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# Ultrasound elastography: a brief clinical history of an evolving technique

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## ABSTRACT

The history of the emerging elastographic technique is presented. Ultrasound imaging of elasticity and tissue strain has gained clinical acceptance as an established technique useful in routine daily clinical practice.

## Introduction

Where are we coming from and where are we going [1, 2]? Developments in ultrasound imaging as we know them today are not self-evident but have undergone a continued and sustained evolution. WFUMB has a website showing the history of ultrasound worldwide [https://wfumb.info/pdfhistory-2/]. In addition, EFSUMB has prepared an online e-book on the history of ultrasound, which displays the history of its members [https://efsumb.org/history/] and is a work in progress. The "History of ultrasound in medicine from its birth to date on the occasion of the 50-year anniversary of EFSUMB" [3] and the "History of ultrasound in obstetrics and gynecology from 1971 to 2021 on the occasion of the 50-year anniversary of EFSUMB" [4] have been published. An editorial and booklet also summarize the birth and 50 years of EFSUMB [5, 6]. In addition, the history of contrast-enhanced ultrasound has been summarized [7]. Highlights of ultrasound over the past 70 years were summarized by Nielsen et al. [8]. The history of student ultrasound education (SUSE) is also being summarized in an ongoing study. The current article focuses on the history and development of elastography in ultrasound and how it became a major imaging modality in medical diagnosis. What followed the more than 2000 years of manual palpation?

Manual palpation during physical examination has been used in clinical practice for many centuries to distinguish harder areas from softer ones in the skin, organs, and/or tissues and to detect tumors. Palpation reflects various characteristics of a certain structure

including the position but also other features, including hardness, mobility, and pulsation. Palpation is subjective and mainly restricted to superficial anatomical structures or larger and deeper organs and neoplasia. In the Western World, the earliest description of this method was found in the Edwin Smith Papyrus scroll containing an ancient Egyptian medical text. It is believed that the author of this text was Imhotep, a priest, physician and presumed architect who lived between 3000 and 2500 B.C. A description of palpation techniques and results is also found in the Corpus Hippocraticum (Greece), a collection of ancient medical texts dating from the 5th to the 2nd century. Similar texts are found in the literature of the Far East but these have not been attributed to a single author.

Manual palpation still plays an important role in clinical practice, particularly in special situations, e. g., rectal digital examination of the prostate gland, intraoperative detection of certain structures, in self-examination of the female breast. However, it is a rather subjective method and is highly dependent on the experience of the person performing it. Elastographic methods are not a mere substitute for palpation but an additional technique that may allow further tissue characterization. The availability of semi-quantitative and quantitative methods to determine tissue stiffness allowed a real breakthrough in the diagnostic workup of patients including freehand, step and physiological displacement, low-frequency vibration, and radiation force techniques including acoustic emission shear wave and other impulse and displacement techniques.

## Early history of elastometry and elastography

Conventional ultrasound techniques are limited to image anatomy, the evaluation of tissue motion in real time, and the display of vessel anatomy blood flow mainly by Doppler techniques. In addition, emerging techniques exploit elastic properties of tissue including stiffness or hardness. The first elastometric and elastographic measurements using Young's or shear modulus were performed following classic mechanical models with the application of pressure and tension. From the physical point of view, elastography quantitatively maps Young's modulus, which corresponds to stiffness and shows the mechanical stress and strain of the material using a simplified approach via Hook's law [9]. However, as mechanical stress is not easily measurable in vivo, a strong assumption of homogeneous mechanical stress was initially assumed. Yet, considering different tissue structures within the human body, the application of pressure and tension as a homogeneous stress factor is not easily attainable [10–12]. In the beginning, simple (linear) properties of the underlying material were assumed with viscous and non-linear properties not taken into account.

Elasticity in general is described as the tendency of whatever material to resume its original size and shape after deformation by any kind of force or stress. Change in size or shape are defined as strain, which might be expressed as a ratio of a diameter (e. g., length) or as a histogram. Solid structures resist changes in shape and volume since they possess rigidity or shear elasticity, as well as volume elasticity. In contrast, fluids resist a change in volume, but not in shape as they possess only volume elasticity. The measurement of elastic properties (elastometry) of biological tissues was first described by King and Lawton. In their experiments, resonance was created with mechanical vibrations. They postulated that the relative elasticity of the examined tissue could be obtained [13]. Using tension experiments, the tissue was described as a mechanically non-linear, anisotropic, and inhomogeneous viscoelastic medium [14]. Mechanical tissue properties were examined by determining the elasticity, particularly in muscle and heart samples [15–19]. In these experiments, a correlation between tissue elasticity and the acoustic reverberation coefficient was found [20]. The measurement and interpretation of superimposing waves have also been used for elastography of non-linear tissue properties [21], such as in femoral muscles using Doppler ultrasonographic techniques and in a model using a vibrator-based model with a mechanically moving piston [22]. The description of these techniques and their corresponding biological tissues was characterized by a lack of uniformly defined terminology.

