Non-invasive evaluation of Hepatic Fibrosis in patients with Chronic Hepatitis C using Elastography

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With regard to the long-term prognosis of hepatitis C, there have been reports of the relationship between the risk of hepatocellular carcinoma and the stage of hepatic fibrosis. Histological diagnosis by liver biopsy is important for assessing the stage of liver fibrosis, but assessment is sometimes difficult due to the invasive nature of the procedure. Recently developed Elastography uses the combined autocorrelation method to rapidly calculate the relative hardness of tissue from the degree of tissue distortion, and display this information as real-time, color images. We examined the usefulness of Elastography for the evaluation of hepatic fibrosis in patients with chronic hepatitis C.

The results indicated that non-invasive assessment was possible with Elastography, with the obtained liver elasticity score becoming significantly higher as the staging increased, satisfactorily reflecting the degree of fibrosis. The view is that Elastography would be useful for determining high-risk cancer groups.

Key Words: Elastography, Liver Elasticity Score, Chronic Hepatitis, Tissue Characterization

1. Introduction

More than one million people worldwide die annually of hepatocellular carcinoma, the third highest cause of death due to malignant neoplasm. Hepatocellular carcinoma often develops from viral hepatitis. It has been reported that the risk of hepatocellular carcinoma is related to the stage of hepatic fibrosis, making it a particularly important factor in the long-term prognosis of chronic hepatitis C. The incidence of hepatocellular carcinoma increases along with progression of the stage[1]. It is therefore vital to devise a treatment plan for preventing lesion progression, such as interferon therapy, after diagnosis of hepatic fibrosis. It has been shown that interferon therapy improves hepatic fibrosis and dramatically reduces the incidence of hepatocellular carcinoma[2], so it is considered important to evaluate the stage of hepatic fibrosis over time even after completion of treatment.

The importance of histological diagnosis by liver biopsy for the assessment of the stage of hepatic fibrosis is widely acknowledged[3)-5)]. However, due to its invasive nature, liver biopsy is limited when constant monitoring of the time course of changes in hepatic fibrosis is required, and non-invasive tests should be performed as well. Measurement of platelet count[6] and the determination of hepatic fibrosis markers are useful as non-invasive tests for evaluation of the liver fibrosis stage but the basic procedure for assessment of staging is the combined use of these tests with imaging diagnostic methods such as ultrasonography.

Abdominal ultrasonography is the most useful imaging diagnostic technique for the assessment of chronic hepatitis. The indexes for assessment of staging include the presence or absence of change on the liver surface, deterioration of liver periphery, a decrease in the volume of the right hepatic lobe and increase in the volume of the left lobe, a coarse internal echo, and narrowing of the hepatic vein. However, for the assessment of staging in borderline cases, ordinary ultrasonography is limited because images

can change very slightly due to differences in the resolving power and/or image settings of the equipment used. Interpretation of the images is also greatly dependent on the experience and subjectivity of the person making the assessment. The general idea of ultrasonic tissue diagnosis is to offset these problems through the quantitative evaluation of tissues obtained from ultrasonographic images. For histological diagnosis of the liver, measurement of the raw signal intensity, the extent of scattering[7)8)] and the speed of transmission of an audible vibration generated by a probe in the liver have been reported as techniques for the assessment of tissue elasticity[9)].

2. Objective

Recently developed Elastography uses the combined autocorrelation method to rapidly calculate the relative hardness of tissue from the degree of tissue distortion, and display this information as real-time, color images[10)11)]. Clinical application of Elastography has so far been reported for the breast, thyroid, prostate and pancreas. We investigated the usefulness of Elastography for the evaluation of hepatic fibrosis in patients with diffuse liver disease.

3. Subjects and methods

The subjects in this study were a total of 43 patients with chronic hepatitis C or cirrhosis diagnosed by tissue biopsy. The indicated stages of fibrosis were F1 in 7 subjects, F2 in 12 subjects, F3 in 15 subjects, and F4 in 9 subjects (Table 1). HITACHI EUB-8500 and HI VISION 900 were used for ultrasonography and the probes used were an EUP-L54M Linear probe (13-6MHz) and an EUP-L53 Linear probe (10-5MHz) respectively. After examination in B-mode, the mode was switched to Elastography, and the probe scanned vertically from the epigastrium to observe a sagittal section of the left hepatic lobe or the right hepatic lobe from the right intercostal space. An identical area was set as the ROI for all subjects, with the liver surface as the top. Because heartbeat distorts the liver, observation was made using a freehand technique, keeping the probe in position by applying slight manual pressure while the subject briefly held his or her breath. This equipment displays real-time tissue elasticity images showing the ROI as a semitransparent, colored area, juxtaposed with B-mode images. The colors in the ROI range from blue to red to show the relative hardness and softness of areas inside the ROI (Fig. 1). The same area in the liver was set as the ROI in all subjects, with the liver surface as the top. The Elastography findings were rated as the liver elasticity scores (Fig. 2).

