

The EFSUMB Guidelines and Recommendations for the Clinical Practice of Elastography in Non-Hepatic Applications: Update 2018

Die EFSUMB-Leitlinien und Empfehlungen für die klinische Praxis der Elastografie bei nichthepatischen Anwendungen: Update 2018

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ABSTRACT

This manuscript describes the use of ultrasound elastography, with the exception of liver applications, and represents an update of the 2013 EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) Guidelines and Recommendations on the clinical use of elastography.

ZUSAMMENFASSUNG

Diese Arbeit beschreibt den Einsatz der Ultraschall-Elastografie mit Ausnahme der Leberanwendungen und ist eine Aktualisierung der Leitlinien und Empfehlungen der EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) von 2013 zum klinischen Einsatz der Elastografie.

ABBREVIATIONS

SE	strain elastography
SWE	shear wave elastography
pSWE	point shear wave elastography
TE	transient elastography
IQR	interquartile range
IQR/M	interquartile range/median
ARFI	acoustic radiation force impulse
BIRADS	Breast Imaging Reporting and Data System
TIRADS	Thyroid Imaging Reporting and Data System
TI	thermal index
MI	mechanical index
SR	strain ratio
SH	strain histogram
EFSUMB	European Federation of Societies for Ultrasound in Medicine and Biology
ECMUS	European Committee of Medical Ultrasound Safety
WFUMB	World Federation for Ultrasound in Medicine and Biology
LoE	levels of evidence
GoR	grades of recommendation

1. Introduction

This manuscript describes the use of ultrasound elastography, with the exception of liver applications, and represents an update of the 2013 EFSUMB (European Federation of Societies for Ultra-

sound in Medicine and Biology) Guidelines and Recommendations on the clinical use of elastography. A taskforce comprising 32 EFSUMB members was established in 2017 to draft a manuscript derived and updated from the previous EFSUMB guidelines on elastography: part 1 (Basic Principles and Technology) and part 2 (Clinical Applications) [1, 2]. For each recommendation levels of evidence (LoE) and grades of recommendation (GoR) were also included to show the clinical role and value of elastography in various non-liver applications. These were assigned according to the Oxford Centre for Evidence-based Medicine criteria (<http://www.cebm.net/oxford-centre-evidencebased-medicine-levels-evidence-march-2009/>). A consensus opinion was established by vote as follows: strong consensus (>95%), broad consensus (>80%), with approval, disapproval or abstaining from each participant. The manuscript was prepared initially by e-mail communication and was discussed in a consensus meeting in Frankfurt am Main, Germany, during February 2018.

2. Training

EFSUMB maintains a policy to attain high quality in all aspects of ultrasound education and to promote excellent professional standards in the practice of elastography. EFSUMB has defined three levels of competence, defined in the document on minimal training requirements [3], and these training levels also apply to the application of elastography. To ensure high-quality scanning and the lowest possible intra-operator variability, EFSUMB recommends that ultrasound elastography should be performed by operators that have passed competence Level 1. This is particularly relevant to the evaluation of focal lesions present in various

organs as these lesions must be first assessed by B-mode and Doppler ultrasound [4]. However, it is possible to train dedicated personnel to selectively perform elastography, e. g. for the thyroid gland [5]. Nevertheless, there has to be an appreciation of the difference between acquisition and interpretation of elastography, as the latter also requires knowledge of the patient's clinical history, hematological and biochemical parameters, and other comparative imaging findings. Furthermore, experience in ultrasonography is important as this influences the ability to perform shear wave measurements, particularly in obese patients [6]. For all ultrasound operators it is important to follow international guidelines, obtain adequate knowledge and training, and to perform elastography in accordance with national medico-legal regulations.

RECOMMENDATION 1

The operator should obtain adequate knowledge and training in ultrasonography and elastographic methods and perform the examination within the medico-legal framework of the specific country (LoE 5, GoR C) (For 20, Abstain 0, Against 0).

3. Terminology

Terminology of ultrasound elastography has been widely accepted [1, 7]. In the following, we briefly refer to the distinction between strain elastography (SE) and shear wave elastography (SWE), which includes acoustic radiation force impulse (ARFI) based techniques and transient elastography (TE). All available ultrasound elastography methods employ ultrasound to measure the internal tissue shear deformations resulting from an applied force but the type of force is important. If the force varies slowly relative to the shear propagation time to the depth of interest, as is the case for transducer palpation or physiological motion, it is considered quasi-static. The signal processing within the scanner for all current commercial ultrasound elastography methods begins with the measurement of tissue displacement as a function of spatial position and time, which is performed using cross-correlation tracking, Doppler, or other signal processing. The various elastography methods differ importantly according to what they do with these displacement data, to create an elastogram or elasticity measurement.

According to the EFSUMB guidelines, there are two options for the property displayed [8, 9]:

- Display tissue strain or strain rate, calculated from the spatial gradient of displacement or velocity respectively, as in SE. SE is a type of quasistatic elastography, because the applied force varies slowly, while the acquired images are qualitative for tissue properties.
- Display shear wave speed, calculated by using the time varying displacement data to measure the arrival time of a shear wave at various locations. There are a number of such methods, which are grouped under the heading SWE, and include transient elastography (TE), point shear wave elastography (pSWE)

and multidimensional SWE (2D-SWE and 3D-SWE). These are based on either a transient shear deformation induced by a controlled applied force (TE) or by quantification of tissue displacement induced by acoustic radiation force impulse (ARFI) [8, 9].

Most SE ultrasound systems do have an indicator (quality index) displayed in real time, indicating that the degree of compressions/decompressions is appropriate to generate repeatable and reproducible SE images [7 – 11]. The pressure and direction of compressions can be changed by the examiner, especially for external ultrasound procedures, with the compressions/decompressions needed by most systems being less than 2%. Quality factors for the shear wave speed estimate are available also for the 2D-SWE techniques. For ARFI-based techniques, an approach similar to that of TE has been employed to assess the quality of the measurement, including the interquartile range (IQR) values (i. e. the difference between the 75th and 25th percentile) and IQR/median. Assessment is considered reliable when the IQR is less than 30% of the median [8, 9]. The values obtained for SWE vary between different machines and are not interchangeable.

For more terminology and quality assurance details, refer to the EFSUMB and WFUMB guidelines on the use of elastography [1, 2, 7 – 11].

4. Safety

Elastography needs a “push” to the organ of interest that can be produced either mechanically or acoustically and may be quasi-static or dynamic. Different techniques are commercially available for the measurement of elastic values for an increasingly wide range of clinical applications. It is essential to know the principle of each of the techniques and how it is applied to understand the implications for patient safety [1 – 3]. A possible risk depends on the technology or type of elastography used and its anatomical application.

4.1 Methods

Techniques which utilize a mechanically induced force to generate SE, strain rate imaging, TE and time harmonic elastography (which uses external vibrations at multiple frequencies to create compound shear wave speed maps) share the same output issues as conventional B-mode ultrasound examination [1]. Therefore, applications of TE measuring quantitative stiffness data were demonstrated to be feasible for children to assess not only liver stiffness data [12, 13] but also spleen stiffness measurement [14] with no increased risk. Also, there is new evidence that patients with cardiac pacemakers or implantable cardioverter defibrillators, have a low potential to be harmed by TE applications [15, 16].

Acoustically induced techniques which require push pulses (known as ARFI imaging, ARFI quantification, pSWE, SWE [2]) on the other hand operate with higher output (higher TI and MI values) [17, 18]. The safety profile is comparable with pulse-wave Doppler mode and the acoustic output will depend on the applied sequence and repetition of pushing and tracking pulses.

A certain amount of energy is required to displace the tissue, even a few microns, using acoustic radiation force to generate shear waves within the tissue (longer pulses of up to 1000 μ s are needed, as compared to short pulses up to 2 μ s for diagnostic ultrasound) [8, 9]. The number of push pulses and repetitions during the measurement determine the amount of energy deposited in the tissue. Simulations have revealed a possible temperature rise of about 5 degrees Celsius if bone is present or sensitive tissues such as the eye and a fetus are involved with the temperature maximum at the focus [19–21]. Also, tracking beams, repeated with high frequencies, use pulse pressures close to the upper Food and Drug Administration limit ($MI \leq 1.9$) to ensure a sufficient signal-to-noise ratio for reliable detection [22]. During ARFI imaging, the displayed indices (MI and TI) may be underestimated.

RECOMMENDATION 2

To comply with safety, the ALARA (as low as reasonably achievable) principle should be applied when using ultrasound elastography (LoE 2b, GoR B) (For 18, Abstain 2, Against 0).

RECOMMENDATION 3

Caution is recommended for shear wave elastography using long pulse sequences, particularly when exposing sensitive tissues (LoE 2b, GoR B) (For 19, Abstain 1, Against 0).

5. Breast

5.1 Background

Breast elastography is used for differentiating benign focal lesions from suspicious focal lesions – benign lesions have low stiffness, while malignant lesions have high stiffness. Both strain and shear wave methods have been evaluated for improving the generally high sensitivity and specificity of the Breast Imaging Reporting and Data System (BIRADS) and it is recommended that they are used as add-ons to the regular B-mode examination.

