Real-Time Elastography Applications in Liver Pathology between Expectations and Results

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ABSTRACT

Real-time elastography has very good results in differentiating tumors of the breast, thyroid, prostate, pancreas and lymph nodes. Because liver biopsy is invasive and has complications, the method has been tried in diffuse or localized liver pathology in the hope of similar results. However, the published studies are isolated and performed on small groups of patients and the working methodology differs from author to author, without a consensus regarding the establishing of the area of interest, the recording and data analysis. The appearance of the elastography software on the convex probe with high penetration, the possibility for elastography to visualize the liver entirely and the development of elastography measurement information programs opened new perspectives in the noninvasive assessment of liver pathology.

Key words: real-time elastography – focal liver lesions – liver fibrosis.

INTRODUCTION

Elastography is an imaging method which estimates tissue elasticity. Extensive studies have been published, which prove the real time elastography (RT-E) efficiency in differentiating the stiffness of the prostate, breast, thyroid or pancreatic tumors [1-6]. Since in these domains there have been good results, the method was tested for liver pathology, hoping for similar results. Hopes were even higher because at the time when the method appeared, there had already been voices who rejected the liver biopsy as a gold standard in assessing liver fibrosis [7]. Thus, while the normal liver is soft and pliable, in chronic hepatitis consistency increases progressively until the loss of elasticity in cirrhosis.

The principle of RT-E application in assessment of liver fibrosis is that the liver changes its consistency as the fibrosis progresses from early stages to cirrhosis [7]. Thus, while the normal liver is soft and pliable, in chronic hepatitis consistency increases progressively until the loss of elasticity in cirrhosis.

Using the Hitachi RT-E system, elastography information is obtained by applying longitudinal pressure on a tissue and measuring displacement of reflection nuclei of this tissue as a result of the applied pressure (Fig. 1). Practically, radiofrequency waves are collected before and after application of the deformation stimulus, and longitudinal displacement of tissue is assessed by tracking the movement of reflection nuclei using autocorrelation techniques. The resulting deformation image is called an elastogram. Each pixel of the region of interest [ROI] corresponds to one of the 256 specific colors. The colour codes can differ between the various providers. In the Hitachi RT-E, the softest lesions are represented in shades of red, the hard in blue and the intermediary ones in green tones.
EXAMINATION METHOD

Real-time elastography can be performed during a normal liver ultrasound examination without the need for any additional equipment.

In diffuse pathology, placing the region of interest in liver elastography varies from author to author, without an established consensus in this regard. Thus, M. Friedrich-Rust et al [8] and Morikava H et al [9] established elastography ROI inside the liver. Another group included in ROI anatomical structures having the same elasticity in all patients despite their subsequent disease: anterolateral abdominal wall [10] (Fig. 2) or small intrahepatic veins [11, 12]. Ascites fluid does not appear to influence the results of RT-E unlike transient elastography [11] (Fig. 3).

To evaluate the focal hepatic lesions, ROI must include the tumor and the surrounding liver parenchyma too. We can thus appreciate the difference in hardness between tumors and surrounding liver tissue.

The recording method and analysis of data obtained by real-time elastography is different, depending on the study group (Fig. 4). Friedrich-Rust et al [8] developed an elasticity score from the color-coded bit-map image produced by the computer program based on 10 static images. Similarly, Morikava et al analyzed 10 static images, captured by the observer at random from the moving images, using a new software Elasto ver 1.5.1 [9]. Our group uses three 10-s movies for every patient because high examiner bias is usually favored when analyzing static images [13, 14].

Ultrasoundography is an operator-dependent technique and different levels of training and experience could also affect the results of real-time elastography. In our center a prospective study was performed in which patients were examined by two doctors with different degrees of experience in ultrasound. The authors found no difference in reproducibility of four measurement positions unlike the liver hardness measurement obtained by using the FibroScan that differs according to measurement position [15]. Measurement results in RT-E differ

![Fig. 1. The principle of real-time elastography. On the examined tissue pressure is applied, deformation of examined tissue is proportional to its elasticity. Distribution of tissue elasticity is displayed on screen in real time and the result appears as color coded images. Rough lesions are represented in shades of blue, the soft ones in shades of red and intermediary ones are green colored.](image1)

![Fig. 2. Example of placement of the region of interest (ROI) in real-time elastography. RT-E in a 54-year-old patient with chronic viral hepatitis C (F1 Metavir). The region of interest is set in such a way as to include both the liver parenchyma (parenchyma with mixed appearance indicative of elasticity) and the tissues surrounding the liver (skin, subcutaneous fatty tissue, external and internal intercostal muscles, diaphragm and peritoneum) that appear rough in elastography (blue).](image2)
when changing the position of the reference area to a deeper one, when measuring the strain ratio of focal lesions in a tissue-mimicking phantom and in normal liver tissue [16].

