Semiquantitative Strain Elastography of Liver Masses

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Objectives—This study was designed to determine the utility of semiquantitative strain elastography in differential diagnosis of solid liver masses.

Methods—A total of 103 patients with focal liver masses underwent abdominal sonographic examinations and freehand elastography of focal hepatic lesions. Eighty-two patients (79.7%) with 93 focal hepatic lesions were included in the study. Twenty-one patients (20.3%) were excluded from the study because of technical limitations of semiquantitative strain elastography and difficulty in detection of normal liver parenchyma on gray-scale sonography. We evaluated different focal hepatic lesions such as hemangiomas, focal nodular hyperplasia, nodular regenerative hyperplasia, adenomas, hepatocellular carcinomas, metastases, and cholangiocarcinomas. The stiffness of the lesions was determined by measurement of strain values on semiquantitative strain elastography. The strain index value (strain ratio of liver parenchyma and focal lesions) of each lesion was calculated. Mean strain index values of benign and malignant liver lesions were compared.

Results—The mean strain index value of malignant liver lesions ± SD (2.82 ± 1.82) was significantly higher than that of benign liver lesions (1.45 ± 1.28; $P < .0001$). Hemangiomas had a significantly lower mean strain index value than other benign lesions ($P < .0034$). There was no statistically significant difference between strain index values of different types of malignant lesions ($P > .05$).

Conclusions—Semiquantitative strain elastography may be helpful for differentiating benign and malignant liver masses. The substantial overlap between strain index values of benign and malignant liver masses limits clinical usefulness of this technique.

Key Words—elastography; liver lesions; sonography; strain in tissue

Sonography has been used as a primary imaging modality in detection of focal solid liver lesions. Characterization of focal solid liver lesions may be difficult on sonography because these lesions may show similar sonographic findings. Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) have been required to characterize focal solid liver lesions by depicting different enhancement patterns of these lesions. However, CT has disadvantages of radiation exposure and use of potentially nephrotoxic contrast material. Magnetic resonance imaging has many implications in evaluation of focal solid liver lesions but it is not an easily applicable imaging technique, and characterization of focal solid liver lesions on MRI requires contrast material administration, which has been determined to be associated with nephrogenic systemic fibrosis. Contrast-enhanced sonography improves focal liver lesion characterization compared to unenhanced sonography; however, it is more operator dependent.

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Abbreviations

CT, computed tomography; MRI, magnetic resonance imaging

Percutaneous biopsy is the last choice, but it has hemorrhagic complications because of its invasive nature.

Ultrasound elastography is a novel imaging technique that displays the elasticity of soft tissues by estimating the strain modules from radiofrequency signals during externally applied compression-decompression (relaxation) cycles.[1] It is an easily applicable, non–contrast-enhanced, and fast imaging method that can be performed during the primary sonographic examination of the patient. Elasticity is defined as the ratio of the tension (stress) needed to produce a relative change in length (strain). Stress can be applied by moving a handheld transducer vertically over the insonified tissue.[2] Tissue elasticity may be altered by pathophysiologic processes such as aging, inflammation, and malignant tumors. In hard tissues, such as malignancy, the tissue components are less compressible, and as a result, they are strained less than softer tissues under uniform stress.[2] In addition to visualization of elasticity on color-coded elastographic images, the strain of tissues can be defined as numerical strain values and compared by cross-correlation of radiofrequency signals. Strain values may be obtained by different mechanisms such as acoustic radiation force impulse imaging or semiquantitative strain elastography.[3] Applications of elastography to several clinical problems, such as in the breast, thyroid, and prostate, have been reported.[4–7] Elastography performed with the acoustic radiation force impulse technique was reported to be effective in differentiation of liver metastasis from other liver lesions.[3,8]

Although an acoustic radiation force impulse shear wave was used as a quantitative elastographic technique for differentiation between focal solid liver lesions, to the best of our knowledge, there is no report in the literature about the utility of semiquantitative strain elastography for this purpose. In this study, our aim was to investigate the utility of strain index measurement by semiquantitative strain elastography in differentiation between benign and malignant solid liver lesions.