5.2 Methods

5.2.1 Strain elastography

SE images in breast ultrasound may be evaluated visually using the Tsukuba score (also known as the Itoh or Ueno score) [23], semi-quantitatively using strain ratio (SR) or strain histograms (SH) [24] or by the lesion size on elastography divided by the lesion size on B-mode ultrasound (E/B ratio) [25]. An optimal elastogram includes the glandular tissue, the surrounding fat, and the lesion [11].

The Tsukuba score is a five-point visual scale, where the lesion is scored according to the extent of stiff tissue. A lesion not stiffer

than the surrounding tissue is designated as 1, a value of 2 or 3 is assigned to lesions with increasing proportions of stiff tissue, a value of 4 is assigned to a lesion that is stiffer throughout, and 5 indicates that the stiffness extends beyond the margins of the mass seen on B-mode. The best cut-off point for discriminating benign from suspicious masses has been shown to be a score between 3 and 4 [26–28]. It has been shown that SE, in addition to B-mode ultrasound, increases the specificity of the examination (up to 97%) and helps to avoid unnecessary biopsies [29].

Anechoic lesions with liquid content show a typical three-layered echo-pattern in SE, called the Blue Green Red (BGR) sign.

5.2.2 Shear wave elastography

For SWE, findings are measured in m/s but may also be reported in kPa depending on the system used. As for SE the optimal image should include the lesion, fat and the glandular tissue. Malignant tumors tend to be more heterogeneous and stiffer than benign tumors. Often the stiffness seems to be most marked at the periphery of the mass and may demonstrate such high values that the system is unable to record a measurement.

5.3 Clinical Applications

5.3.1 Evaluation of breast masses

An early study using SR in 99 nonpalpable benign and malignant breast masses established an optimal cut-off of 2.24 and stated that the higher the SR, the higher the risk of malignancy [30]. The cut-off for SR has since been evaluated in several studies with different systems and is incomparable between different vendors, as seen in other organ applications. In a recent meta-analysis [31], the accuracy of SR was evaluated based on 9 studies (2087 tumors) with a sensitivity of 0.88 and a specificity of 0.83. The E/B ratio (ratio of the lesion size with SE to the lesion size with B-mode ultrasound) increases with increasing tumor grading, with low grade tumors having a ratio close to 1 [11].

In the BE1 multicenter study SWE results were studied retrospectively and several parameters were examined. One finding of the study was that the addition of SWE resulted in some BIRADS 3 lesions appearing stiffer and potentially allowed for an upgrade to a 4a mass, requiring a biopsy. If SWE had been included and used in this way, the overall sensitivity and specificity would have increased to 98.6% and 78.5% versus 97.2% and 61.1% for B-mode ultrasound alone [32]. Increasing stiffness has also been shown to correlate with increasing tumor grading [33–36].

In cysts with pure liquid, no signals are obtained from the shear waves and the lesion is seen as black. However, in cysts with a higher viscosity shear wave signals may be obtained depicting the cyst as having a low stiffness.

5.3.2 Evaluation of axillary lymph nodes

Both SWE and SE have been used in the evaluation of axillary lymph nodes, with one study reporting a sensitivity and specificity of 82.8% and 69.6%, respectively, using SWE to distinguish between benign and malignant lymph nodes using a cut-off of 1.44 m/s [37]. Using SE, the sensitivity was 60% and the specificity was 79.6% for the diagnosis of malignancy [38]. Another study

compared the AUROC for elastography with the AUROC for conventional B-mode ultrasound. The values were 62 % and 92 %, respectively, and no significant improvement was shown when elastography was added to B-mode ultrasound (AUC: 93 %) [39].

5.3.3 Prognosis

The key factors for prognostic information are provided by histological and pathological analysis, based on cancer sub-typing and also immuno-histochemical analysis. Univariate analysis has demonstrated a significant correlation between stiffness of a breast cancer and prognostic factors. For SWE, studies reported an increased stiffness for cancer grading of more malignant tumors, larger lesion size, tumor and lympho-vascular invasion in invasive breast cancer. Triple-negative carcinomas (testing negative for oestrogen, progesterone and HER2 receptors), which are often evaluated with BIRADS 3 on B-mode ultrasound, are quite difficult to assess in clinical practice. SWE is reported to show increased stiffness in these cases and can lead to the correct assessment [33–35, 40].

A study reporting the analysis of 396 breast cancers showed that SWE is an independent predictor of lymph node metastasis when using E-mean (mean elasticity values for a defined region of interest) as a descriptor. When the breast cancer had E-mean < 50 kPa, only 7 % of the lymph nodes were metastatic, whereas 41 % of the lymph nodes were positive when E-mean was higher than 150 kPa [41].

5.3.4 Efficacy of neoadjuvant therapy

The tumor response to neoadjuvant chemotherapy may be evaluated with different imaging modalities. In a study with a small sample size of 15 patients, the possibility of predicting response to neoadjuvant chemotherapy with SE was reported [42]. However, larger studies for SE using commercially available systems are not available. A significant correlation between response to treatment and the decrease in heterogeneity and tumor stiffness has been reported [43, 44]. Currently, imaging methods other than elastography should be used in the evaluation of tumor response to neoadjuvant chemotherapy.

5.4 Limitations and artifacts

Pre-compression with the transducer should be avoided as this increases the stiffness of all tissues. Normal fatty tissue has E-mean values ranging from 5–10 kPa (using SWE) if the scale is from 0–180, although the color scale may be changed. If the color changes according to these values, the pre-compression should be adjusted [45].

RECOMMENDATION 4

Ultrasound elastography could be used to increase diagnostic confidence in the characterization of a breast lesion (LoE 2a, GoR B) (For 20, Abstain 0, Against 0).

RECOMMENDATION 5

A BIRADS 3 lesion appearing stiffer on breast ultrasound elastography should be considered for biopsy (LoE 2a, GoR b) (For 20, Abstain 0, Against 0).

6. Prostate

6.1 Background

The screening standard for prostate abnormalities has been the combination of digital rectal examination and the serum prostate specific antigen (PSA) level. However, PSA screening leads to a substantial number of unnecessary biopsies in patients with no or indolent cancer who do not need immediate treatment [46] and has a high false-negative rate (17–21 %) [47]. Saturation biopsy (up to 40 cores) can rule out prostate cancer, but has many limitations, including cost and morbidity, and over-diagnosis of microscopic tumor foci [48]. SE and SWE assessment and identification of stiff prostatic tissue with a transrectal ultrasound approach can be useful as described in previous elastography guidelines [1].

6.2 Methods

6.2.1 Strain elastography

Hypoechoic stiff lesions of the prostate are suspicious for malignancy [49]. Slight compressions are induced using the transrectal transducer. The use of an inflatable balloon has been suggested to improve the standardization of compressions. The elastography box should cover the entire gland and the surrounding tissues, but avoid the bladder. Semi-quantitative information can be derived by measuring the SR between two regions of interest.

Using stepwise scanning of the prostate from base to apex, SE allows detection of stiff regions and provides stiffness comparisons between lesions and the adjacent prostatic tissue. Most studies report a significant improvement in prostate cancer identification with SE, including guidance for targeted biopsies [50–53]. However, there are still controversies and one recent study reported the inability to differentiate prostate cancer from chronic prostatitis [54]. The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy for identifying cancer index lesions for focal therapy were 58.8 %, 43.3 %, 54.1 %, 48.1 %, and 51.6 %, respectively [55]. Though improvement in biopsy guidance is reported in many studies [53, 56, 57], others did not confirm this result [58].

6.2.2 Shear wave elastography

Unlike SE, SWE requires no compression on the rectal wall [59]. Optimized settings include maximizing penetration and setting up an appropriate scale. The image can cover the entire gland in the transverse section when the prostate is not markedly enlarged. Otherwise, each side of the prostate is imaged separately from base to apex for review and measurements of elastography values. For each plane, the transducer is maintained in a steady

position until the image stabilizes. Hypoechoic stiff lesions are suspicious for malignancy. The ratio between the mean elasticity values of two regions can be calculated.

In young healthy subjects the entire prostate exhibits a uniform low stiffness appearance with low elasticity values [60, 61]. In benign prostate hyperplasia, the peripheral zone remains homogeneous with low stiffness, while the central and transition zones become heterogeneous and stiff, particularly when there are calcifications. Typical benign peripheral lesions have a similar stiffness as the surrounding normal parenchyma, while cancers are stiff [60, 61]. The best cut-off stiffness value to maximize the negative predictive value for malignant lesions was found to be 35 and 37 kPa in two studies with 2D-SWE [57, 58] with a sensitivity, specificity, PPV and NPV of 63 %, 91 %, 69.4 %, and 91 %, respectively. The SWE ratio provided additional information as it considers the increased stiffness of the peripheral zone from calcification and chronic prostatitis. The ratio showing the best accuracy to differentiate between the nodule and the adjacent peripheral gland for benign and malignant lesions was 1.5 ± 0.9 and 4.0 ± 1.9 , respectively ($p < 0.002$) [61].

