2012) [15].

B) Point shear wave elastography

Comparable to ARFI strain imaging, this method uses ARFI to cause tissue displacement in single focal site in normal direction. Unlike ARFI strain imaging, tissue displacement itself is not measured. Rather, by absorbing acoustic energy, portions of the longitudinal waves produced by ARFI are intra-converted to shear waves (Nightingale, 2011) [27]. The speed of the shear waves perpendicular to the plane of stimulation, C_s, is measured and either reported directly or converted to Young's modulus E in order to provide a quantitative estimate of tissue elasticity. Unlike 1D-TE, pSWE can be carried out with a standard US probe and standard US equipment (Friedrich *et al.,* 2012) [15].

When it comes to liver applications, pSWE has a number of advantages over 1D-TE. In order to choose a homogeneous region of the liver parenchyma devoid of big arteries or dilated bile ducts, the operator can first directly see the liver employing B-mode ultrasound. Additionally, pSWE generates shear waves that originate locally inside the liver, as opposed to 1D-TE, which produces shear waves by stimulation at the body surface. As a result, pSWE is less impacted by obesity and ascites (Ferraioli *et al.,* 2015) [12].

C) Two-dimensional (2D) Shear wave elastography

Most recent SWI method that makes use of acoustic radiation force is two-dimensional (2D) SWE. Unlike pSWE and ARFI strain imaging, which use a single focus point, many focal zones are interrogated in rapid succession, faster than shear wave speed. As a result, a nearly cylindrical shear wave cone is created, permitting for real-time 2D shear wave monitoring to quantify Young's modulus *E* or shear wave speed and construct quantitative elastogram. One advantage of this method is that it enables the operator to be guided by information on tissue stiffness and architecture by displaying color quantitative elastogram in real time on B-mode image (Ferraioli *et al.,* 2015) [12].

Magnetic resonance elastography

Dynamic elasticity imaging method called magnetic resonance elastography (MRE) quantitatively evaluates shear modulus (or stiffness) of tissues using mechanical waves (Muthupillai *et al.,* 1995) [26]. Most significant early clinical use of the technique, which is becoming available as an enhancement on traditional MRI scanners, has been for noninvasive evaluation of hepatic fibrosis, that causes liver tissue to become more rigid (Venkatesh *et al.,* 2008) [39]. 3 basic steps of MRE are

1. External motor is used to create shear waves in tissue at frequencies in range of 50 and 500 Hz.
2. A unique MRI method is used to image waves inside the body.
3. After data is processed, quantifiable images showing tissue's stiffness are produced.

Clinical Application of Ultrasound Elastography

Assessment of Liver Fibrosis with Different Liver Elastography Techniques

Since the right liver lobe has produced the most consistent results, it is advised to sample measurements there because cardiac motion can skew elastography readings (Toshima *et al.,* 2011) [37]. Skin pressure from the transducer should resemble that of standard anatomical B-mode imaging. When utilizing SWE methods, acoustic radiation force push pulse should be applied perpendicular to liver capsule. To reduce the pulse's refraction, measurements should be made at least 1 to 2 centimetres from liver parenchyma and 4 to 5 centimetres deep into the skin (Lorenzo *et al.,* 2019) [22]. The operator should confirm that there are no vascular, biliary, or rib shadows in the 1.0 cm of examined tissue that extends below and above user-designated ROI. Furthermore, the patient must be trained to cease breathing at end of normal expiration or inspiration in order for measures to be taken in neutral position, since deep expiration might inflate stiffness measurements.

Quantification of Portal Hypertension:

Most significant side effects of CLD (chronic liver disease) and cirrhosis is portal hypertension (PH). When portal pressures and HVPG (hepatic venous pressure gradient) rise to a level that the body cannot handle, complications including ascites, variceal bleeding, as well as hepatic encephalopathy may develop (Takuma *et al.,* 2015) [35]. Invasive diagnostics such as upper gastrointestinal endoscopy to determine existence and severity of esophageal varices and direct measurement of HVPG utilizing angiographic techniques are gold standards for evaluating PH in cirrhotic individuals.