Six blind reviewers experienced in ultrasonography assessed the scores, the mean score was obtained for each subject, and the stagings of each of the liver biopsy samples were compared. Statistical analysis was performed to determine the correlation between the mean liver elasticity score and ALT, total bilirubin, albumin, choline esterase, total cholesterol, prothrombin time, platelet count and Type IV Collagen 7S.

Table 1 : Subject Characteristics

	Patients with Fibrosis Stage (F) (n=43)				
	F1 (n=7)	F2 (n=12)	F3 (n=15)	F4 (n=9)	p value
age (yr)	65.0±6.2	57.7±5.9＊	61.0±8.4	70.0±11.8＊	＊p<0.05
gender (n: M/F)	2/5	7/5	10/5	7/2	n.s.
ALT (IU/l)	23.25±6.19＊	45.67±26.10	65.00±38.79＊	53.50±40.74	＊p<0.05
Total Bilirubin (mg/dl)	0.45±0.10	1.15±0.46	0.77±0.22	1.17±0.15	p<0.05, vs F4
Albumin (g/dl)	4.30±0.14	4.20±0.42	4.10±0.33	3.52±0.66	p<0.05, vs F4
Choline Esterase (IU/l)	293.0±56.5	334.3±50.2	225.5±55.6	149.8±80.8	p<0.05, vs F4
Total Cholesterol (mg/dl)	187.8±35.3＊	151.8±33.9	162.8±28.7	131.8±36.8＊	＊p<0.05
Prothrombin Time (%)	95.98±9.73	80.73±39.15	91.25±7.75	74.70±8.82	n.s.
Platelet count ($\times 10^4/\mu l$)	18.56±5.38	15.97±3.50	16.43±5.62	10.10±4.67	p<0.05, vs F4
TypeⅣ Collagen 7S (ng/ml)	4.51±0.20	4.71±0.66	6.33±1.75	10.11±1.09	p<0.05

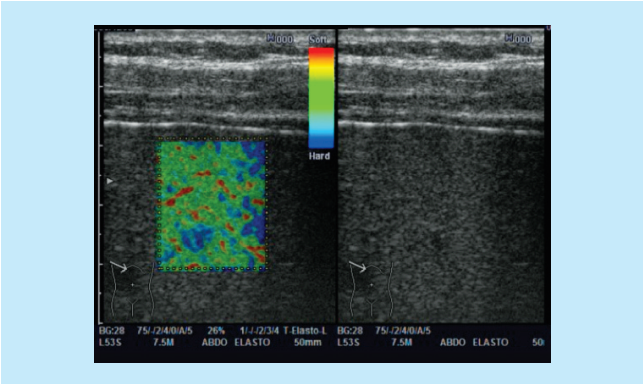

Fig. 1 : ROI Setting for Elastography

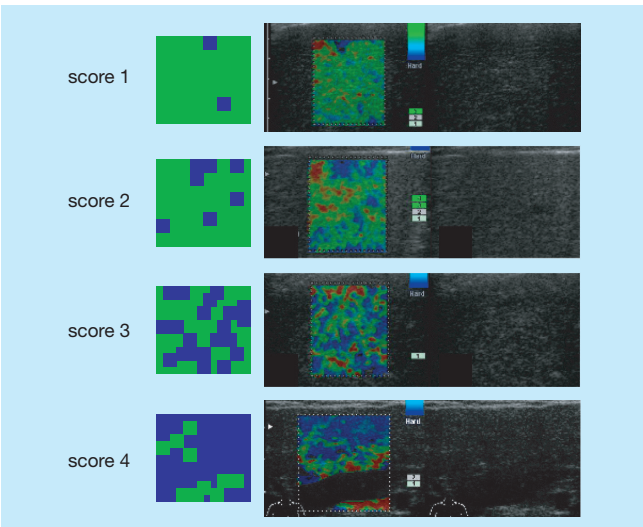

Fig. 2 : Liver Elasticity Score

Score 1 : The entire colored area of the ROI is distorted (the entire colored area is shown as relatively uniform light green).

Score 2 : Partially mottled blue regions are shown in the light green colored area.

Score 3 : Light green and blue are mixed in the colored area (almost a fifty-fifty mix).

Score 4 : Most of the colored area is shown as blue.