6.3 Clinical applications

Several studies indicate that elastography provides useful additional information to conventional transrectal ultrasound for prostate cancer detection. Applications that have been more extensively investigated include the characterization of abnormal areas, the detection of lesions not seen with any previous imaging technique and biopsy targeting. Additionally, elastography could be combined with other imaging techniques in the same examination to address the heterogeneous growth pattern of prostate cancer. Improvement in detection and prediction of cancer was seen during multiparametric ultrasound when elastography is used as a triage test followed by contrast-enhanced ultrasound or as an adjunct during image fusion of magnetic resonance imaging and transrectal ultrasound [62–65].

6.4 Limitations and artifacts

Both techniques suffer from intrinsic limitations: not all cancers are stiff and not all stiff lesions are cancers (particularly in the presence of calcifications and fibrosis). The transrectal technique carries an intrinsic risk of inadvertently applying excess pre-compression because of the end fire arrangement of the transducer.

Limitations of SE include the non-uniform force over the gland and intra- and inter-operator dependency. 2D-SWE has additional limitations such as a slower frame rate and the small elasticity box which only allows examination of half the gland at a time.

RECOMMENDATION 6

Transrectal ultrasound elastography of the prostate could be used to identify suspicious target regions for biopsy in order to increase the diagnostic yield of biopsy (LoE 2b, GoR b) (For 20, Abstain 0, Against 0).

7. Thyroid

7.1 Background

Chronic thyroiditis and malignant tumors increase diffuse or focal thyroid stiffness [66]. Elastography is emerging as a potential indicator for these abnormalities and may provide additional information to support clinical decision-making.

7.2 Classification systems – TIRADS

Accurate estimation of the malignancy risk by ultrasound could help to select thyroid nodules with a high risk of cancer for fine needle aspiration and biopsy (FNAB). More recently, an assessment concept called “grading system” or “reporting system” termed “Thyroid Imaging Reporting and Data System” or TIRADS has emerged, allowing thyroid nodules to be classified into categories related to their ultrasound patterns [66–74].

7.3 Methods

SE is the initial method which has been implemented on most commercially available ultrasound systems, thus evidence is quite consolidated on this topic, with a number of studies and meta-analyses being published [75–81]. More recently, SWE has become available for thyroid evaluation with multiple studies reported [82–85].

7.4 Clinical applications

7.4.1 Strain elastography

Two different methods of assessing SE outcome have been reported, namely semi-quantitative scoring systems involving five, four, or two color patterns respectively [86–88] and SR, which compares the strain values of the nodule to those of the surrounding thyroid parenchyma (parenchyma-to-nodule ratio) or the surrounding muscles (muscle-to-nodule ratio) [4, 89]. Although no consensus has been reached about the cut-off values to use for SR (as low as 1.5 for benign nodules and as high as 5 for malignant nodules have been suggested), it has been shown that the SR has a lower inter-observer variability and is more easily learned than simple color patterns [4]. Importantly, most studies on SE were performed in selected populations with a high prevalence of malignant nodules. It has been shown that SE has a lower sensitivity and specificity in a low-risk population [4, 90]. Furthermore, tumors other than papillary carcinomas may have an unexpectedly low stiffness [4, 91, 92]. In patients with coexistent diffuse thyroid disease, the role of SE in detecting malignant nodules has still not been validated [4]. The most recent meta-analysis [81] included 13 studies on SE performed from 2007 to 2016, with sensitivities ranging from 48 % [93] to 97 % [94] and specificities ranging from 64 % [95] to 100 % [94]. The pooled sensitivity and specificity of the meta-analysis was 84 % (95 % CI, 76 %–90 %) and 90 % (95 % CI, 85 %–94 %), respectively, with pooled accuracy of 94 % (95 % CI, 91 %–96 %).

7.4.2 SWE

The mean SW elasticity for malignant thyroid nodules is 19.60–52.18 kPa with a reported cut-off value of 26.6–65 kPa [96–

104]. For benign nodules the mean elasticity is lower at 15.3–28 kPa [96–104]. Studies included nodules from 2–71 mm and most were papillary carcinomas. Therefore, cut-off values have a wide range and a single threshold cannot be established [82, 83, 85]. The sensitivity for SWE has been reported as 63.8–93.8%, and the specificity as 50–88.2% [96, 97, 100, 102, 104–106]. The most recent meta-analysis [82] included 14 studies and 2851 thyroid nodules with cut-off values ranging from 26.6 to 85.2 kPa. It concluded that 2D-SWE has a fairly good diagnostic accuracy although the sensitivity and specificity are average. Studies using ARFI indicated that it enables the evaluation of tissue stiffness and the mean SWE velocity for malignant nodules is 3.13–3.9 m/s [96, 107–111] with a cut-off value 2.15–3.77 m/s [96, 107–111]. Interestingly, a recent meta-analysis [81] showed that SE and SWE are not significantly different in terms of sensitivity (SWE pooled sensitivity = 79% [95% CI, 73%–84%]) but SE is superior to SWE in terms of specificity (SWE pooled specificity = 87% [95% CI, 79%–92%]) and accuracy (SWE pooled accuracy = 83% [95% CI, 80%–86%]).

7.5 Limitations and artifacts

The thyroid is among the most extensively investigated non-liver application after the breast. Nevertheless, the relevance in the malignant/benign differential diagnosis remains unclear. Recent American Thyroid Association and Korean guidelines do not consider stiffness as an indicator of malignancy. However, elastography was recently mentioned by both the French TIRADS and the EU-TIRADS as a complementary imaging tool [70, 112]. Thus, elastography should not replace B-mode US assessment but should be used as a complementary tool for assessing nodules for fine-needle aspiration, especially due to its high negative predictive value (only 3% false-positive results) [70].

RECOMMENDATION 7

Ultrasound elastography of the thyroid could be used as part of nodule characterization, particularly with use of semi-quantitative methods (LoE 2A, GoR A) (For 17, Abstain 3, Against 0).

8. Pancreas

8.1 Background

Elastographic properties of the pancreas may be studied with a transabdominal approach, as well as with an endoscopic or intra-operative ultrasound approach. Pancreatic transabdominal ultrasound elastography requires clear visualization of the gland (which is not always possible with external ultrasound), whereas endoscopic ultrasound (EUS) is a minimally invasive technique that provides high-resolution images of the pancreas, with the close vicinity of the transducer and the pancreas avoiding artifacts (fat, gas, etc.).

8.2 Methods

For the elastographic assessment of the pancreatic parenchyma and focal pancreatic lesions, SWE [7, 113–133] as well as SE [7, 119, 120, 123, 124, 131, 134–177] may be used. Transabdominal elastography can be performed both by using SE with qualitative and semiquantitative information, and SWE with qualitative and quantitative data. EUS can be performed currently only with SE techniques with qualitative and semi-quantitative evaluation [178]. For the semi-quantitative approach, both SR and SH can be used in order to obtain an estimate of the elasticity [153].

The normal pancreas has a uniform intermediate stiffness throughout the head, body, and tail [123, 124, 129, 130, 132]. Embryologically, the pancreas develops from two primordia, a dorsal and a ventral part. With SE, elasticity properties seem to be almost similar in the two parts of a healthy pancreas with a homogeneous low stiffness appearance [158]. Studies in normal volunteers affirmed that the mean wave velocity value obtained in a healthy pancreas with the ARFI technique is approximately 1.40 m/s [114].

8.3 Clinical applications

8.3.1 Effect of aging, gender, anatomical segment, and other variables

With advancing age, pancreatic elasticity may decrease as has been shown consistently for SE [134] and SWE [121, 129, 131]. Data on the influence of gender, body mass index (BMI), and pancreatic echogenicity are not consistent, with most studies demonstrating no significant influence of these variables on shear wave velocity [113, 116, 121, 129, 131]. One study using SE with SH analysis showed lower mean strain values in patients with a hyperechoic pancreas and higher BMI [134]. In another study shear wave velocity was significantly lower in men compared to women [129].

8.3.2 Acute pancreatitis

The consistency of the pancreatic parenchyma usually becomes stiffer in acute pancreatitis as compared to the healthy pancreas, which is identifiable with SE and SWE, including ARFI [116]. Necrosis is identified as a low stiffness area. However, studies using elastographic techniques in patients with acute pancreatitis are conflicting [116, 130, 179, 180]. One prospective study failed to find significant differences in pancreatic shear wave velocities between patients with acute pancreatitis and healthy volunteers [130]. Three other studies showed significantly higher pancreatic shear wave velocities in patients with acute pancreatitis compared to persons with a normal pancreas [116, 179, 180]. In one of these studies, shear wave velocities of patients with acute pancreatitis were higher than in chronic pancreatitis patients [179]. Another prospective study compared transabdominal ARFI imaging with B-mode ultrasound and computed tomography (CT) at hospital admission for the diagnosis of acute pancreatitis. SWE was more accurate (100%) for the diagnosis of acute pancreatitis than CT (76%) and B-mode ultrasound (53.4%). The authors were able to identify segmental involvement of the pancreas as well as parenchymal necrosis [180].

8.3.3 Chronic pancreatitis

Qualitative SE displays the pancreatic parenchyma in chronic pancreatitis with a heterogeneous colored (honeycombed) pattern, with predominantly stiffer strands. Nevertheless, differential diagnosis between chronic pancreatitis and pancreatic tumor can be challenging during elastography because both diseases have a similar stiffness. Therefore, elastography alone is not able to distinguish chronic pancreatitis from malignant tumors [164].

