Cancerous tissue becomes stiffer as the density of blood vessels and/or cells increases. This stiffening is believed to start from the early stages of development of the cancer. Visualization of stiffness data, therefore, could enable early-stage differentiation of benign and malignant tissue. Elastography has been developed for non-invasive imaging of tissue elasticity (stiffness) using a diagnostic ultrasound system. The transducer is used to gently compress the tissues, and the resultant pattern of induced strain gives diagnostic information about the tissue stiffness. Hitachi was the first company to commercialize Real-time Tissue Elastography (hereafter RTE) as a method for tissue stiffness visualization. Now, RTE is clinically applied in many medical institutions.

The guidelines of the World Federation for Ultrasound in Medicine and Biology (hereafter WFUMB) classify Elastography methods as shown in Table 1. Elastography methods can be classified into two main types: strain imaging and shear wave imaging. RTE is classified as strain imaging, while Shear Wave Measurement (hereafter SWM) is classified as shear wave imaging method. The different principles are explained below.

Principles of Real-time Tissue Elastography (RTE) (Strain Elastography)

Under a constant applied force, soft tissue will show significant strain while stiff tissue shows little strain (Fig. 2). These tissue characteristics can be color-coded and displayed as a strain map which can be superimposed on the corresponding B-mode image. Areas demonstrating relatively less strain (stiffer parts) in the region of interest (ROI) will be colored blue, areas demonstrating relatively more strain (softer parts) in red, with the areas of mean stiffness in green (Fig. 3).

Principles of Shear Wave Measurement (SWM) (Point Shear Wave Speed Measurement)

A focused ultrasound pulse is transmitted by the transducer. From the resultant displacement of the tissue, shear waves are generated and propagate off-axis. Tracking pulses are used to detect the propagation velocity of the shear wave (Vs) by measuring the difference in arrival time (time lag) between the two points a known distance apart (distance) (Fig. 4).
Neoplastic Disease of the Breast (Workflow and Evaluation with RTE)

- Clinical Benefits of Elastography

It is anticipated that the use of Elastography in breast cancer screening could reduce the recall rate and improve the positive predictive value. Additionally, when used for detailed breast examination, it is expected to improve specificity. This could reduce the number of patients receiving unnecessary biopsies. In breast-conserving surgery, Elastography has been reported as an effective tool for the determination of the limit of the excision. Moreover, Elastography can be effective in the visualization and differential diagnosis of the intraductal component that often appears as a non-mass-forming lesion.

- Techniques Proposed by WFUMB

Guidelines for Breast Elastography were announced at the WFUMB World Congress in 2015, following the 2014 Convention of the Japan Society of Ultrasonics in Medicine (JSUM). The guideline proposes three different Elastography imaging techniques as shown in Table 2 and recommends selection of the appropriate technique according to the lesion.

<table>
<thead>
<tr>
<th>Method</th>
<th>Technique</th>
<th>Depth of lesion</th>
<th>Size of tumor imaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Manual Compression</td>
<td>Try not to apply pressure.</td>
<td>In some cases</td>
<td>(large breasts or deep lesions) Minimal vibration may be required.</td>
</tr>
<tr>
<td>Minimally Vibration</td>
<td>Apply extremely fine vibration with a few cycles/second.</td>
<td>This method can be used for relatively shallow lesions to moderately deep lesions.</td>
<td>It allows elastography imaging of small targets several millimeters in size such as non-mass abnormalities.</td>
</tr>
<tr>
<td>Significant Vibration</td>
<td>Apply fairly significant compression/release. (approximately 2 mm).</td>
<td>As long as the tumor is fairly large, adequate elastography images of lesions at most depths can be obtained.</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Elastography techniques based on the WFUMB guideline

- RTE-specific Functions Supporting Ultrasound Examination of the Breast

Our high-quality RTE (Fig. 5) is furnished with unique functions for efficient ultrasound examination of the breast. These enable significant improvement in workflow. In addition, they enable acquisition of objective and highly reproducible data independent of the proficiency of the examiner.

Examination workflow (Supported functions)
- RTE Scan (No Manual Compression method)
- Frame Selection (Auto Frame Selection)
- Strain Ratio Measurement (Assist Strain Ratio)

Stable real-time visualization

Stable Elastography images can be obtained using any one of the three techniques proposed by WFUMB.

Single-click automatic frame selection (Auto Frame Selection)

From multiple frames obtained during RTE, the system automatically selects the most appropriate frame for measurement on freeze (Fig. 6).

Fat Lesion Ratio (FLR) is a semi-quantitative method for the assessment of strain. ROIs are set both in fat and in the tumor (lesion) to obtain a Strain Ratio. Assist Strain Ratio is a function that automatically sets the ROIs for FLR measurement, improving both the reproducibility and objectivity as well as reducing the time required for measurement.