Magnetic resonance elastography (MRE) was initially developed at the Mayo Clinic, Rochester, MN, in 1995 [23–27]. In this modality, a static shear modulus is calculated from the phase shift of the MR signal and the corresponding sites in three dimensions with high-speed volume acquisition. The extended scan times of MRE and the application of vibrators to generate appropriate shear waves were problematic due to the high demand regarding operation time [28–34]. The advantages include that MRE is not restricted by the presence of air, gas, or bone, whereas the advantages of USE include that elastometry of soft tissue strain and elasticity is faster, more convenient, more accurate, and more precise. For an extensive review of the history of ultrasonic elasticity imaging technology development, refer to the articles by Wells and Parker [9, 35].

### Definitions, Elastography, and Elastometry

Elastography is a qualitative method and describes the pictorial representation of tissue stiffness. Elastometry is a quantitative method with objective measurements. Currently, two main sonographic elastography techniques are used in medicine: compression elastography (also called strain or static elastography or simply elastography) and shear wave elastography (elastometry). The term "static elastography" was used in contrast to dynamic elastography (MRE, sonoelasticity) and transient elastography. Shear wave elastography is quantitative, and compression or static elastography is qualitative or comparative (harder or softer compared to the environment). Compression elastography is particularly useful for characterizing circumscribed changes, and shear wave elastography is useful for studying diffuse (infiltrative) changes of parenchymal organs.

Ophir and colleagues in Houston, Texas, USA first used the term "elastography" in 1991 [36]. This group was the first to present elastographic images comparing tissue stiffness in following publications [37–41]. External pressure was used to compress the tissue and the subsequent deformation was recorded using ultrasound with cross-correlation between the pre- and post- compression signals. Using a simple mechanical model, the modulus of elasticity can be derived from the measured strain and the applied stress (Hooke's law). The tissue strain was estimated from the deformation which was combined with assumptions about tissue geometry, homogeneous stress, and material models through image reconstruction algorithms that generated images of the underlying qualitative material elastic moduli, the so-called elasto-

gram [36]. As subsequent elasticity imaging methods were introduced, this method became known as "compression elastography". Several years passed before compression elastography became commercially available. In fact, due to challenges with computation time and material model assumptions, commercial implementations do not generate "elastograms", but rather bypass the reconstruction step and provide images of the tissue strain. As such, commercial implementation of compression elastography is broadly called "strain imaging". Strain imaging became commercially available in the early 2000's (i. e., "real-time elastography" by Hitachi, Tokyo, Japan was introduced in 2003). Siemens also introduced its ''eSie Touch Elastography Imaging'' with accepted clinical applications focusing on the differentiation of benign from malignant lesions in the breast and the prostate. The stiffness of the tissue is shown on a color image superimposed on the standard B-mode ultrasound image [10].

Since that time, all major ultrasound manufacturers have provided strain imaging features, and many other clinical applications have been explored and thousands of studies have been published.

Using a linear tissue model, stiffness parameters were postulated and derived from the observed tension in the target tissue. Cross-correlation was used to compare the measurements in the native and compressed states. A major disadvantage was the linear estimation function of the underlying tissue model, the assumption of spatially homogeneous stress, and the high number of measuring procedures. The first trials were performed in human muscles and breast [42].

### An anecdote about the color schema used in strain elastography

The attempt by scientific experts to call for a manufacturer-independent standardization of color coding at the EFSUMB guideline conference on elastography in Bologna in September 2012 was not able to prevail against the color associations of the company representatives, which had traditional meanings. For the Japanese manufacturing company Hitachi, "red" (the red circle in the center of the Japanese flag, the sun) symbolized vitality and strength, and thus has positive emotional connotations as the color of life. Thereby the color "red" stands for the sun and for the qualities clear, bright, brilliant, vital, benign and thus "soft(er)". For manufacturers from Western cultures (for example, Supersonic Imagine), on the other hand, red is a color associated with aggressiveness and danger and is understood as a warning signal in a medical and technical context (fire). Therefore, ultrasound manufacturers from Europe and the USA code the tissue property "hard" with the color "red" in their elastography modules [43]. The manufacturer-dependent difference in the colors used to denote "stiffer" or "softer" must be taken into account during the examination.

### Ultrasound elastometry

This definition is focused on measurements. The term was used in the early years of development but has now been replaced by the term elastography.

### Freehand elastography

The development of freehand elastography was achieved by palpating the body using a hand-held transducer. The very first related ideas and reports were published by Christopher R. Hill [44], who inspired Jeff Bamber to explore this line of work in elastometry when he was a young postdoc [45–47]. The abstracts were presented at the World Federation for Ultrasound in Medicine and Biology conference Washington DC, United States (1988). This ended up being the strain imaging method implemented on most commercial systems, and differed from Ophir's original concept of strain imaging, which used a motor-driven transducer. Eventually Ophir stopped developing that approach and switched to the freehand method introduced by Bamber et al. [48].

The work done by Bamber et al. then developed in two directions [49].