Both SWE and SE may be used to assess pancreatic fibrosis and chronic pancreatitis and in particular to grade the severity of fibrosis (based on simple scoring systems with 4 grades) and chronic pancreatitis [115–117, 122–124, 127, 131, 136, 138, 142, 146, 151, 164, 167, 169, 170, 179, 181–185]. In patients with chronic pancreatitis, pancreatic shear wave velocities [116, 124, 127, 131, 186], SR [148] and SH [146] are significantly higher than in healthy volunteers or patients with a normal pancreatic parenchyma. Several studies have shown a significant correlation between SWE [117, 123, 184] and semi-quantitative SE [138, 167, 169, 185] and histological pancreatic fibrosis stage. Moreover, SWE [122, 124, 169] and SR [141] are significantly correlated with stages of chronic pancreatitis derived from EUS-based criteria for the diagnosis of chronic pancreatitis. Another recent study showed significantly higher pancreatic SWE velocities in patients with clinical markers of severe disease (disease duration > 10 years, chronic analgesic treatment, lower body weight) [127]. A direct relationship between the SR of pancreatic parenchyma and low stiffness peripancreatic tissue and the probability of pancreatic exocrine insufficiency was shown in a study using EUS-SE [136]. Another study reported an inverse correlation between preoperative SW velocity and postoperative exocrine function in patients undergoing pancreatic resection [117].

EUS elastography might be helpful in identifying patients with autoimmune pancreatitis, due to the unique appearance of diffuse stiff tissue with an elastographic pattern visible both in the mass lesion and in the adjacent pancreatic parenchyma, with mainly stiff color signals that were evenly spread over the head and the body of the pancreas [161, 187].

8.3.4 Preoperative indications

Recently, elastography has been used prior to pancreatic surgery to examine the gland stiffness in order to assess the risk of surgical complications. Evaluation of pancreatic stiffness might be an objective index to estimate pancreatic fibrosis and predict the risk of postoperative pancreatic fistula. Data from several studies suggest that SWE [115, 117, 184, 188] and SE [138, 170, 185] may be used for this purpose. In particular, a pancreatic parenchyma with a low stiffness as determined by semi-quantitative SE [138, 170] or SWE [117] proved to be an independent predictor of postoperative pancreatic fistula.

8.3.5 Pancreatic ductal adenocarcinoma and other solid pancreatic neoplasms

In pancreatic ductal adenocarcinoma (PDAC), shear wave velocities are significantly higher than in normal pancreatic parenchyma

obtained in healthy subjects [116, 125, 133] as well as in pancreatic parenchyma surrounding the tumor [125]. Shear wave velocities measured in PDAC usually exceed 3 m/s [116, 125, 126, 133]. However, there is a significant overlap of SWE velocities between malignant solid lesions, benign solid lesions, and chronic pancreatitis [116, 126]. One study demonstrated a significantly higher difference between the SWE velocities of malignant lesions and surrounding pancreatic parenchyma compared to the difference values between benign lesions and surrounding parenchyma [126]. No large prospective comparative studies evaluating the accuracy of SWE for the characterization of solid pancreatic lesions are available.

More evidence is available on the clinical value of EUS-SE for the differential diagnosis of solid pancreatic lesions [172, 189–192]. An early study described EUS elastography patterns in healthy subjects, in diffuse chronic pancreatitis and in focal pancreatic lesions [139]. All malignant pancreatic tumors and serous cystadenomas showed a honeycomb pattern of medium stiffness, and were well delineated against healthy parenchyma. However, this pattern was also observed in half of the chronic pancreatitis patients, so that the specificity of the method was reported at only about 60%, attributed to fibrotic structures producing similar mechanical properties in cancer and chronic pancreatitis [139, 164]. Therefore, elastography is not sufficient to contribute to the early diagnosis of pancreatic carcinoma in chronic pancreatitis [139, 164].

Qualitative [137, 139, 163, 164, 193–195] and semi-quantitative SE approaches (SR, SH analysis) [135, 142–144, 149, 150, 152–156, 175, 177, 196–199] have been used for the differential diagnosis of benign and malignant focal pancreatic masses, with both showing high overall accuracy. Computer-aided diagnosis techniques might improve the accuracy for the differential diagnosis of focal pancreatic masses, with artificial neural networks being used most often [154, 156]. Several multicenter studies [155, 156, 194] and other prospective studies [135, 149, 150, 152, 177, 197, 198] consistently showed a very high sensitivity (over 90%), but considerably lower specificity and negative predictive values for the diagnosis of benign versus malignant focal pancreatic masses. These findings have been summarized in meta-analyses, affirming the very high sensitivity (95%–99%) and negative predictive value of EUS-SE, but limited specificity (64%–76%) and positive predictive value to diagnose pancreatic malignancy [172, 189–192]. Significant differences in favor of qualitative or semi-quantitative assessment techniques have not been observed in meta-analyses. Therefore, there is expert consensus that SE cannot replace a cytopathological diagnosis of focal pancreatic disease [162, 200, 201]. Combining several EUS-based advanced tools of tissue characterization may provide the best results in differential diagnosis of focal pancreatic lesions [135, 143, 144, 149, 202–205]. Nevertheless, when EUS-guided sampling is negative or inconclusive, suspicious findings with elastography and contrast-enhanced techniques will influence further clinical decisions by indicating repeat sampling or direct referral to surgery. On the other hand, the finding of a solid pancreatic lesion with elastographic properties of low stiffness and without hypo-enhancement in contrast-enhanced EUS is nearly always predictive for the benign nature of the lesion. Since the negative

predictive value of EUS-FNA for the diagnosis of a malignant solid pancreatic lesion is only 72% [203–207], such a finding may prevent potentially nondiagnostic or risky procedures [195, 207].

8.3.6 Cystic pancreatic tumors

Elastography can have a role in pancreatic cystic lesions, both with SE and with SWE, in particular with ARFI. SWE has been shown to be accurate for the differentiation between serous and mucinous cystic pancreatic lesions [133, 208–212]. Serous cystadenomas are filled with serous fluid exhibiting similar physical properties as water, while numerous and dense septa together with a fibrous scar can be present in a mucinous cystadenoma. Therefore, the microcystic serous cystadenoma appears as a very stiff lesion with EUS-SE [139, 164, 196]. With ARFI, shear wave velocity in serous cystadenoma is infinitely high and numerical values cannot be obtained. Due to the more complex fluid content, shear wave velocities in mucinous cystic lesions are very high, but numerical values may be obtained in most cases [133, 208–212].

8.4 Limitations and artifacts

EUS-elastography suffers from technical limitations and artifacts. Some issues are common with transabdominal ultrasound, such as the need to obtain a close proximity to the target and to avoid anatomical planes allowing slip movements anterior to or within the imaged region [1]. In particular, large vessels in the imaged area represent the main reason for shear stress damping. Issues peculiar to EUS are essentially caused by the small size of the transducer providing a limited stress source to image the region of interest. In addition, it is very difficult to standardize the pressure exerted by the echoendoscope tip to the gastrointestinal wall, resulting in variability of the color mapping. Lastly, respiration and heartbeat-induced movements of the target lesion may cause a complete lack of color signal within the region of interest. As far as the color mapping of EUS elastography is concerned, disadvantages include subjective differences in color vision and image categories that may not correspond well to pathology [194]. The selection of frames for the SR or SH measurements is user-dependent. In addition, unrepresentative elastograms or reference tissues with a different distance to the stress source may result in method bias [213]. For these reasons, finding an optimal cut-off for differentiating pancreatic tumors from benign disease has been challenging.

RECOMMENDATION 8

Transabdominal and endoscopic ultrasound elastography may be used as additional imaging tools for the diagnosis and grading of chronic pancreatitis (LoE 2b, GoR B) (For 20, Abstain 0, Against 0).

RECOMMENDATION 9

Endoscopic ultrasound elastography could be used as a complementary imaging tool for the characterization of solid

pancreatic lesions. However, it cannot decisively differentiate focal pancreatitis from pancreatic carcinoma (LoE 2a, GoR B) (For 20, Abstain 0, Against 0).

RECOMMENDATION 10

When a combination of endoscopic ultrasound elastography with contrast studies suggests pancreatic cancer despite a negative or inconclusive biopsy, repeated sampling or surgery should be considered (LoE 2b, GoR B) (For 12, Abstain 7, Against 1).

9. GastroIntestinal Tract

9.1 Background

The gastrointestinal tract wall may be visualized by ultrasound as a layered structure consisting of typically 5 layers [214, 215]. When examining the intestine, it is preferable to use frequencies above 7.5 MHz to enable optimal visualization of wall layers, thickened bowel wall and focal lesions. This also applies for SE and SWE.

9.2 Methods

SE and SWE are the methods used for elasticity imaging and measurements in bowel examinations. Studies investigating elastography of bowel wall lesions are predominantly based on SE.

9.2.1 Image interpretation and evaluation

Pathological lesions that increase wall thickness are most relevant for SE and SWE. This is because the bowel wall is a thin structure on ultrasound imaging that has natural peristalsis and allows considerable movement on both the serosa and the luminal sides. This tends to add artifacts to strain imaging and makes a targeted SWE or SE measurement more difficult and user-dependent. The bowel wall may become thickened in both neoplastic and inflammatory disease, predominantly in Crohn's disease (CD). In particular, SE has been applied in order to clinically distinguish fibrotic from inflammatory lesions in CD and to distinguish rectal adenoma from adenocarcinoma.