- Differentiation Between Benign and Malignant Breast Tumors

Elasticity Score (Tsukuba Elasticity Score)

The areas showing reduced or no strain in the tumor (blue) using RTE were compared to the hypoechogenic area in the B-mode image and scored using five different categories. Fig. 7 shows the comparison results.

<table>
<thead>
<tr>
<th>SCORE 1</th>
<th>Stream is seen throughout the hypoechogenic area. (The tumor lesion is coded blue, even in the surrounding area.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCORE 2</td>
<td>Partially hypoechogenic area with no strain. (The lesion is seen as a hypoechogenic area within the hypoechogenic area.)</td>
</tr>
<tr>
<td>SCORE 3</td>
<td>No strain is seen at all the core of the hypoechogenic area, but strain is seen at the rim. (The lesion core value and the rim in gray.)</td>
</tr>
<tr>
<td>SCORE 4</td>
<td>No strain is seen within the hypoechogenic area. (The lesion is seen in color.)</td>
</tr>
<tr>
<td>SCORE 5</td>
<td>No strain is seen in the hypoechogenic area nor in the surrounding area. (The lesion and the surrounding area are gray.)</td>
</tr>
</tbody>
</table>

FLR (Fat Lesion Ratio)

The FLR is the ratio of the mean strain in the target to that of the adjacent fat. This semi-quantitative measurement gives a numerical value that assesses the stiffness of the target area relative to the fat (Fig. 8). This method can be used for both large tumors but also for a stiffness assessment of non-mass forming tumors. The WFUMB Guideline includes references to cutoff values for FLR.
Clinical Images

Mass-forming Lesions

The entire fibroadenoma appears green (soft lesion), while the invasive ductal carcinoma is coded blue (stiff tumor).

Fibroadenoma

Invasive ductal carcinoma

Non Mass-forming Lesions

Mammary gland abnormalities

Ductal carcinoma in situ (DCIS)

Mucinous Cancer vs. Fibroadenoma

Both tumors have similar appearances on B-mode, smooth with a well-defined boundary, but display different stiffness with RTE.

Mucinous cancer

Fibroadenoma

Clinical Benefits of Elastography

In the diagnosis and treatment of diffuse liver disease, it is extremely important to determine which patients are suitable for antiviral therapies, predict their curative effects, and correctly diagnose the degree of liver fibrosis. Though regarded as the gold standard for diagnosis, a liver biopsy is an invasive examination and therefore cannot be repeated frequently. Ultrasound Elastography has been reported as an effective method for evaluating the level of fibrosis non-invasively in all diffuse liver diseases and could provide an alternative to liver biopsy.

Features of Each Method

For liver fibrosis assessment, the following two Elastography methods can be used: assessment with RTE and the Liver Fibrosis Index (LF Index), and shear wave speed measurement with SWM. The features and an evaluation of these two methods follows:

Features of Liver Fibrosis Assessment Using RTE

(1) Provides an accurate measurement of the degree of liver fibrosis. Assessment with RTE (LF Index) is known to be unaffected by inflammation, congestion, or jaundice.※

(2) Allows measurement in patients with ascites.

(3) Assessment can be made with a standard convex transducer.

Imaging Method

With the transducer placed in a right intercostal space (around S5/S8) between the anterior and mid axillary line, scanning is performed to obtain a RTE image of the liver using heart beat-induced strain (Fig.10).

Assessment with RTE

- Comparison with the New Inuyama Classification

As liver fibrosis develops in patients with hepatitis, the tissue shows local variations in stiffness. The stiffer regions (blue areas) increase in number and size, and the RTE image takes on a mottled appearance.※ Hepatitis staging is diagnosed using an invasive biopsy, but RTE allows a non-invasive assessment that can be used frequently in follow-up observation and treatments.

Table 3: New Inuyama Classification

<table>
<thead>
<tr>
<th>Stage of fibrosis</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0: No fibrosis</td>
<td>F1: Periportal fibrosis</td>
</tr>
<tr>
<td>F2: Bridging fibrosis</td>
<td>F3: Bridging fibrosis with lobular distortion</td>
</tr>
<tr>
<td>F4: Hepatic cirrhosis</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 11: Comparison of liver RTE images with New Inuyama Classification stages

※Point
<RTE-specific Functions for Liver Fibrosis Assessment>

Liver Fibrosis Index (LF Index) measurement

The LF Index is a unique measurement for liver fibrosis assessment. From an analysis of the RTE image pattern of the liver with hepatitis C, the hepatitis stage can be estimated as an LF Index value (Fig. 12). The formula is calculated based on a multiple regression analysis with nine independent feature values as independent variables, and histopathological fibrosis diagnosis F stages as dependent variables. The LF index correctly reflects the degree of liver fibrosis without influence from inflammation, jaundice, and so on.