1. A combined autocorrelation algorithm for overcoming computer speed limitations, first published by Shiina et al. [50], was subsequently further developed and commercially released by Hitachi in about 2003.
2. A general strain imaging algorithm for freehand use mentioned in two prize-winning conference presentations [51] (winner of the BMUS oral presentation prize) and [52] (winner of the RSNA INFO-RAD presentation certificate of merit) eventually became the algorithm commercially released by Zonare Ltd., in about 2008, on their Z.one Ultra scanner [53].

### Sonoelastography

The terms sonoelastography and dynamic elastography broadly refer to dynamic elasticity imaging methods that use harmonic vibrations (with fixed frequencies, which differ from transient excitation) to mechanically excite tissue and reconstruction algorithms to estimate tissue material properties and ARFI-based techniques. The term sonoelastography was the result of a collaboration between the NIH (Rehabilitation Division) and the Tokyo Institute of Technology. Elasticity measurements were performed on patients and compared [54]. Krouskop et al. (1987) reported one of the first quantitative measurements of tissue elasticity using gated pulsed Doppler to track the velocity of internal tissue displacements generated by an externally applied vibration [22]. These first 1D noninvasive measurements of the elastic modulus of soft tissue in vivo were aimed at predicting the interaction of a prosthetic socket with an amputee's residual limb.

Vibration amplitude sonoelastography was introduced by Lerner and Parker in 1987–88 [55–60]. Robert Lerner, a radiologist at the University of Rochester, had the experience of palpating prostate carcinomas that were not visible on ultrasound [35]. Subsequently, in 1987, Lerner and Parker conducted preliminary studies on vibration amplitude sonoelastography (sonoelasticity imaging) [57, 61]. The principle involved applying a low-frequency vibration (20–1000 Hz) externally to initiate internal vibrations in the tissue under investigation.

External vibrators generated shear waves in tissues, which were then monitored using Doppler sonography [57]. Transient elastography was introduced by Mathias Fink and collaborators from 1997 at the Laboratoire Ondes et Acoustique (now Institut Langevin) to

overcome the influence of boundary conditions observed in sonoelastography.

## Measurement of the stiffness of living tissue using ultrasonic radiation force

Sugimoto's group from the Tokyo Institute of Technology investigated the possibilities of tissue hardness measurements using the radiation force of focused ultrasound (ARFI) [62].

The authors used the force of a focused ultrasound beam to assess the longitudinal displacement of the tissue (like in strain elastography). A major possible disadvantage is that different elastic waves show significant interactions, such as conventional longitudinally orientated ultrasound waves (1500 m/s) modified by compression may be superimposed on the much weaker shear wave characteristics (1 m/s). However, in this study, the measurement is performed while avoiding the time zone affected by this shear wave after the radiation force is stopped. There is almost no effect on the displacement measurement in the focal region [63–66].

The deformation is measured by the pulsed Doppler method. As an advantage, this technique makes it possible to evaluate tissue hardness based on only the time dependence of relative displacement. By using the Voigt model, the viscoelastic value is derived from the change in deformation. Two-layer agar samples were employed, and a fundamental experiment was carried out to obtain the viscoelastic diagrams. These diagrams demonstrate the feasibility of the hardness measurement. The study was conducted between 1988 and 1993. For the first time, theoretical and experimental studies of *in vivo* measurement about tissue hardness were performed using focused ultrasound.

In 1988, in response to the request to display more qualitative information, such as hardness information, rather than just grayscale images, Professor Sadayuki Ueha of Tokyo Institute of Technology gave Tsuneyoshi Sugimoto, who was a master's student at the time, "tissue hardness measurement using radiation force" as a research topic. He continued this research as a doctoral research theme. The first problem was what was the hardness felt by the medical doctor. However, it was clear that, in general, biological tissue is a complex and viscoelastic body, and in vivo measurement is ultimately required. Because of that, no practical measurement method was established at that time. Therefore, with the cooperation of Professor Kouichi Itoh of Jichi Medical University, the relationship between the amount of pressurization and the amount of deformation was investigated for various human organs. As a result, it became clear that the hardness felt by human beings is related not only to elastic information but also to viscous information. After that, T. Sugimoto measured the deformation of tissue in the living body and its temporal decay due to the radiation pressure of focused ultrasound using the pulse echo method or the pulse Doppler method. A method to extract the feature quantity related to hardness from the deformation measurement was proposed. Moreover, in order to extend the proposed method to in vivo hardness evaluation, relative value measurement is indispensable. Then, a viscoelastic diagram was devised with elastic hardness on the vertical axis and viscous hardness on the horizontal axis. Furthermore, in order to evaluate the viscoelastic value of the biological tissue on the basis of the time change of displacement, a theoretical study was performed using the Voigt viscoelastic model, after the biological tissue was deformed by the radiation pressure of focused ultrasonic waves. As a result of the examination, it was clarified that the index value corresponding to each viscoelastic value of the model can be derived from the time change of displacement and the viscoelastic diagram can be created.