9.3 Clinical applications

9.3.1 Distinction between fibrous and inflammatory strictures in Crohn's disease

Several studies on CD in animal models and human specimens conclude that stiffness is associated with the presence of fibrotic strictures. Some studies indicate that SE and SWE elastography can differentiate fibrosis from inflammatory lesions [216–218]. A study compared SE in terminal ileum stenosis in CD reporting a higher visual score of tissue stiffness in fibrosis using magnetic resonance (MR) enterography as a reference [219]. Another ex vivo study on bowel specimens from CD and neoplastic lesions

also showed that higher stiffness was present in both CD lesions and in adenocarcinoma, but not in adenomas [220].

The results from seven small series were included in a systematic review of 154 CD lesions in 129 patients [221], suggesting that stiffness was significantly higher in fibrotic stenosis. Nevertheless, the systematic review mentions “inhomogeneous and scarcely comparable” endpoints, as authors used either absolute strain values or a strain ratio with various anatomic structures for comparison (mesenteric fat surrounding the bowel wall or abdominal wall muscles). In a study of ten patients, SE using the mean strain in the bowel wall of affected and unaffected bowel segments pre-, intra- and postoperatively found significant differences in strain values in affected and unaffected segments which correlated well with the histological distribution of connective tissue and collagen content [222]. Also, the strain measurements had an acceptable intraclass correlation coefficient (ICC) in the three examinations. A study of 23 consecutive patients undergoing surgery for CD [223] found excellent differentiation of patients with severe ileal fibrosis by histology but also by using SR (including an excellent inter-rater agreement). Conflicting findings are reported in a prospective study on SE in 26 patients undergoing surgery for stricturing CD. On preoperative ultrasound, the SR did not correlate with histological scoring of fibrosis or inflammation [224]. Strain imaging of bowel lesions in CD may predict the response to anti-inflammatory treatment. In a prospective study of 30 patients with CD, the five patients who needed surgery had significantly higher SR measurements at baseline and there was a significant negative correlation between the SR at baseline and wall thickness following 52 weeks of anti-tumor necrosis factor (TNF) therapy [225]. SWE should not be used as a method to distinguish fibrotic from inflammatory lesions in CD based on current evidence.

9.3.2 Characterization and staging of rectal tumors

The differentiation and staging of rectal tumors can be performed using SE as an add-on to B-mode endoscopic rectal ultrasound (ERUS). Thus, SE may improve the staging of rectal cancer and differentiate adenoma from adenocarcinoma, when compared to ERUS alone and with MR imaging (with high interobserver agreement of recorded videos and images) [226–228]. Another group found good correlation between diffusion-weighted MR imaging which is associated with fibrosis, and SWE of malignant rectal tumors [229]. Another study assessed the performance of ERUS for rectal tumors using SWE using an 8 MHz endorectal transducer, finding that the tumor stiffness measurements corresponded accurately to the pathological tumor T-stage and diagnostic accuracy of tumor staging improved from 76.7 % to 93.3 % [230].

RECOMMENDATION 11

Ultrasound strain elastography can be used to characterize bowel wall lesions in Crohn's disease (LoE 3b, GoRC) (For 19, Abstain 1, Against 0).

RECOMMENDATION 12

Ultrasound elastography may improve the staging of rectal cancer when used as an add-on to endoscopic rectal ultrasound and magnetic resonance imaging (LoE 2b, GoRC) (For 17, Abstain 3, Against 0).

10. Spleen

10.1 Background

Spleen stiffness measurement is an elastography technique used to assess the severity of chronic liver disease, mainly in conjunction with liver stiffness measurements for the evaluation of liver fibrosis or portal hypertension-related complications. Various SWE techniques have been investigated to predict the presence of clinically significant portal hypertension, esophageal varices or to predict long-term prognosis.

10.2 Methodology

Spleen elastography should be performed after at least 3 hours of fasting and after at least 10 minutes of rest [231, 232], with the patient in dorsal decubitus and with the left arm in maximal adduction [233]. The transducer should be placed between the left intercostal spaces in an area with a good ultrasound window needed for TE [234], or at least 2 cm below the capsule for non-TE techniques [235, 236], with the measurement preferably being performed at the inferior pole [237].

10.3. Clinical applications

a) Assessment of liver fibrosis

Using spleen stiffness as a surrogate marker for staging liver fibrosis, two studies [238, 239] demonstrated a pooled sensitivity and specificity for detecting significant fibrosis (F2) and cirrhosis (F4) of 0.70 and 0.87 and 0.77 and 0.82, respectively with an AUROC of 0.88 and 0.85, respectively [22].

b) Assessment of clinically significant portal hypertension

Spleen stiffness correlates well with the hepatic vein portal gradient and has an excellent diagnostic accuracy (AUROC = 0.92) for clinically significant portal hypertension, irrespective of the technique used [240], with TE showing a better correlation with the hepatic vein portal gradient than measuring liver stiffness [234]. For values ≥ 46 kPa, the AUROC for clinically significant portal hypertension varies from 0.846 to 0.966, with good sensitivity (0.77–0.88) and specificity (0.79–0.91) [234, 241].

For pSWE, the overall correlation with the hepatic vein portal gradient is similar and better than for liver stiffness measurements [242], but for values > 10 mmHg, the association is weaker [242, 243]. However, for pSWE, the plotted sensitivity is higher than for other techniques (0.98 vs. 0.62–0.83), while the specificity is lower (0.78 vs. 0.89–0.93), thus raising the possibility of the heterogeneity and variability of this technique [240, 244].

As for 2D-SWE, the diagnostic accuracy varied significantly, as AUROC analysis shows: 0.63 (for a cut-off value of 34 kPa) [245], 0.725 [235] or 0.84 [237]. Despite the fact that the last two studies recommend different cut-off values to rule-in (≥ 40 or 35.6 kPa) or out (≤ 22.7 or 21.7 kPa) clinically significant portal hypertension, the diagnostic accuracy remains low for the study by Procopet et al. [235] (12/40 correctly classified), but satisfactory for the study by Jansen et al. [237] (66/111 patients correctly classified). However, if a combined approach is used (both spleen and liver stiffness measured), only 11/109 patients (89.9% accuracy) are misclassified [237].

c) Assessment of oesophageal varices

TE of splenic stiffness has a good accuracy to detect the presence of oesophageal varices (80.4%), but it is unable to differentiate the grade [233]. Values ≤ 40 kPa were proposed to rule-out oesophageal varices, while values ≥ 55 kPa were suggested to rule them in [234]. In a meta-analysis, the pooled sensitivity and specificity to detect varices was satisfactory (0.76 and 0.78, respectively), while the sensitivity is better (0.86 vs. 0.69) for the detection of varices needing treatment [246]. A modified calculation algorithm for TE was proposed, so that values > 75 kPa could be measured, which proved to be the sole independent predictor of the need to treat [247]. Therefore, a dedicated transducer and calculation algorithm were developed, showing better performance compared with the original algorithm and with liver stiffness [248].

For pSWE, the sensitivity and specificity for detecting oesophageal varices varies from 0.31 and 0.79 [249] up to 0.95 and 0.92 [243]. However, the pooled performance for detecting the need to treat appears to be lower than for TE [246], although the analysis did not take into account a report which showed very good positive and negative predictive values: 0.97 and 0.89, respectively [243].

With 2D-SWE, [245] there is no discrimination between patients with and without varices needing treatment. In a much larger cohort, however, the AUROC for detecting oesophageal varices of any grade was 0.8, while the probability is only 10% for patients with compensated cirrhosis if the spleen stiffness is lower than 25.6 kPa (10). If 2D-SWE SSM (≤ 38 kPa) is used in a step-wise approach alongside liver stiffness (≤ 19 kPa) and platelet count ($\leq 100 \times 10^3$), the oesophageal varices can be ruled-out with 83% accuracy and 74% of unnecessary endoscopies could be eliminated [248].

d) Assessment of prognosis and response to therapy

Spleen stiffness can also predict liver-related complications, as the only independent predictor of decompensation besides the MELD score (if higher than 54 kPa), in a cohort of compensated hepatitis C virus (HCV) cirrhosis, during a 2-year follow-up period [250]. No data is available regarding the role of spleen stiffness in monitoring the response to non-selective beta-blockers. Spleen stiffness (assessed by pSWE) seems to decrease after TIPS placement [251, 252], suggesting that spleen stiffness could be an additional tool to evaluate TIPS efficiency.

Small series also suggest that successful antiviral therapy of HCV cirrhosis induces a small reduction of spleen stiffness during follow-up, which is not always significant and it is not as important or as persistent as liver stiffness reduction [253, 254], reflecting more likely a reduction of hepatic inflammation.

e) Miscellaneous

Spleen stiffness was also used to assess patients with non-cirrhotic portal hypertension. In extrahepatic portal vein obstruction, spleen stiffness increases and is higher in patients with a history of bleeding [255]. In patients with idiopathic portal sinusoidal disease, spleen stiffness is markedly increased, in contrast to quasi-normal liver stiffness values [256, 257]. Furthermore, a combination could be used in children with biliary atresia before or after Kasai portoenterostomy to predict outcome or to monitor subsequent liver disease and portal hypertension [258, 259]. Spleen stiffness by TE was also positively correlated with the grade of bone-marrow fibrosis in patients with primary myelofibrosis, suggesting that this could be a simple noninvasive method to monitor disease progression [260].