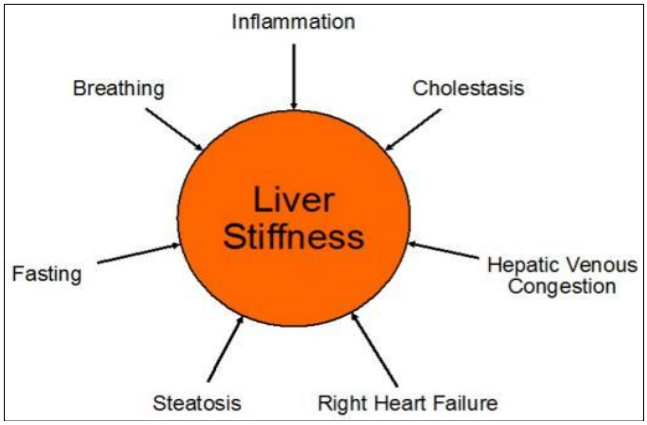

Fig 1: Factor affecting the liver measurements

Breast

According to National Cancer Institute, BC is most prevalent, with a lifetime diagnosis incidence of about 12.3%. Complete recovery is possible if breast cancer is detected early enough with screening testing.

US and mammography are two most popular techniques of imaging for BC screening. Both, however, have drawbacks, including low specificity of B mode US as well as false negative findings of dense breasts in mammographic examination (Saarenmaa, 2001) [31]. To enhance the noninvasive characterisation of breast lesions, USE offers an additional tool.

Strain Imaging of Breast Lesions

Using strain imaging, several factors was utilized to distinguish between benign as well as malignant breast masses. Strain ratio (fat-to-lesion ratio FLR), EI/B mode ratio (width or length ratio), as well as Tsukuba score (elasticity score) are most often used metrics (Ueno *et al.,* 2007) [38]. Stiffness map of tissue around and inside lesion serves as basis for Tsukuba score, which is 5 point color scale that is calculated using comparing stiffness of lesion to that of nearby tissue. The following criteria are used to assign Tsukuba scores:

1) Lesion has been equal or less than stiffness to nearby tissue;
2) Lesion was mixed (decreased, increased or equal) stiffness zones compared to nearby tissues;
3) Lesion has been stiffer than nearby tissue, moreover has been of smaller size on elastogram than B-mode US;
4) Lesion has been stiffer than nearby tissue, moreover has been of same size on elastogram as well as B mode US; and
5) Lesion has been stiffer than nearby tissue; moreover has been larger on elastogram than B mode US (Barr *et al.*, 2015) [2].

Greater scores equate to a higher probability of malignancy; lesion with score of 1 to 3 are likely benign, whereas score of 4 to 5 necessitates a biopsy.

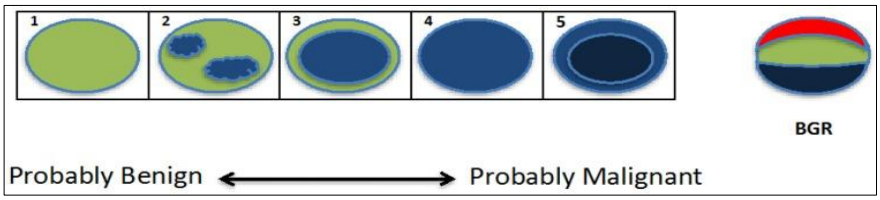

Fig 2: Tsukuba score

Shear Wave Imaging of Breast Lesions

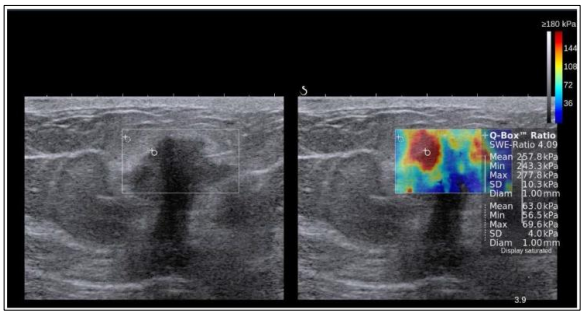

Fig 3: Side-by-side display of anatomical B-mode US image (left) and overlaid color map of simultaneous shear wave