## Strain imaging, principles, and basic mechanisms

During conventional B-mode sonography with grayscale imaging, organs, including circumscribed lesions within the organs, can be palpated with the transducer by applying compression. Using this technique, the relative strain (or compression) of the target lesion can be evaluated in comparison to the surrounding tissues [67]. This can be semi-quantitated using a defined scale. The aim of this procedure is to gain information regarding tissue properties such as consistency, rigidity, size, and deformability. Ultrasound frequencies from 1 to 20 MHz with pulse repetitive frequencies of 1–10 kHz are used. In strain images, softer tissues will show a higher degree of deformation than stiffer tissues for a given compression (or applied stress). This deformation is visualized by ultrasonographic image processing with the examination being performed using standard ultrasound probes without any additional devices (pressure measurements, vibrators, etc.) similar to Doppler examination. The calculation of the strain is performed in real time with the results superimposed onto the conventional B-mode image [68].

### Probe systems, standardization of manual compression

#### Clinical strain measurement techniques

Relative strain is obtained by measurements and transformed into images with the extended autocorrelation method by the ultrasound systems. Color coding with a blending of transparency up to 100 % color saturation represents data translation of the obtained strain values. Using a measuring menu, a region of interest (ROI) within the elastographic window of the target lesion can be positioned and relative strain data obtained as the mean (%) of the areas within the ROI. These values can numerically supplement the color data, as is the case with thyroid examinations [69–73].

#### Strain Ratio

#### Fat-to-lesion relationship

Linear correlations between different strain parameters were first investigated using appropriately sophisticated phantoms with embedded target structures. These results permit the definition of these properties more quantitatively in terms of strain ratios. If ROI "A" is positioned over the lesion to be examined (e. g., a tumor appearing in blue) and a second ROI "B" is placed over a reference tissue, e. g., fat deposits, then the lesion A (ROI A) is expected to appear with very low values (low elasticity) in relation to the reference structure (fat ROI B) which will show much higher values (high elasticity). In the clinical environment, these observations correspond to characteristics found in the human breast. The fatty tissue of this

organ can be regarded as the reference structure from which strain parameters can be determined and expressed as the ratio B/A (fat-to-lesion), which is a dimensionless number. If this ratio is around 1.2, a lesion is highly likely to be benign, whereas for a ratio of greater than 8.5 malignancy is suspected. This ratio comparing the tissue of interest to fat benefits from the fact that fat tissue has very similar stiffness values from patient to patient. The fat-to-lesion ratio reduces other variabilities due to the experiment and technology. Consequently, the number of false-positive test results was reduced, particularly for benign lesions. A cut-off of 3.2 was defined [74–79].

### Strain Histogram

More recent developments regarding elastography data processing include signal averaging of the last recorded strain sequence with subsequent quantitative color coding. With the strain-histology mode, an ROI can be placed within the elastobox with discrimination of the elastography data. The difference with respect to the above-described method is that discrimination of elastographically generated data is possible using this technique. This ROI is placed over a suspected area (with blue color elements) and a histogram of the relative stretching in a blue area is generated within the range 0 (blue) to 255. This ROI is of statistical importance with regard to size and circumference. Quantitative values (from 0 to 255) are then available based on the data derived from appropriate numerical tables. In addition, a statistical distribution of the non-stretchable areas (blue) can be given. Within the ROIs blue areas will be recorded in clusters and calculated with regard to area and circumference, thereby enabling a statistical description (complexity, standard deviation). This technology is thought to noninvasively evaluate parenchymatous organs such the liver for staging fibrosis in addition to the classic gold standard of biopsy. However, the results that have been obtained in European cohorts do not allow the technique to be recommended in this setting [80, 81].

## Transient Elastography

Transient elastography began at the laboratory of Mathias Fink, in Paris, France in the late 1990 s [82–85]. The principle of transient elastography is to measure the speed of shear waves generated by a low-frequency transient vibration generated at the surface of a medium. The displacements induced in the medium by the propagation of the shear waves are tracked using ultrasound with a high frame rate (typically higher than 1000 frames per second). Initial developments by Catheline during his PhD under the supervision of Fink consisted of a transmission setup in which a mini-shaker and a single element ultrasound transducer were located on opposite sides of the to-be-measured medium [85, 86]. It was during the Sandrin PhD that the technique was extended to work in reflection mode, with the ultrasound probe directly located on the mini-shaker, thus resulting in a more compact and clinically applicable device. This research was the origin of the shear elasticity probe [83], while the diffraction effects associated with shear wave generation were better understood [87]. The transient elastography technique was initially a 1D technique. To extend transient elastography to 2D imaging, Fink had the idea of modifying the electronics of a time-reversal mirror made of an ultrasonic array (that he developed in the early 90s) to make an ultrafast ultrasound scanner able to acquire several thousands of images per second to track the propagation of shear waves in 2D [88].

Fink and Sandrin developed this ultrafast imaging ultrasound scanner [89] to obtain elasticity maps of biological tissues [67, 69]. The initial idea of Fink's group was to put the ultrasonic array on a low-frequency shaker to both generate the shear wave in the body and to observe it with the ultrasound array [88]. However, the probe was heavy and not easy to manipulate.