10.4 Limitations and artifacts

TE can be performed in only 85–90% of cases, mainly because of high BMI, presence of ascites, lung or colonic gas interposition, or transverse spleen diameter < 4 cm [233, 234, 247]. An additional 12–21% of patients reach the maximum value (75 kPa) measured by the conventional machine [233, 247], hence the applicability of TE is approximately 70%. The applicability of 2D-SWE is similar and appears to be related to a higher BMI and smaller spleen size [261]. As for pSWE, the applicability is higher (up to 97%) [242], but the reproducibility is influenced by small spleen size and central obesity [244].

RECOMMENDATION 13

Ultrasound elastography of the spleen can be used as an additional noninvasive method to assess portal hypertension (LoE 2b, GoR B) (For 20, Abstain 0, Against 0).

11. Kidney

11.1 Background

Renal elastography has been used for the noninvasive assessment of chronic kidney disease (CKD), particularly for the early stages when renal function is not yet significantly affected, or for disease monitoring [262]. The hypothesis that the development of glomerular and interstitial fibrosis should lead to stiffness changes is supported by experimental findings in a rat model of CKD [263].

11.2 Methods & confounding factors

11.2.1 Strain elastography

SE can only be used for superficial kidneys, usually renal transplants, mainly a qualitative technique that supposes uniform deformation of the tissue of interest, with a limited role due to the depth of the organ, the difficulty to apply reproducible homogeneous external deformation and the inability to achieve absolute stiffness measurements [264].

11.2.2 Shear wave elastography

TE allows quantitative evaluation of the tissue stiffness and has been widely used for liver fibrosis estimation [2, 265], but the volume of tissue involved in the measurement is at a fixed depth and has a length of 40 mm, making this technique unsuitable for renal stiffness estimation.

The inter-operator agreement of pSWE used in transplanted kidneys obtained in different studies was fair or moderate with the ICC ranging between 0.31 [268] and 0.47 [269]. In studies performed in native kidneys, the reproducibility of the method was strong, with ICCs between 0.60 [270] and 0.71 [271]. The inter-operator agreement obtained in the elastographic assessment of the kidneys (native and transplant) was lower compared to studies of liver stiffness (ICCs are over 0.80), because of confounding factors. Currently, there are few studies available using 2D SWE techniques in the assessment of the kidneys [272, 273].

11.3 Clinical applications

11.3.1 Normal kidney stiffness

A limited number of studies (most of them using pSWE) report normal kidney stiffness, and are different depending on the type of pSWE device used. In adult native kidneys, normal cortical stiffness values range from 2.15 to 2.54 m/s with one system [114, 270, 271, 277–279] compared to 1.23 to 1.54 m/s with a different system [280]. In 9–16-year-old children, higher pSWE stiffness values were found, ranging from 3.00 to 3.33 m/sec (mean 3.13 ± 0.09 m/s, corresponding approximately to 29.4 kPa). In a study performed in healthy people aged 18–30, 31–50, 51–65, and above 65 years, pSWE was 2.94 ± 0.60 , 2.26 ± 0.82 , 2.48 ± 0.8 and 1.82 ± 0.63 m/s, respectively [277]. In the same study, a statistically significant difference was found between women and men. Surprisingly, normal kidney stiffness was found to exhibit an inverse, statistically significant relationship with patient age ($p = 0.0003$). Using pSWE, similar values were found in a small series of normal volunteers with superficial kidneys, with a cortical average stiffness of 15.4 ± 2.5 kPa [281]. The stiffness of the renal medulla was found to be lower than the cortical stiffness [272], except for in one study using pSWE [278].

11.3.2 Kidney stiffness for the assessment of renal pathology

In renal transplantation, serum creatinine levels and estimated Glomerular Filtration Rate (eGFR) are poor predictors of the severity of histological lesions. A noninvasive test that could provide diagnosis and/or prognosis early on to avoid repeated biopsies and to allow early targeted therapeutic intervention could improve pa-

tient management. Several studies report a correlation between renal stiffness and fibrosis or renal function. In experimental models of glomerulosclerosis, the cortical stiffness was correlated to the degree of renal dysfunction [263]. In humans, this correlation remains highly variable in both native and transplanted kidneys. Some authors reported a correlation between renal stiffness and fibrosis or renal function with several techniques [270, 278, 282–285].

In other studies, the correlation between CKD stages and kidney stiffness was negative, as shear wave velocity was found to decrease with increasing stages of CKD [270, 286] or decreasing eGFR [287, 288]. The cut-off values of renal stiffness proposed by different studies could only predict advanced stages of CKD. In the remaining studies, no correlation was found between renal stiffness and the degree of CKD or interstitial fibrosis and tubular atrophy, even in diabetic CKD [270, 272, 278, 288–294]. The renal perfusion changes might impact renal stiffness and explain some discrepancies between results [284], as intrarenal blood flow is decreased with the progression of fibrosis. Thus, renal blood flow decrease could be the cause of the decrease of stiffness with the progression of CKD, and could have a bigger influence on stiffness compared to renal fibrosis.

Additional preliminary applications include stiffness assessment in the case of reflux nephropathy and tumor. In a study of 28 children, CKD degree increased SWE values mainly in the kidney involved with vesicoureteral reflux (6.57 ± 0.96 m/s) but also in the contralateral kidney (4.09 ± 0.97 m/s) while the normal value in the pediatric population without renal disease was 3.13 ± 0.09 m/s [295]. The increased stiffness even in the contralateral kidney may result from increased glomerular filtration and minimal fibrosis. Renal elastography might also play a role in the detection and characterization of renal masses, improving the identification of ill-defined lesions and providing information about tumor stiffness [296].

11.4 Limitations and artifacts

Anatomical confounding factors include renal anisotropy, blood perfusion and hydronephrosis. The effect of anisotropy has been demonstrated in muscle and kidney elastography due to their spatial organization [275, 276]. When shear wave propagation is parallel to the renal tubules and interlobular arteries (and the ultrasound beam is perpendicular to these structures), the velocity of the shear waves is increased [262]. Elasticity measurements performed in the perpendicular direction to the long axis of the pyramids exhibit higher values for all renal compartments. Renal perfusion strongly affects renal elastography, with a drop in the medulla ranging from 44% to 72.7% in renal artery occlusion, and an increase over 500% in renal vein thrombosis [276]. Hydronephrosis also results in a renal elasticity increase, with a correlation between urinary tract pressure and cortical stiffness varying from 119% to 137% between 5 and 40 mmHg [276]. Additional confounding factors include the type of technology and effect of transmit frequency, attenuation of transmit pulse (deteriorating signal-to-noise ratio). Using ARFI, the shear wave velocity was reduced by 27% when the depth increased from 2–3 cm to 6–7 cm (2.95 ± 0.41 m/s and 2.16 ± 0.61 m/s, respectively) [277].

Measurement depth influences the reproducibility of the method, a lower reproducibility being found in patients with deep kidneys, either native kidneys at a depth more than 4 cm or transplanted kidneys.

RECOMMENDATION 14

No current recommendation can be given for the application of ultrasound elastography in native kidneys (LoE 2b, GoR B) (For 10, Abstain 0, Against 0).

RECOMMENDATION 15

Ultrasound renal elastography can be used as an additional tool for the diagnosis of chronic allograft nephropathy (LoE 2b, GoR B) (For 9, Abstain 1, Against 0).

12. Lymph nodes

12.1 Background

Noninvasive discrimination of malignant and benign lymph nodes is important for further diagnostic and clinical decision-making. Whereas contrast-enhanced ultrasound is not recommended for the assessment of lymph nodes [297], elastography has a better diagnostic performance [298], with evidence for the examination of superficial lymph nodes and mediastinal lymph nodes. Superficial lymph nodes have been investigated by percutaneous US using SE and SWE. Mediastinal lymph nodes have been investigated by endoscopic ultrasound using only SE.

12.2 Methods

SE is the method most frequently described, as the technique is more widely available on most commercial systems, with more consolidated evidence with a number of single research studies and two meta-analyses published. More recently, SWE has been evaluated with one meta-analysis published.

12.3 Clinical applications

12.3.1 Differential diagnosis of lymphadenopathy

Assessment of superficial lymph nodes using SE presents conflicting data. Two recent meta-analyses demonstrated a high accuracy in differentiating between benign and malignant lymph nodes. The first meta-analysis included 578 patients with 936 lymph nodes with a sensitivity of the scoring and SR measurements of 76 % and 83 %, respectively [299]. The second meta-analysis included 545 patients with 835 lymph nodes and indicated a sensitivity of the elasticity scoring and SR measurements of 74 % and 88 %, with a specificity of 88 % and 91 %, respectively [300].