In SWI, quantitative measurement of shear wave velocity(m/sec) or Young's modulus(kPa) in lesion acquired for every pixel in FOV (field of view) box that is shown color map, or as single value in limited fixed ROI (region of interest) (Barr *et al.*, 2015) [2]. Breast USE often uses a color range from 0(dark blue = gentle) to 180kPa(red=hard) (Lee *et al.*, 2014) [21]. Increased stiffness (red, yellow, and green) on the elastogram indicated a malignant origin, and a later biopsy revealed ductal adenocarcinoma. The incorporation of the elastography test in veterinary clinic oncology and research was suggested by Feliciano *et al.* (2017) [11].

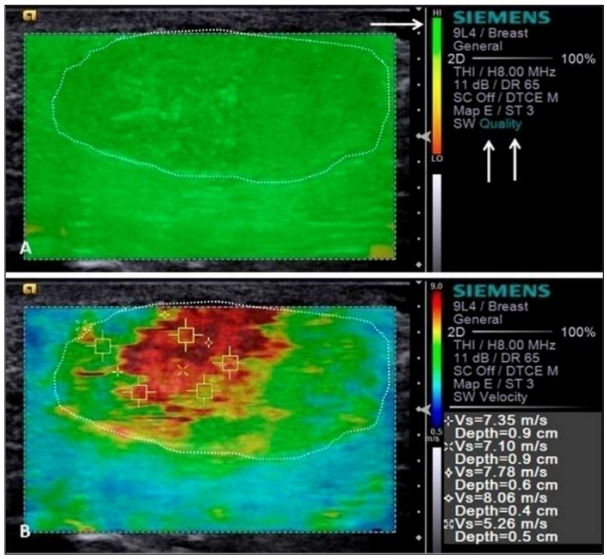

Fig 4: AFRI image of Canine mammary tumour

Thyroid

According to Yoon *et al.* (2015) [41], thyroid nodules is prevalent result in general population, appearing ~50% of pathologic exams at autopsy and up to 67 percent of adults by high-resolution B-mode US (Frates *et al.*, 2005) [14]. Given that thyroid cancer morbidity as well as mortality rise using disease stage, it's critical to identify minority of thyroid nodules are malignant. Only 4 to 8 percent thyroid nodules collected using FNA (fine needle aspiration) determined to malignant, despite a high prevalence of thyroid nodules (Faquin *et al.*, 2016) [10]. Thyroid nodules are first chosen for FNA using B-mode US characteristics. Malignancy is suggested by characteristics including spiculated edges, taller than wide form, apparent hypoechogenicity, as well as microcalcifications (Moon *et al.*, 2011) [24]. After that, FNA is usually utilized to confirm malignancy.

Thyroid Ultrasound Strain Imaging

Stimulus types and scoring methods can be used to categorize thyroid ultrasound strain imaging tests. External compression delivered by operator using ultrasound transducer is most often employed stimulus in thyroid ultrasound strain imaging. As an alternative, physiologic stimulation that uses carotid artery pulsations to cause nearby thyroid gland to move was investigated along promising outcomes. Two qualitative elasticity scores (Rago criteria, 5-point score akin to breast ultrasound elastography, or Asteria criteria, 4 point score) along with semi-quantitative thyroid stiffness index (strain in thyroid nodule/strain in background normal thyroid) are used as

scoring systems for thyroid ultrasound strain imaging. (Rago *et al.*, 2007) [30].

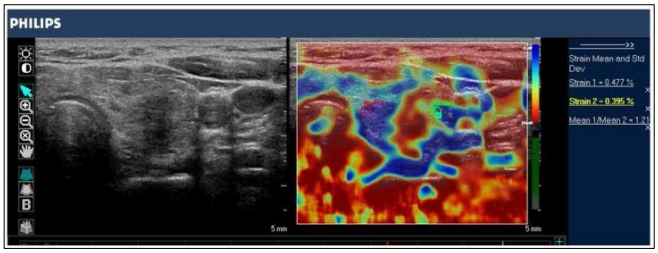

Fig 5: B-mode image (left) as well as color-coded elastogram (right) of thyroid nodule in left thyroid gland.