**RT-E RESULTS IN DIFFUSE LIVER PATHOLOGY**

The first studies that have evaluated hepatic fibrosis by RT-E showed promising results. The first group of researchers who published the results of RT-E was led by M. Friedrich-Rust [8]. The authors obtained good results for assessing fibrosis: the AUCs, a measurement of the diagnostic accuracy of a test, were 0.75 for the diagnosis of significant fibrosis (F ≥ F2), 0.73 for the diagnosis of severe fibrosis (F ≥ F3), and 0.69 for the diagnosis of cirrhosis (F = F4). Another group of researchers used a quantitative measuring technique called the elastic ratio [12] or elasticity index [17] that had a good correlation with the histologic fibrosis stage. A pilot study conducted by our group including patients with chronic hepatitis C showed a good correlation between the histologic fibrosis stage and the average histogram [14].

**RT-E RESULTS IN LIVER TUMORAL PATHOLOGY**

Currently, there are many studies published which prove the RT-E efficiency in the diagnosis of the prostate, breast, thyroid or pancreatic tumors [1–6] and only a few studies related to liver tumors [18–21]. In the RT-E, liver tumors are viewed due to the difference in hardness between the tumor and surrounding liver tissue. Interpretation of results is difficult. Thus, experienced surgeons perceive intraoperatively liver metastases as rough; hepatocellular carcinoma (HCC) is less rough and benign tumors have a soft consistency. They are similarly perceived in RT-E if the tumor appears in the normal liver. If the liver consistency changes, for example in liver cirrhosis, the surrounding cirrhotic liver tissue may influence the investigation results. Thus, the tumor may appear softer than the surrounding rough liver, regardless of its benign or malignant etiology. Another aspect which is difficult to interpret in liver tumor pathology is the differentiation between regenerative nodules and HCC.

The first study which aimed to assess and validate the diagnostic accuracy of transabdominal RT-E for diagnosis of small HCC nodules in cirrhotic patients was conducted by the team led by L. Gheorghe [18]. The study showed a good performance of RT-E in differentiating hepatic nodules. The area under the ROC curve of the mean intensity value of blue color used for the discrimination of regenerative and malignant small nodules was 0.94 (CI 95% 0.91–0.97).

The study led by Kato K was conducted with the linear probe, but using the intraoperative approach [19]. The authors have proposed to differentiate the two common malignancies using the RT-E, HCC and metastatic adenocarcinoma, a different objective from the previous study. Based on the distribution and degree of strain within the lesion, the authors developed a qualitative classification system, named elasticity type of liver tumour (ETLT). The focal liver lesions were classified into four types: type A, the entire lesion had even strain (the lesion was homogeneously green) to type D, the lesion had no strain (the lesion was homogeneously blue). Using this new classification system, 21 (95.5%) of 22 HCCs were classified as type B, with an accuracy of 92.7%, while all 24 metastatic adenocarcinomas were assigned to either type C or type D, with an accuracy of 89.1%. These results are in agreement with observations obtained by surgeons through palpation: metastases are rough, while HCC has a softer consistency. In this study the number of other types of focal liver lesions was too small to indicate any trend in the elasticity images.

Another group of authors has developed a new RT-E method, called elasticity imaging (EI), for intraoperative applications during liver surgery [20]. The results are similar to the previous study. In addition to the new RT-E method, the study brings another innovation: RT-E application in...
Fig. 4. The analysis of data in RT-E. Obtaining the mean histogram from the area of interest in a patient with a normal liver [a] and the calculation of the 11 parameters offered by the quantitative software integrated into the Hitachi system [b]. Another method of analyzing elastographic data is calculating the strain ratio between the liver parenchyma (A) and the hepatic vein (B). Example of a patient with hepatic cirrhosis, where the elasticity of the hepatic vein is significantly above that of the liver parenchyma: strain ratio = 13.7 [c].
the detection of malignant lesions hardly visible in standard ultrasound. From 45 malignant lesions, 15 were difficult to identify using B-mode IOUS alone because of the isoechoic content, obscure contours or heterogeneous background but were clearly delineated by elasticity imaging.

In a study conducted by our group, we found statistically significant differences between the mean values of the histogram analysis for hemangioma, HCC metastases and cholangiocarcinoma: 161.4, 187.2, 204.2 and 208.9, respectively [21]. The results were similar to previous studies, hemangiomas having a lower hardness compared with malignant lesions and metastases which were tougher than hepatocarcinoma (Fig. 5).

**PERSPECTIVES**

The appearance of an elastography module on the convex probe which visualizes the liver completely and the focal lesions regardless of how deep they are located, along with the precise quantitative analysis of elastography films, opens new perspectives in the diagnosis of liver tumors. At present, RT-E cannot be considered the only method of diagnosis, but being performed with the same ultrasound system may be associated with the contrast enhanced ultrasound. It may also find applications in the detection of lesions hardly visible in standard ultrasound (Fig. 6). Thanks to its lack of invasivity, low cost and short waiting time, the RT-E can be used as a complementary method of diagnosis in the diffuse or tumoral pathology of the liver.

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Fig. 6. Examples of RT-E applications in detecting malignant formations hardly visible in standard ultrasound in patients with hepatic cirrhosis. Due to heterogeneous background and isoechoic content and obscure contours of the tumour, the hepatic tumor was difficult to identify in the standard ultrasound, but very clearly delineated through RT-E (arrows) (a, b).