A meta-analysis including 481 patients with 647 lymph nodes evaluated the role of SWE in superficial lymph nodes. SWE for the discrimination of malignant and benign lymph nodes achieved a

sensitivity of 81 % and specificity of 85 % [301]. The latest meta-analysis regarding the value of EUS elastography for the differentiation of malignant and benign lymph nodes included 6 studies with 368 patients and 431 lymph node, with SE demonstrating a sensitivity of 88 %, and a specificity of 85 % [302]. Newer studies including patients investigated by endobronchial ultrasound (EBUS) had similar performance [303, 304].

12.3.2 Preoperative Assessment of Lymph Nodes in Patients with Known Primary Cancer

With preoperative lymph node assessment for metastatic involvement, no systematic review is available. Two studies investigated SWE in the prediction of metastatic involvement from thyroid cancer. A retrospective analysis [305] found that using the Mean Elastic Modulus with a cut-off set to 29 kPa led to 66.67 % sensitivity and 72.62 % specificity, 78 % PPV, 64.71 % NPV and 0.748 AUC, whereas the combination with B-mode ultrasound lead to 98.04 % sensitivity, 45.45 % specificity, 73.53 % PPV, 93.75 % NPV and 0.811 AUROC. Other authors found that the best SWE parameter for predicting metastatic involvement was the maximum value of elasticity with the cut-off set to 40 kPa, leading to 80 % sensitivity, 93.1 % specificity and 0.918 AUC [306].

12.4 Limitations and artifacts

Elastography is unlikely to be suitable for a differential diagnosis, but is more likely to be useful for targeting malignant lymph nodes for fine needle aspiration if multiple lymph nodes are present [307]. It cannot be assumed that the entire lymph node is involved in malignancy, but may range from a few undetectable cells to involvement of a small area. Only a limited number of studies with small sample sizes are available and invariably have a selection bias [308, 309]. Some malignant lymph nodes cannot be discriminated by tissue stiffness alone, as is the case with the lymph nodes of lymphoma [310]. There is no standardization of the technique particularly in SE, making study comparisons difficult [311]. Often with lymph node imaging in EUS, there is a relative depletion of surrounding tissue as a normal reference for SR calculation, including the gastrointestinal wall advocated as the standard comparison for tissue reference [309].

RECOMMENDATION 16

High-frequency transcutaneous and endoscopic ultrasound elastography can be used as additional tools for the differentiation between benign and malignant lymph nodes (LoE 2a GoR B) (For 20, Abstain 0, Against 0).

RECOMMENDATION 17

Ultrasound elastography can be used for identifying the most suspicious lymph nodes and/or suspicious areas within the lymph node to be targeted for sampling (LoE 5, GoR D) (For 19, Abstain 1, Against 0).

13. MusculoSkeletal

13.1 Background

In comparison with the previous guidelines, there has been an increase in studies regarding musculoskeletal (MSK) elastography [2].

13.2 Methods

Published data concerning the use of SE, ARFI imaging, and SWE for elastographic evaluation of the MSK structures, especially for tendons, muscles and nerves, are available.

13.3 Clinical applications

13.3.1 Tendons

In SE the healthy Achilles tendon is mostly rigid (86.7 – 93 % of the tendon has high stiffness) [312, 313] and there is an increase in stiffness with age [314]. Using SWE, different values of shear wave velocity or elastic modulus were obtained depending on the machine used, tendon position, or plane of imaging [113, 315, 316]. In Achilles tendinopathy the SR (comparing tendon with Kager's fat) is higher and the tendon becomes less stiff [317]. SE proved to be superior to B-mode ultrasound (sensitivity 99 %, specificity 78 %, accuracy 95 %) [318], underlining the ability of SE to detect pathology before the appearance of the B-mode ultrasound morphologic changes [319, 320]. No differences between athletes and controls nor between the dominant and non-dominant leg were found in SE evaluation of the patellar tendon [321]. With age, a significant decrease in shear wave velocity values was detected, with SWE having the capacity to detect aging tendons before morphologic abnormalities were observed on B-mode ultrasound [322, 323].

For lateral epicondylitis the addition of SE to B-mode ultrasound findings improves the sensitivity for detecting tendon pathology [324, 325]. Using B-mode ultrasound in combination with SE resulted in a better correlation with histologic results. In the rotator cuff, SE can detect small partial tears of the supraspinatus tendon [326]. In patients with tendinopathy, a significant decrease in the shear wave velocity of the supraspinatus muscle was observed [327]. Currently, no observations monitoring tendon healing are available in longitudinal studies.

13.3.2 Muscle

Using SE, the normal relaxed muscle appears as an inhomogeneous mosaic of intermediate or increased stiffness with scattered less stiff and stiffer areas, especially at the boundaries of the muscle [328, 329]. In SWE the normal relaxed muscle has a lower shear wave velocity (which increases during contraction) and the boundary fascia or aponeurosis show intermediate shear wave velocity [330].

Physiological factors (age, sex, muscle performance, fatigue, or training) and pathological changes (trauma, degeneration, or neuromuscular disease) influence muscle elasticity [331 – 337]. Normal and abnormal ranges of shear wave velocity of various

muscles are available [327, 333, 336, 338] but the results are limited, without establishing any reference values.

SWE for the evaluation of muscle stiffness in various neurologic conditions (Parkinson disease, chronic stroke, cerebral palsy, multiple sclerosis or Duchenne dystrophy) is a reliable quantitative imaging technique for diagnosis, treatment decisions and follow-up and may be an alternative to electromyography [333, 338 – 342].

In inflammatory myopathies SE demonstrated that the involved muscles become stiffer, and significant correlations with histological findings were obtained [328, 343]. Acute muscle and fascial tears show a lower shear wave velocity [330], but no prospective studies have been published.

13.3.3 Ligaments and fascia

Using SWE in patients with adhesive capsulitis, the coracohumeral ligament proved to be stiffer in the symptomatic shoulder [344]. The increased stiffness of the transverse carpal ligament evaluated on SE may be one of the causes for carpal tunnel syndrome [345]. The plantar fascia becomes less stiff with age and in subjects with plantar fasciitis abnormality is seen when using ARFI imaging (pixel intensity), SE or SWE even in the absence of pathological findings on B-mode ultrasound examination [346 – 350], suggesting a role of elastography in the diagnosis of early stages of plantar fasciitis.

13.3.4 Nerves

Median nerve strain is significantly lower in patients with carpal tunnel syndrome than in controls [351], and the perineural area surrounding the median nerve is stiffer than in healthy volunteers [352]. The SE can be used to follow up the median nerve recovering after carpal tunnel release [353] or after local corticosteroid injection [354] but does not have the capability to categorize the severity. The combined use of B-mode ultrasound and SE has been suggested [355].

Using pSWE the shear wave velocity of the median nerve was 3.857 m/s in patients with carpal tunnel syndrome and 2.542 m/s in the control group ($p < 0.05$) [356]. Using 2D-SWE the mean shear modulus of the median nerve was 66.7 kPa in patients and 32.0 kPa in the control group ($p < 0.001$) [357]. Both methods have high sensitivity and specificity for carpal tunnel syndrome diagnosis and are highly reproducible. The increased stiffness was attributed to nerve fibrosis or edema.

The elasticity of the tibial nerve in diabetic patients is reduced compared with a control group and decreased further after developing diabetic peripheral neuropathy [358 – 360].

The joints and limb position and the patients' age should be taken into consideration during a nerve ultrasound examination [361].

13.4 Practical points

SE is an operator-dependent technique, with a recommendation to record several (at least 3) compression-relaxation cycles as cine-loops and then select the best elastograms for evaluation. The examination transducer should be perpendicular to the tissue

to avoid anisotropy, as the B-mode ultrasound appearance influences the quality of the elastogram.

The use of standoff devices for SE of the superficial structures does not influence the elastogram (a minimum 3 mm distance between transducer and lesion being necessary) [362], but the inclusion of gel within the region of interest should be avoided (may mask minimal differences in tendon stiffness) [329].

The SWE examination of muscles and tendons should be performed with the lightest transducer pressure. The dimension of the region of interest does not influence the mean elastic modulus [363].

The transducer must be oriented longitudinally to the muscle fibers in order to achieve accurate and reliable SWE measurements. The shear waves propagate faster in contracted tendons and muscles and along the long axis of tendons [330]. The ligaments should be examined in the same position as the corresponding joints [344].

13.5 Limitations and artifacts

When a solid structure is delimited by an incompressible shell, SE analysis of the internal structure is limited (the eggshell effect) [364]. Cystic masses characteristically have a mosaic of all levels of stiffness. Low stiffness lines may appear at the interfaces between tissues (due to tissue shifting), around calcifications, behind bone or at the superficial edge of a homogeneous lesion. Fluctuant changes at the borders of the Achilles tendon in an axial elastogram can be seen due to varying contact with the skin [365].

A limitation of SWE is depth of penetration. Superficial structures may be better visualized by applying a 5 mm layer of coupling ultrasound gel as standoff. SWE examination is influenced by the transducer pressure and angle, and the shear modulus depends on the orientation of the transducer relative to the examined structures [330, 366].

RECOMMENDATION 18

Ultrasound elastography can be used as a supplementary tool to increase confidence in diagnosing tendinopathy, particularly for Achilles tendinopathy, for evaluating muscle stiffness and for plantar fasciitis (LoE 2b GoR B) (For 19, Abstain 1, Against 0).