4. Results

4.1 Patients

Of the hematological data derived from the patient characteristics reviewed in this study, a significant difference was observed only in Type IV Collagen 7S at all stages. A significant difference between F4 and other stages was observed for total bilirubin, albumin, and choline esterase (Table 1).

4.2 Examination of Elastography observations and hepatic tissue staging

It was easy to utilize distortion due to heartbeat for Elastography observation of the liver.

Slight distortion of the liver by heartbeat itself was observed when a subject held his or her breath for a few seconds, and the aforementioned signals were shown within the Elastography ROI in all subjects.

Fig. 3 to 6 show histopathological images of liver biopsy tissue and Elastography images of each stage. The results of observation showed that as the stage progressed, there tended to be more signals inside the Elastography ROI that showed as blue. Statistical analysis for comparison of stages revealed that the mean liver elasticity score became significantly higher with progression of stage (Fig. 7).

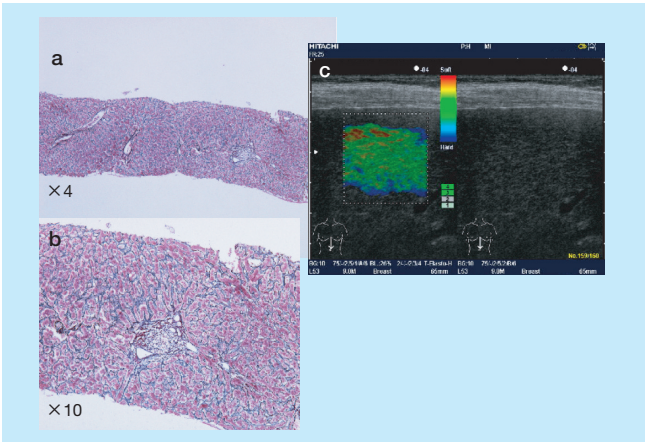

Fig. 3 : Case 1 : 52-year-old male
a, b : Histopathological images of liver biopsy samples, stage F1.
c : The Elastography ROI is almost entirely uniform green with some red areas.
The liver elasticity score was judged to be 1.

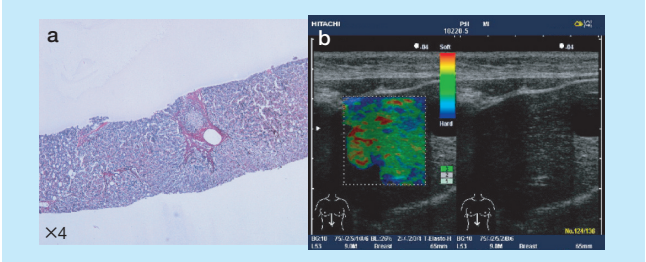

Fig. 4 : Case 2 : 54-year-old female
a : Histopathological image of liver biopsy sample, stage F2.
b : The Elastography ROI is uniform green with some mottled blue areas.
The liver elasticity score was judged to be 2.

4.3 Correlation between blood chemistry values, blood hepatic fibrosis markers and Elastography

The correlation between the mean liver elasticity score and ALT, total bilirubin, albumin, choline esterase, total cholesterol, prothrombin time, platelet count and Type IV Collagen 7S was examined. Only Type IV Collagen 7S showed a significant correlation with the mean liver elasticity score (Fig. 8).

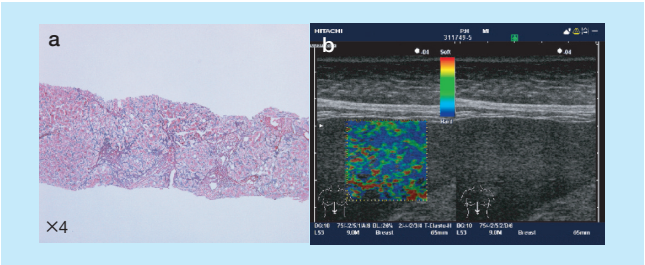

Fig. 5 : Case 3 : 66-year-old male
a : Histopathological image of liver biopsy sample, stage F3.
b : The Elastography ROI shows green and blue signal to almost the same degree.
The liver elasticity score was judged to be 3.

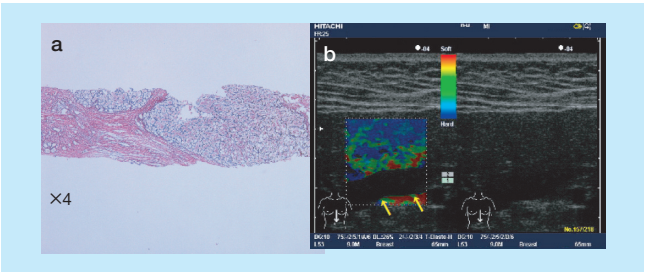

Fig. 6 : Case 4 : 65-year-old male
a : Histopathological image of liver biopsy sample, stage F4.
b : The Elastography ROI shows mostly blue signals, with fewer green than blue signals.
The liver elasticity score was judged to be 4.
(There is signal dropout where distortion in a deep area prevents calculation (arrow)).