They later decided to use ultrasonic radiation force to generate the shear waves using the supersonic mode. Interestingly, Fink, Sandrin, and Manneville also applied the ultrafast imaging ultrasound scanner to flow imaging including vortex [90, 91]. The Princeps patent of transient elastography [Princeps Transient Elastography patent US 6,770,033] which was filed in 1999 covers different embodiments of the technology. Initially proposed for the food industry (yogurt and camembert) applications, transient elastography ultimately became established in the medical field ▶ **Table 1**.

### Transient elastography in the food industry

The results from applications in the food industry were less successful than initial expectations [92]. Real-time assessment of the viscoelastic properties of yogurt during manufacturing was performed in 1998. Although encouraging results were obtained based on yogurt purchased at the grocery store, about 15 days after manufacturing, tests at the manufacturing site were very disappointing. As a matter of fact, fresh yogurt was ultrasound transparent in the first couple of days, thus preventing any attempt to perform ultrasound elastography. In the case of meat or muscle, tissue anisotropy leads to major difficulties triggered by the complexity of the shear wave propagation. Another problem is the attenuation of ultrasound waves by fat which was a major obstacle to the noninvasive determination of the stage of maturation of cheese such as camembert (unpublished data).

### Transient elastography in the medical field

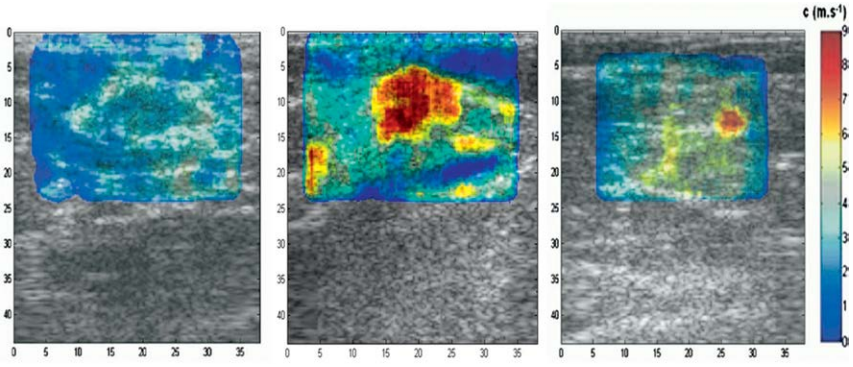
In June 2001, Laurent Sandrin and colleagues founded the firm Echosens (www.echosens.com) to further develop the transient elastography technique which was still immature. They created algorithms to reliably measure shear wave speed in vivo and designed an elastography device able to control and synchronize the low-frequency vibration while performing pulse-echo ultrasound acquisitions. The improved technique named Vibration-Controlled Transient Elastography (VCTE) was patented in 2002 [Vibration-Controlled Transient Elastography patent US 7,578,789] ▶ **Fig. 1**.

In parallel, they initiated a marketing survey to identify the potential market applications. During a meeting together with clinicians, the disadvantages regarding focal lesions such as breast and prostate cancers were discussed. The argument was that the differentiation of benign from malignant tissue by elastography might not be entirely reliable since even benign tissue can show different degrees of stiffness. A new important criterion regarding the evaluation of liver stiffness for fibrosis assessment was proposed. As stated in Hippocrates' (c. 460 – c. 370 BC) aphorisms, liver fibrosis is a well-known continuous process clearly associated with increased stiffness. Therefore, the Echosens team decided to focus

▶ **Table 1** Modern ultrasonographic elastography according to Cui et al. 2022 [126].

| Technique | Measurement | Stimulation | Method | Indicator | Company | System |
|---|---|---|---|---|---|---|
| Strain imaging | Strain or displacement | Manual compression | Strain elastography | Elasticity score<br>Strain ratio<br>E/B size ratio | Esaote<br>Hitachi<br>Aloka<br>GE<br>Philips<br>Toshiba<br>Ultrasonix<br>Mindray<br>Samsung<br>Siemens | ElaXto<br>Real-time tissue elastography<br>Elastography<br>ElastoScan<br>eSieTouch elasticity imaging |
| Shear wave imaging | Shear wave speed | Mechanical vibration | Transient elastography | Young's modulus (kPa) | Echosens | FibroScan |
| | | ARFI | p-SWE | Shear wave speed (m/s)<br>Young's modulus (kPa) | Siemens<br>Philips | VTQ<br>ElastPQ |
| | | | 2D SWE | Shear wave speed (m/s)<br>Young's modulus (kPa) | Siemens<br>SuperSonic Imagine | VTIQ<br>SWE |
| | | | 3D SWE | Shear wave speed (m/s)<br>Young's modulus (kPa) | SuperSonic Imagine | SWE |

VTQ: Virtual Touch quantification; VTIQ: Virtual Touch image quantification; SWE: ShearWave elastography; ARFI: Acoustic radiation force impulse; p-SWE: Point-SWE.