RECOMMENDATION 19

Ultrasound elastography can be used for the diagnosis and follow-up of carpal tunnel syndrome and diabetic peripheral neuropathy (LoE 2b, GoR B) (For 19, Abstain 1, Against 0).

14. Testis

14.1 Background

Traditionally the presence of a focal lesion in the testis was addressed by removing the testis for histological examination, on the premise that nearly all of these lesions are malignant. However, access to modern ultrasound technology has rendered this approach obsolete, and as many as 80% of incidentally discovered lesions are benign [367]. The use of newer contrast-enhanced ultrasound and elastography techniques [368], combined as multiparametric ultrasound [369], has resulted in a more cautious approach to incidental focal testicular lesions [370]. The use of elastography to assess the stiffness of abnormal areas of the testis to ascertain stiffness as a sign of underlying malignancy is an attractive proposition to add to the overall multiparametric assessment.

14.2 Methods

14.2.1 Strain elastography

SE has been the most employed technique for the assessment of testicular lesions [371–375]. Early studies, predominantly retrospective, have commented on the possibility of differentiating malignant from benign lesions with certainty using SE and SR. However, these findings have not been confirmed in recent studies, with specificities between 25.0% and 37.5% in differentiating benign from malignant lesions [375–377]. A number of case series detailing the use of SE and SR (some in combination with contrast-enhanced ultrasound) have described the findings in Leydig cell tumors [378], epidermoid cysts, hematoma, lymphoma, focal infarction, capillary hemangioma, adrenal rest cells [379–384] and in extra-testicular lesions [385], without comparison between the findings of these different lesions.

14.2.2 SWE

There is limited information regarding the use of SWE in the evaluation of testicular lesions. Investigation of the role of SWE in the overall assessment of background parenchyma has suggested that values may be elevated in the case of testicular microlithiasis [386], infertility [387], undescended testis [388]. It also has the potential to differentiate seminomas from non-seminomatous lesions [389] and has been evaluated in burnt-out tumors [390]. No prospective study reporting the differences in SWE in focal testicular lesions has been published.

14.3 Clinical applications

The use of all forms of elastography in the assessment of focal testicular lesions is promising, with tissue stiffness confirmed with both SE and SWE techniques, but with overlap in findings between benign and malignant neoplasms. The current status would allow elastography to be an adjunct to the overall ultrasound examination rather than a standalone technique.

14.4 Limitations and artifacts

For testicular lesions, the values obtained for SWE vary between different machines and are not interchangeable [391]. The prob-

lems associated with the areas of fibrosis adjacent to the tunica albuginea hamper the assessment of focal lesions adjacent to this region [392]. Measurements using SWE between the center and peripheral zones differ and the point of measurement requires standardization [393, 394].

RECOMMENDATION 20

Ultrasound elastography for the evaluation of focal testicular lesions can only be recommended in conjunction with other ultrasound techniques, as there is overlap between benign and malignant neoplasms (LoE 3A GoR B) (For 19, Abstain 1, Against 0).

15. Vascular

15.1 Background

It is well established that ageing and atherosclerotic disease increases arterial stiffness [395]. Elastography biomarkers are emerging as potential indicators for diseases such as stroke, hypertension, diabetes mellitus and cardiovascular disease, and may provide additional information to support clinical decision-making.

15.2 Methods

The majority of studies are based on SE. Early studies used intravascular ultrasound and more recent studies have focused on noninvasive techniques including SWE. These techniques have been compared with alternative imaging techniques, histology, clinical outcome measures and/or in experimental phantoms and simulations.

15.3 Clinical applications

15.3.1 Strain elastography

Plaque characterization is a challenging, clinically important application for which evidence of clinical benefit is growing [396]. Evidence from animal and human studies [397–403] typically associates vulnerable plaque with regions of high strain. The potential to detect and age thrombus has been demonstrated in animal models [404, 405]. A clinical application to differentiate acute from chronic deep vein thrombosis (DVT) has been demonstrated in humans [406–408], and a systematic review concluded that elastography imaging is a feasible adjunct to current first-line imaging for DVT [409]. However, at least one recent study was not able to differentiate acute DVT from subacute DVT [410]. Other potential vascular applications include cardiac, abdominal aorta and the use of elastography biomarkers for disease [411–414].

15.3.2 SWE

The feasibility of quantifying Young's modulus in arteries has been demonstrated in human [415], ex-vivo animal [416, 417] and phantom [418–420] studies. Identification of the vulnerable car-

otid plaque is emerging as a promising clinical application. Phantom studies have demonstrated the feasibility of Young's modulus estimates but highlight errors due to the requirement for a different wave propagation model than used by current commercial systems [418–421]. Nevertheless, human studies show good reproducibility and potential clinical benefit [422–426], with evidence that Young's modulus of carotid plaque correlates with qualitative (Gray-Weale scale) appearance [422, 425, 426] and quantitative (grayscale median) B-mode ultrasound measurements [422, 426], and helps to provide improved diagnostic performance of carotid plaque vulnerability [422, 426]. Studies found a lower mean Young's modulus for vulnerable plaque, although values differ (50 kPa vs. 79 kPa [426]; 62 kPa vs. 88 kPa [422]; 81 kPa vs. 115 kPa [425]). Evidence is limited for other vascular applications such as cardiac [427–429] and DVT [430, 431].

15.4 Limitations and artifacts

Vascular imaging is challenging due to the small heterogeneous tissue size, the dynamic environment resulting from pulsatile blood flow, thin vessel walls, non-linear tissue elasticity and shear wave propagation model assumptions which may not be valid due to the potential for Lamb wave propagation in vessel walls [415, 418]. Studies should report the shear wave velocity or calculation used to convert velocity to Young's modulus as future scanners may implement different models of wave propagation. Vascular applications are promising, especially for the assessment of carotid plaque, where larger, multicenter studies are required to validate initial findings, establish cut-off values and optimize methodologies.

RECOMMENDATION 21

Vascular ultrasound elastography is an area of active research. However, it cannot currently be recommended for clinical decision-making (LoE 5, GoR C) (For 20, Abstain 0, Against 0).

16. Intraoperative

16.1 Background

All surgical disciplines make use of preoperative imaging to visualize a pathology for improved surgical planning.

16.2 Methods

Improved ultrasound technology has resulted in high-frequency small transducers with better resolution including 3 D ultrasound, contrast-enhanced ultrasound and elastography.

16.3 Clinical applications

The utility of intraoperative ultrasound is less obvious. The advantages include intraoperative navigation without ionizing radiation exposure or relevant workflow interruption, assessment of the extent of resection, and organ shift monitoring and compensation (most important for the brain). Disadvantages for ultrasound elas-

tography include organ deformity intraoperatively due to a number of factors including tumor resection sequelae and post-interventional swelling. The use of intraoperative elastography has been reported for the liver [8, 9, 432–435], brain [436–443], pancreas [115, 185], prostate [444], lung [445] and other organs [446].

RECOMMENDATION 22

Intraoperative ultrasound elastography is an area of active research. However, it cannot be currently recommended for clinical decision-making (LoE 5, GoR C) (For 20, Abstain 0, Against 0).

Conflict of interest

Odd Helge Gilja: Advisory Board/Consultant fee from: AbbVie, Bracco, GE Healthcare, Samsung, and Takeda
Paul S. Sidhu: Speaker honoraria, Bracco, Siemens, Samsung, Hitachi, GE and Philips
Christoph F. Dietrich: Speaker honoraria, Bracco, Hitachi, GE, Mindray, Supersonic, Pentax, Olympus, Fuji, Boston Scientific, AbbVie, Falk Foundation, Novartis, Roche; Advisory, Board Member, Hitachi, Mindray, Siemens; Research grant, GE, Mindray, SuperSonic
Vito Cantisani: Speaker honoraria, Canon/Toshiba, Bracco, Samsung
Dominique Amy: Speaker honoraria, Hitachi, Supersonic, EpiSonica
Marco Brock: Speaker honoraria, Hitachi
Fabrizio Calliada: Speaker honoraria, Bracco, Hitachi, Shenshen Mindray
Dirk Andre Clevert: Speaker honoraria, Siemens, Samsung, GE, Bracco, Philips; Advisory Board, Siemens, Samsung, Bracco, Philips
Jean-Michel Correias: Speaker honoraria, Hitachi-Aloka, Canon/Toshiba, Philips, Supersonic, Bracco, Guerbet; Research collaboration, Bracco Sonocap, Guerbet NsSafe and Secure protocols
Mirko D'Onofrio: Speaker honoraria, Siemens, Bracco, Hitachi; Advisory Board Siemens, Bracco
Andre Farrokhi: Speaker honoraria, Hitachi
Pietro Fusaroli: Speaker honoraria, Olympus
Roald Flesland Havre: Speaker honoraria, GE Healthcare, Conference participation support from Pharmacosmos, Ultrasound equipment from Samsung Medison
André Ignee: Speaker honoraria: Siemens, Canon/Toshiba, Hitachi, Boston Scientific, Bracco, Supersonic, Abbvie
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Mickael Tanter: Speaker honoraria, Supersonic; Co Founder and shareholder, Supersonic; Research collaboration, Supersonic
Peter Vilmann: Speaker honoraria, Pentax, Norgine; Advisory Board, Boston Scientific; Consultancy MediGlobe
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