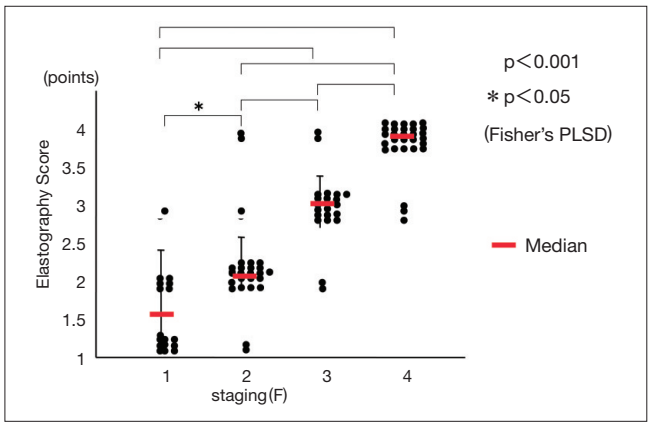

Fig. 7 : Comparison of Histopathological Stage and Elastography Score

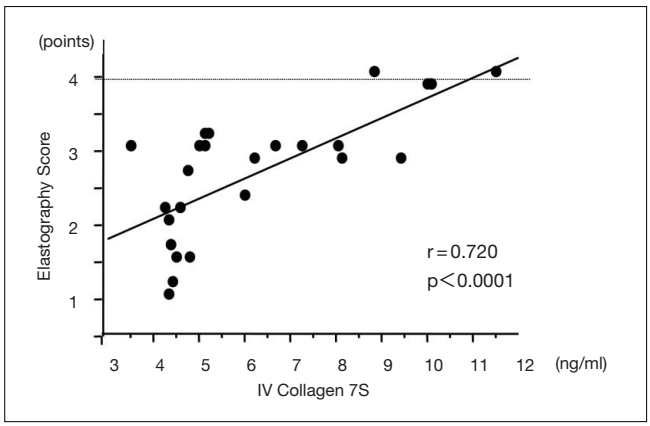

Fig. 8 : Correlation between Type IV Collagen 7S and Elastography Score

5. Discussion

Evaluation of histopathological tissue obtained by liver biopsy has been the conventional gold standard for evaluation of hepatic fibrosis. However, patients sometimes refuse a liver biopsy because of the pain associated with the procedure, the time it requires and the economical burden. As a result, biopsy evaluation may be omitted and hematological data used instead. Since evaluation by hematological data, has its limits, however, evaluation by non-invasive imaging diagnosis is also required.

Transient Elastography (Fibro Scan) was recently developed for non-invasive evaluation of tissue elasticity in the livers of patients with hepatic fibrosis, and its usefulness has been reported. Because this technique involves the generation by a probe of audible external vibrations and the measurement of the speed at which these vibrations are propagated through the liver, however, there are technical limitations that may prevent measurement in highly obese patients, patients with ascites, patients with severe hepatic atrophy, and patients with narrow intercostal space. The Elastography reviewed in this study enabled observation and evaluation even in patients with these unfavorable conditions, and verification of position was easy because the images were juxtaposed with B-mode reference images. Since Elastography is an application preinstalled in the ultrasonography equipment, it is not necessary to purchase any other special equipment for evaluation of hepatic fibrosis. Adopting the equipment for clinical application would therefore be easy.

Although this investigation showed that assessment of the liver elasticity score by Elastography may be influenced by the subjectivity of the evaluator, it is thought that accuracy would improve after the evaluator has become accustomed to the procedure. This disadvantage is expected to solve when evaluation is automated and quantified.

With respect to clinical application in the future, Elastography could be used for screening chronic hepatic disease during medical examinations or for visually explaining the risk of cancer when obtaining informed consent from a patient considered suitable for interferon therapy. It is also anticipated that it will be used to determine the stage of patients who refuse biopsy, for the evaluation of stages during and after IFN treatment (for the evaluation of improvement of fibrosis), for understanding the stages in patients not treated with IFN, and for evaluating patients with diseases other than viral hepatitis (NASH etc.).

In conclusion, Elastography liver elasticity scores became significantly higher with progression of staging, accurately reflecting fibrosis. The view is that it would be particularly useful for determining high-risk cancer groups.

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