\[
\text{LF Index} = -0.00897 \times \text{MEAN} - 0.00502 \times \text{SD} + 0.0232 \times \% \text{AREA} + 0.0253 \times \text{COMP} + 0.775 \times \text{SKEW} - 0.281 \times \text{KURT} + 2.08 \times \text{ENT} + 3.04 \times \text{IDM} + 40.0 \times \text{ASM} - 5.54
\]

Correlation between liver biopsy histology F stages and LF Index values

A LF Index validation study of 245 cases of chronic hepatitis B, C and hepatic cirrhosis was conducted and revealed significant differences between F1 and F2, F1 and F3, F1 and F4, F2 and F4, and F3 and F4. The RTE LF Index highly correlates with the stage of hepatic fibrosis and is effective for evaluation before and after treatment (Fig. 13).

Compatibility with convex transducers

Convex transducers support RTE and hence enable RTE to be performed immediately as an extension of the conventional routine ultrasound examination. They provide a wide field of view for visualization making it easy to direct the imaging towards the heart. This results in RTE images with high reproducibility. In addition, convex transducers offer good penetration and can reduce the incidence of poor imaging in conventionally difficult-to-image cases, such as patients with fatty liver disease (Fig. 14).

SWM-specific Functions for Liver Fibrosis Assessment

It has been reported that liver fibrosis assessment using shear wave speed measurement methods can ascertain the degree of fibrosis as well as that of inflammation, because the degree of inflammation, congestion, and jaundice affects the measurement results.

<Shear Wave Measurement (SWM)>

Once the ROI is placed at the measurement site in the liver parenchyma, the measured value will appear in approximately two seconds.

<Features of SWM>

1. Measurement without time lag
   A fast, single-click measurement. Automatic image recording.

2. Automatic multiple measurements for reliability
   Multiple values, m x n, are calculated by transmitting n pulses for each measurement as shown in Fig. 16. The median of the effective values is calculated and displayed as the Vs value.

3. Evaluation of the measurement reliability using VsN
   The measurement of the true shear wave propagation velocity in tissue can be affected by breathing or other body movements from the patient, or lack of steadiness of the examiner’s hand. In such cases, it may be difficult to determine the reliability of the measurement based on the value of the shear wave propagation velocity (Vs). The reliability indicator (VsN) shows the ratio of effective values from the total number acquired with each measurement. This function allows the user to determine the reliability of the measurement.
Clinical Case: Combinational Elastography

Non-invasive Diagnosis of Liver Clinical Condition by Real-time Tissue Elastography and Shear Wave Measurement: Get More Accessible by One Probe
Norihisa Yada, Masatoshi Kudo, Department of Gastroenterology and Hepatology, Faculty of Medicine, Kinki University

Combinational Elastography

Vs values measured with SWM vary significantly under the influence of not only fibrosis but also inflammation, jaundice or congestion. On the other hand, changes in the relative strain in chronic liver disease examined by RTE reflects only the progression of liver fibrosis and the measurement is seldom affected by these factors. Therefore, the level of inflammation, jaundice and congestion can be estimated by simultaneously performing Shear Wave Measurement and Real-time Tissue Elastography (Combinational Elastography) and analyzing the difference in the data obtained from these 2 techniques. This interpretation method is described using the case of a 27-year old male suffering from acute hepatitis B.

Clinical Case

Mild enlargement of the liver and a small volume of ascites were found in B-mode examination, and the ALT was increased to 1290IU. Jaundice and congestion were not found. LFI (LF Index) was 1.2 before treatment, equivalent to an estimated fibrosis stage of F1. With shear wave imaging, on the other hand, liver stiffness by FibroScan was 8.8kPa, which is equivalent to F3. The divergence is most probably due to the influence of inflammation because the patient had no jaundice or congestion. We may consider that, assuming F1 is in the approximate range of 3 to 4kPa, that 3 to 4 out of the 8.8kPa before treatment is accounted for by the influence of fibrosis and the remaining 4 to 5kPa reflects the influence of inflammation. Actually, liver stiffness gradually decreased with decreasing ALT and recovered to 3.8kPa after 6 weeks. The divergence between the shear wave and strain imaging results had also disappeared (Fig. 18).

Summary

Combinational Elastography using the Vs measurement obtained by SWM, with evaluation using RTE at the same time is useful for correctly assessing the clinical condition of the liver. Development of the SWM technique and RTE with a convex transducer has made it possible to perform Combinational Elastography in series following the normal ultrasound examination, using one transducer. Non-invasive diagnosis of liver disease has become more easily accessible using ultrasound Elastography.

Fig. 18: Treatment Course and Interpretation in an Example Case

ACLT improved quickly as a result of treatment. Likewise, liver stiffness also improved. T-Bil and LFI remained at the same level throughout treatment.

Blue-shaded area is considered to reflect fibrosis and the red-shaded area inflammation.

References