The elastogram indicates a malignant nodule becausehe tumor is red (stiff tissue) as well as normal thyroid tissue is blue (soft tissue). Histology, which revealed papillary thyroid cancer, validated this.

Thyroid Shear Wave Imaging

SWI of thyroid nodules delivers quantitative measures, as opposed to strain imaging.

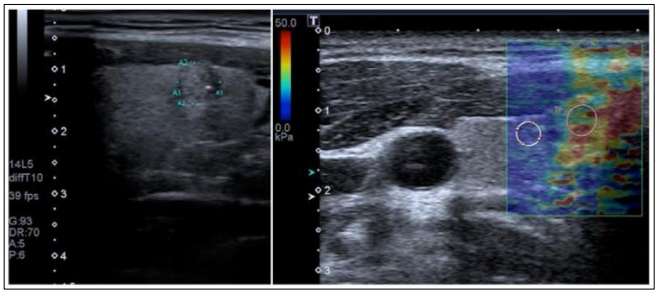

Fig 6: Shear Wave Imaging of thyroid

A tiny heterogeneous thyroid nodule (lesion within region of interest) using poorly described edges as well as microcalcifications in right thyroid lobe is shown in transverse B mode picture(left), which may indicate malignant origin. The corresponding color elastogram, which was acquired using 2D SWE on Toshiba Aplio 500(right), indicates that the nodule is malignant because it is more rigid (pink ROI; 32.7kPa) than the nearby normal parenchyma (white ROI; 7.4kPa).

Kidney

Two main kidney fibrotic diseases where USE possibly therapeutically helpful are interstitial fibrosis in allograft kidneys and CKD in native kidneys. Both of these illnesses have the potential to cause significant morbidity, death, and expensive medical bills. About 14% of people have CKD, which can develop into end-stage kidney disease that requires kidney transplantation or dialysis (Saran *et al.*, 2015) [32]. The most common technique for staging renal fibrosis at the moment is biopsy. Reducing the requirement for renal biopsy, ultrasound elastography techniques of strain imaging as well as SWI may helpful in noninvasively detecting the stage and tracking renal fibrosis (Anvari *et al.*, 2015) [1].

Although the accuracy of strain elastograms may be limited due to the challenge of delivering external compression to native kidney at retroperitoneal site, strain imaging was utilized to evaluate native kidneys (Saran *et al.*, 2015) [32]. Menzilcioglu *et al*. (2015) [23] compared the native kidneys of patients with as well as without CKD using SE. Discovered that CKD patients had a considerably higher average strain index value of renal parenchyma (1.81±0.88) than did healthy people (0.42±0.30). Since SWI is independent of external compression, for evaluating renal fibrosis in both native as well as transplanted kidneys, it is better than strain imaging.

Characterization of Focal Renal Lesions

Given that B mode US characteristics arn't exclusive to malignancy, USE may also useful in describing localized renal lesions. For instance, whereas benign angiomyolipomas (AMLs) usually show up as hyperechoic lesions on B-mode ultrasound, around 10% of instances of RCC (renal cell carcinoma) might show up hyperechoic lesions. Ten percent of the time, RCC can also be hypoechoic, which could lead to a mistake for benign cysts. There would be no need for further tests using intravenous contrast and/or CT or MRI if USE could differentiate benign from malignant kidney tumors. According to Goya *et al.* (2015) [18], a number of research have used both strain imaging and SWI to answer this topic.

Prostate

After skin cancer, second most frequent disease in males, is prostate cancer, which also ranks second in terms of cancer-related deaths, after lung cancer. If an aberration is discovered, 12-core sextant biopsy of prostate guided by transrectal ultrasonography (TRUS) is often next diagnostic procedure to rule out prostate cancer (Correas *et al.*, 2015) [7]. Restrictions of untargeted biopsy include possibility of false negative findings, bleeding and infection during the operation, and a high chance of discovering indolent tumors, which may or may not have therapeutic value (Woo *et al.*, 2015) [40].

Along with targeted biopsy, another potential indication for TRUS elastography including identification of lesion not observed using any prior imaging method and description of abnormal area before identified by any imaging method (e.g., prostate multi-parametric MRI, B-mode US, color Doppler US) (Correas *et al.*, 2013) [7].