Fibroadenoma Birads 3 | Infiltrating ductal carcinoma grade III – Birads 5 | Infiltrating ductal carcinoma grade III – Birads 5

▶ **Fig. 1** First clinical images of shear wave elastography (SWE) using ultrafast ultrasound imaging and acoustic radiation force generation for breast cancer diagnosis.

their efforts on in-vivo liver parenchyma stiffness evaluation. The clinical usefulness of transient elastography to evaluate quite homogeneous and continuously increasing fibrosis accumulation appeared promising.

The technique was initially tested during a pilot study at Institut Mutualiste Montsouris (Paris, France) in 2001–2002. Stiffness results obtained with VCTE were compared with the fibrosis stages determined by pathologists from liver biopsies [93]. In a following multicentric study, the first clinically relevant results with evaluation of patients with chronic hepatitis C were published [94]. In December 2003, FibroScan obtained CE marking and was introduced on the market as the first commercially available noninvasive quantitative elastography device.

With FibroScan, shear waves are not only measured but can also be visually demonstrated. The tip of the probe is made of an ultrasound transducer mounted on the shaft of an electrodynamic ac-

tuator. The tip is actuated by transient excitation generated by the actuator, which induces shear waves in the tissues. Interestingly, only the longitudinal component of the shear waves is registered [87] since the displacements are measured on the ultrasound axis which is also the propagation axis of the shear waves. The controlled attenuation parameter (CAP) to detect and grade liver steatosis was introduced in 2010 [95]. Echosens was the first manufacturer to commercially offer stiffness measurement and ultrasound attenuation measurements in vivo. Since 2001, the company continues to develop the VCTE technique which is used in all devices named FibroScan [10].

## Acoustic Radiation Force Impulse (ARFI) based shear wave elastography

ARFI was developed by different researchers and commercially introduced by the Siemens company for the noninvasive measurement of liver stiffness. Sarvazyan et al. first proposed radiation force to make modulus maps [96]. Nightingale et al. first demonstrated in vivo use of radiation force of focused ultrasound to generate images [97] by measuring, point by point, the local displacement induced in tissue by the radiation force of a focused ultrasonic beam. Fink's group then decided to extend the radiation force concept to directly create a transient shear wave of high-amplitude to replace the one created by the mechanical shaker in 2D transient elastography. The two fundamental ideas behind the SSI technique are as follows: first, they proposed interleaved focused beam transmissions for shear wave generation and ultrafast plane wave transmissions for simultaneous ultrafast imaging. Second, they proposed to electronically control the radiation force pattern to create a fast moving "seismic" source of shear waves. If the source moves at a supersonic speed, it generates a high amplitude plane shear wave like in the "sonic boom" created by a supersonic plane. It was a very efficient way to produce shear waves in tissue. Tanter and Fink patented this SSI technique in September 2002 that led to the creation of Supersonic Imagine company in 2005. Bercoff, Tanter, and Fink used ultrafast imaging to detect the shear wave propagation produced by this supersonic seismic source [98]. This was the origin of the so-called supersonic shear wave scanner [98]. The supersonic shear imaging technique utilizes the underlying ultrafast ultrasound imaging technique developed for transient 2D elastography, but it replaces the vibrator with acoustic radiation pressure. First clinical validation of shear wave elastography using the SSI technique was published in 2008 [95] for breast cancer diagnosis. For a detailed review of the concept of ultrafast ultrasound imaging and applications in elastography and beyond, refer to [99].

Siemens introduced the first commercial SWE system in 2008. The Aixplorer (Supersonic Imagine, Aix-en-Provence, France) was then introduced in 2009 by Supersonic Imagine first for breast applications [98, 100–102] and other manufacturers followed [103].

ARFI-based shear wave elastography is an ultrasound technique, which is capable of measuring tissue elasticity quantitatively and also qualitatively (color-coded) when using 2D-SWE technology. Frequency-defined push pulses, with higher intensity and longer duration compared to that used for conventional B-mode images, lead to tissue vibrations at a region of interest (ROI) contributing to the generation of shear waves (the higher the frequency, the higher the registered velocity). The velocity of these shear waves can be determined using the same ultrasound transducer. Based on certain assumptions, this velocity can be converted to tissue stiffness (kPa) using the Young's modulus $E = 3\rho Vs^2$ [9]. As ARFI-based shear wave elastography did not rely on ultrafast frame rates, the shear wave propagation was not tracked in real time but rather reconstructed in a stroboscopic manner using several successive radiation force pushes and different imaging lines. This repetition of radiation force transmissions resulted in a higher acoustic energy deposit and thus limited the elastography frame rate and capabilities of ARFI-based shear wave elastography for real-time mapping of elasticity. McAleavey et al. developed a method called spatially modulated ultrasound radiation force (SMURF) [104]. In this method, instead of a sharp focal area, a spatially modulated pattern is used to create a unique spatial frequency within a tissue region.

### Fibrosis staging

It can be summarized that although VCTE has by far the highest level of evidence (more than 4,000 peer-reviewed publications in 2023), the number of publications on SWE has increased significantly in recent years due to the rapid evolution and spread of radiation force-based technologies. Several studies have demonstrated that both pSWE and 2D SWE techniques have similar accuracy to VCTE for the evaluation of liver fibrosis [5, 6, 103, 105]. However, VCTE and FibroScan are still considered to be the reference technique and the reference device, respectively, given the simplicity of use and high level of standardization of the technology.