Prostate Strain Imaging

Prostate tissue is manually compressed and decompressed using a transrectal transducer as the basis for strain imaging. Zhang *et al*. (2014) [42] executed meta-analysis encompassing SE data from 7studies (508patients) compared to histopathology following radical prostatectomy, showing pooled sensitivity of 72percent as well as specificity of 76percent for prostate cancer detection.

Prostate Shear Wave Imaging

Numerous Research demonstrated that SWI can effectively distinguish between benign tissue and malignant tumors.

Tendon Examination

Several scholarly works have addressed the subject of elastographic analysis of tendons. Achilles tendon examination is the primary focus (Ophir *et al.*, 1991) [28]. According to De Zordo *et al*. (2010) [9], tendons with noticeably higher compliance (red) typically had alterations in classic USS, although tissues that seem moderately soft in EUS did not depart from normal in B-mode assessment.

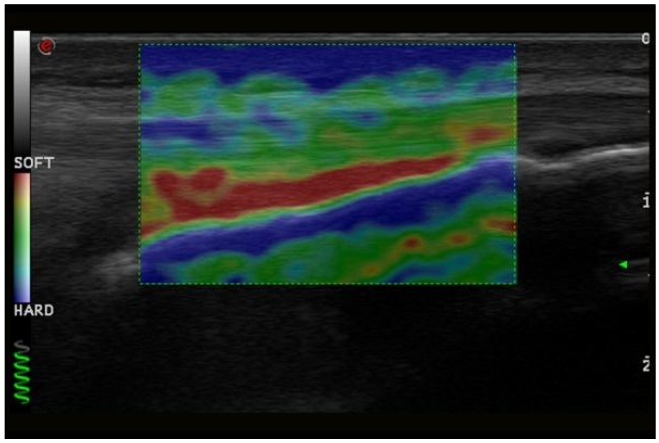

Fig 7: Normal image of Achilles tendon

Technical Limitations of Ultrasound Elastography:

Given the increasing clinical interest in creating new USE methods or improving ones that already exist, It's necessary to comprehend the technological constraints that impede measurement repeatability. USE is known to be impacted by several technical confounders.

Additionally, fluid or subcutaneous fat slows the spread of external stimuli applied to skin's surface (such as FibroscanTM), that might render measurements inaccurate when there is abdominal ascites or obesity (Palmeri and Nightingale, 2011) [27]. Furthermore, it is challenging to compare results from one manufacturer's system to another due to the variability of commercial settings and system design (Ferraioli *et al.*, 2012 and Cosgrove *et al*. 2013) [8].

Measurements using techniques that use external stimuli, such strain elastography, are hardest to replicate of the USE methods discussed above. According to Ferraoli *et al.* (2015) [12], the ROI selection process is also operator-dependent and may create unpredictability. Furthermore, strain concentration artifacts around particular structures may be caused by the amount of stress an operator induces. This can distort strain field as well as produce distortions in pictures or inaccurate measurements (Tang *et al.*, 2015) [36].

Conclusion

The most well-validated use of USE is for assessment of diffuse liver disease, which was widely used for non-invasive liver fibrosis detection and staging and for tracking effectiveness of liver treatment. Breast lesion that is focal. Additionally, USE has been thoroughly examined and is included as a related feature in the BI-RADS US lexicon's second edition. Although there is promising evidence that USE can also be used to guide TRUS-directed prostate biopsies, grade renal fibrosis, thyroid nodules, evaluate malignancy of focal liver lesions, lymph nodes, focal renal masses, as well as more, objective large-scale investigations are still needed. Additionally, it is necessary to work toward standardizing techniques so that values from different research may be compared and to create innovative results for existing technical restrictions as well as biologic/physiologic confounders. In upcoming years, USE will be widely used in clinical settings due to its enormous potential for a variety of clinical applications and ongoing development. However, USE is a potential approach that is being developed quickly and is being actively researched. USE holds considerable clinical promise despite the limitations mentioned above, as measurements have demonstrated a remarkable connection with both focal and diffuse illness conditions in numerous organs.

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