### 2D Shear Wave Elastography

Two-dimensional shear wave elastography (2D-SWE) began in the laboratory of Mathias Fink, in Paris, France in the late 1990s [82–85, 89]. Standard ultrasound imaging was not able to efficiently track shear wave propagation in 2D due to its limited maximum frame rate of several hundred images per second. Fink and Sandrin [89] developed ultrafast ultrasound imaging which was initially obtained by only focusing in receive mode. Frame rates of several thousands of images per second were obtained and used to track shear wave propagation in 2D (both longitudinal and transverse tissue displacements) [82]. The absence of transmission focus yields a reduced penetration depth and lower contrast on B-mode ultrafast images. To solve this problem, Fink's group later introduced (in 2009) a multiple plane waves approach (today called coherent compound plane wave imaging) to synthesize virtual transmission focusing [106]. Bercoff, Tanter, and Fink further developed the technology in combination with radiation force for the generation of shear waves [107]. They first focused on studies with human breast, liver, and prostate, aiming at differentiating benign from malignant lesions and later on musculoskeletal applications [108, 109] and cardiovascular pathologies [110, 111]. With Jacques Souquet and Claude Cohen-Bacrie, they founded Supersonic Imagine with other colleagues in 2005. Both Echosens and Supersonic Imagine originated from Fink's laboratory.

### Further Developments

Echosens pioneered the field of liver stiffness and ultrasound attenuation assessments. Other manufacturers are developing or have already developed software for quantifying US beam attenuation. Preliminary results show that proprietary technologies implemented in ultrasound imaging systems seem more accurate than CAP for grading liver steatosis [112, 113]. Another available method for quantifying liver steatosis is based on the computation of the speed of sound. Initial results appear promising [114–116]. The backscatter coefficient also seems accurate for quantifying liver fat [117, 118].

## Modern elastography in clinical practice

Currently, the terms "elastography" and "elasticity imaging" are used broadly to describe imaging methods that provide information about tissue stiffness, including strain imaging, compression elastography, sonoelastography, acoustic radiation force impulse imaging, ultrasound shear wave elastography, magnetic resonance elastography, optical coherence elastography, et cetera.

Presently the following ultrasonic elastographic methods are widely being used in clinical medicine: strain imaging, ARFI imaging (both provide relative images of tissue stiffness), shear wave elastography (including vibration-controlled transient elastography), and cardiac strain imaging [119]. Shear wave elastography is quantitative, whereas strain and ARFI imaging yield qualitative images (harder vs. softer compared to the surrounding structures). The qualitative methods have mainly been used to characterize circumscribed lesions and heterogeneous tissues, whereas shear wave elastography allows both the evaluation of diffuse infiltrations of organs and circumscribed lesions [68, 120, 121].

Elastography has now found wide application including in pediatric patients with a large number of publications [122]. In addition to the assessment of liver fibrosis, the status assessment of breast lesions and thyroid nodules, multiparametric imaging of the prostate in the search for prostate carcinoma, there is a variety of other applications including the status assessment of lymph nodes, the assessment of the strength of any focal lesions compared to the surrounding parenchyma, the assessment of the age of vascular thrombi, assessment of the vascular wall, intestinal wall assessment in Crohn's disease, and last but not least for neurosurgery of brain tumors [35, 70]. Shear wave elastography was also recently identified as "the new wave of cardiovascular biomechanics" [123] since myocardial stiffness is assumed to be a very relevant biomarker of cardiac pathologies [124]. Recent studies suggest that diastolic myocardial elasticity is higher in heart failure with preserved ejection fraction (HFpEF) patients. Systolic myocardial elasticity was also shown to noninvasively measure cardiac myocardial contractility. Another challenging application is the combination of strain elastography and semiquantitative methods with endoscopic ultrasound.

By quantifying the elasticity of muscles, joints, ligaments, nerves, and soft-tissue musculoskeletal masses, shear wave elastography is also very promising for the follow-up of various traumatic and pathologic conditions of the musculoskeletal system [125].

## Elastography in endoscopic ultrasound (EUS)

Endoscopic ultrasound strain elastography is an important investigative component in the evaluation of focal lesions in the pancreas, gastrointestinal tract, and all structures in the sonographic window of EUS and lymph nodes [127–129]. Elastography in EUS evolved with the use of electronic EUS probes. Strain elastography in EUS is not without controversy. In order to be able to evaluate the findings, investigators must familiarize themselves with the method and study data. Profound background knowledge is required. The findings must be viewed in the overall context of B-mode, color Doppler imaging, and contrast-enhanced harmonic EUS imaging data. In EUS, strain elastography is used to evaluate the hardness of lymph nodes [130–133], pancreatic lesions [130, 134–142], and intramural wall structures of the gastrointestinal tract. The result of strain elastography in EUS is only one piece of the overall examination and is subject to some influencing factors. Elastography is possible with both longitudinal and radial probes. The transducer of the EUS probe is coupled to the wall with slight pressure. The interesting lesion should be centered. The elastography window, the region of interest, must be sufficiently large to detect the lesion of interest in comparison to surrounding tissues. By comparing the elasticity of the lesion with the surrounding tissue, the strain ratio can be calculated [131, 141, 143, 144]. Additional software can be used to calculate the mean histogram value from multiple images [132, 137]. Difficulties in deriving a strain elastography image in EUS result from very small lesions, deeply located lesions, and pulsations from the heart or large vessels. Limitations regarding the differentiation between benign and malignant lesions are caused by fibrosis (lymph nodes and pancreas) [136–139, 145], tumor necrosis, and liquid and semiliquid components. A lymph node or pancreatic lesion must be assessed in the overall evaluation of sonomorphology, color duplex imaging, and contrast-enhanced harmonic EUS together with strain elastography. Elastography in EUS is quite helpful for making clinical decisions. Lymph nodes can be selected for EUS-FNA using strain elastography. A pancreatic lesion that is hypervascularized and endosonographically soft is highly unlikely to correspond to ductal adenocarcinoma [146].

## Current terminology and guidelines on the use of ultrasound elastography

The first European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines and recommendations on the clinical use of elastography described the basic principles and technology and clinical applications in detail [147–149]. This was followed by the publication of the World Federation for Ultrasound in Medicine and Biology (WFUMB) 2015 and the Society of Radiologists in Ultrasound (SRU) 2015 [150]. All of these guidelines list the relative advantages of the different elastographic methods. The 2013 EFSUMB guidelines and recommendations on the clinical use of elastography were updated in 2017, with a focus on the assessment of diffuse liver disease [103, 105]. An update was also provided by WFUMB for liver elastography [80] and by the SRU [151]. In

addition to the 2013 EFSUMB guidelines, updates for non-hepatic applications were published in 2019 [70].

The basic principles of elastography remain unchanged since they were outlined in the first part of the original EFSUMB guidelines and WFUMB guidelines on this subject [147, 148]. The term *elastography* is considered a type of remote palpation that allows measurement and display of biomechanical properties associated with the elastic restoring forces in the tissue that act against shear deformation. This view unifies the different types of elastography, namely strain imaging, acoustic radiation force impulse imaging, and shear wave elastography (SWE) and explains why they all display images with contrast for the same underlying information, associated with the shear elastic modulus. The type of elastography most suited for the assessment of diffuse liver disease is SWE, which measures the speed of a shear wave in the liver. In the 2017 update [103, 105], VCTE is regarded as a type of SWE, although it differs from other SWE methods because it uses a body-surface vibration to create a shear wave, which then travels to the liver, whereas the other methods use acoustic radiation force to remotely create the shear wave within the liver. VCTE also generates shear waves at lower frequencies (around 50 Hz) compared to radiation force-based methods (around 200 Hz) leading to different shear wave speed values due to shear wave dispersion.

A variety of methods that measure shear wave speed should be grouped under the term SWE [81, 147, 148]. Ultrasound elastography uses ultrasonic echoes to observe tissue displacement as a function of time and space after applying a force that is either dynamic (e. g., thumping or vibrating) or varying so slowly that it is considered "quasi-static" (e. g., probe palpation). The displacement measurements may be represented in an elasticity image (elastogram), or as a local measurement, in one of three ways:

- Tissue displacement may be displayed directly, as in the method known as acoustic radiation force impulse (ARFI) imaging,
- Tissue strain may be calculated from the spatial gradient of displacement and displayed, producing what is termed strain elastography (SE), or
- When the force is dynamic only, the time-varying displacement data may be used to record at various positions the arrival times of propagating shear waves. These are used to calculate either regional values of shear wave speed (without making images) using methods referred to as transient elastography (TE, including VCTE) and point shear wave elastography (pSWE), or images of shear wave speed using methods referred to as 2D (or 3D) shear wave elastography (SWE). All of the methods in this third group come under the heading of SWE [80, 103, 105].

In order to properly introduce the method of elastography to the general public, the corresponding "How to perform" recommendations are available in addition to the guidelines [152–154].

## Conclusions and future perspectives

Compared to more than 2000 years of palpation, it is possible to look back on the successful and effective development of elastography thanks to the effective work of a large number of teams in the last 35 years. Elastography is an important additional imaging modality in many specialties. It should be actively used by investigators. In the evaluation of liver fibrosis, histology can be omitted in a large number of patients. In the overall context with B-mode sonography, color Doppler imaging, and contrast-enhanced US or EUS, lesions and their status can be more reliably delineated. Developments that compensate for the limitations of elastography, e. g., increased fat content, would be desirable to more accurately predict fibrosis even in hepatic steatosis. More accurate tissue analysis would be helpful to further delineate focal lesions. In contrast to the modern technique, there is still a widespread perception that elastography is mainly nice and colorful but not very helpful. Through continuing education and communication of information, this misconception should be eliminated so that examiners are even better able to make accurate diagnoses.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## Conflict of Interest

The authors declare that they have no conflict of interest.

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