Table 1. Types and Mean Strain Index Values of Focal Solid Liver Lesions

Lesion Type	n	Strain Index
Hemangioma	26	0.92 ± 0.14
Focal nodular hyperplasia–adenoma–nodular regenerative hyperplasia	10	1.75 ± 0.16
Metastasis	28	3.22 ± 0.47
Hepatocellular carcinoma	24	3.24 ± 0.48
Cholangiocarcinoma	5	4.32 ± 0.44

Values are mean ± SD.

Materials and Methods

Approval for the study was obtained from the local Ethics Review Board, and informed consent was obtained from all patients before sonographic and elastographic examinations. Between November 2010 and November 2011, a total of 103 consecutive patients with focal liver lesions were prospectively examined by semiquantitative strain elastography. Among this group, 82 patients (42 male and 40 female) with a mean age of 52 years (range, 17–71 years) and with 93 focal solid liver lesions were included in this prospective study. Nine patients with multiple liver metastases or multicentric hepatocellular carcinomas in which normal liver parenchyma could not be detected were excluded from the study because comparison of strain index values between solid lesions and spared liver parenchyma could not be performed. Twelve patients were excluded from the study because of an inability to hold breath properly (n = 6), presence of ascites (n = 4), and deep-seated (>8-cm) lesions (n = 2).

The lesions examined by elastography are summarized in Table 1. Diagnoses of hemangiomas were based on the hyperechoic appearance on gray-scale sonography, lack of vascularity on color flow Doppler imaging, early peripheral nodular contrast enhancement during the hepatic arterial phase and centripetal fill-in enhancement during the portal venous phase on dynamic CT and MRI, and unchanged mass dimensions 12 months after lesion detection. Adenomas, focal nodular hyperplasia, nodular regenerative hyperplasia, metastases, hepatocellular carcinomas, and cholangiocarcinomas were diagnosed by percutaneous biopsies after semiquantitative strain elastography. The primary organs that metastases arose from are summarized in Table 2.

Imaging and Analysis

Freehand real-time elastographic examinations were performed with a 3.5-MHz convex probe on an Aplio XG ultrasound machine (Toshiba Medical Systems, Co, Ltd, Ottawara, Japan) by a radiologist specializing in abdominal

Table 2. Primary Tumors of Metastases

Primary Tumor	n
Colon	7
Stomach	5
Pancreas	5
Ovary	5
Gastrointestinal stromal	3
Breast	2
Esophagus	1

sonography. After fitting the semiquantitative strain elastographic image box to fully cover the lesion in the liver, a compressive and decompressive force was applied, keeping the same area of the lesion in the field of view. We applied the probe with vertical pressure, avoiding lateral movement.

Subcostal scanning was used for all elastographic examinations. During probe movement, gray-scale images of the lesions were shown on the sonographic screen. The elasticity images were produced automatically on the ultrasound machine by comparing two adjacent frames during compression and relaxation by continuously moving the probe. After 7 to 8 compression-relaxation cycles, the elastographic examinations were finalized, and strain value measurements were obtained. Compression and relaxation waveforms were shown on the elastographic screen as above and below the baseline of the waveform scale, respectively (Figures 1 and 2). Strain measurements were obtained from appropriate relaxation waves, which had a sinusoidal shape in the waveform scale. Relaxation waves were used for strain measurements according to the manufacturer's recommendations and the Aplio user manual. The color-coded image scale ranged from red for components with highest strain (ie, softest components) to blue for those with lowest strain (ie, hardest components). Green indicated intermediate strain in the region of interest. On semiquantitative strain elastography, strain represents the degree of tissue displacement as a response to induced pressure. The strain index value represents the ratio of the strain of focal solid liver lesions to that of normal liver parenchyma. The strain index value increases when the lesion is harder (stiffer) than the parenchyma.

Strain values of tissues were measured by putting equal- or near-equal-sized regions of interest in the lesion and liver parenchyma. Regions of interest were intended to be at the same level as possible to perform the measurements.

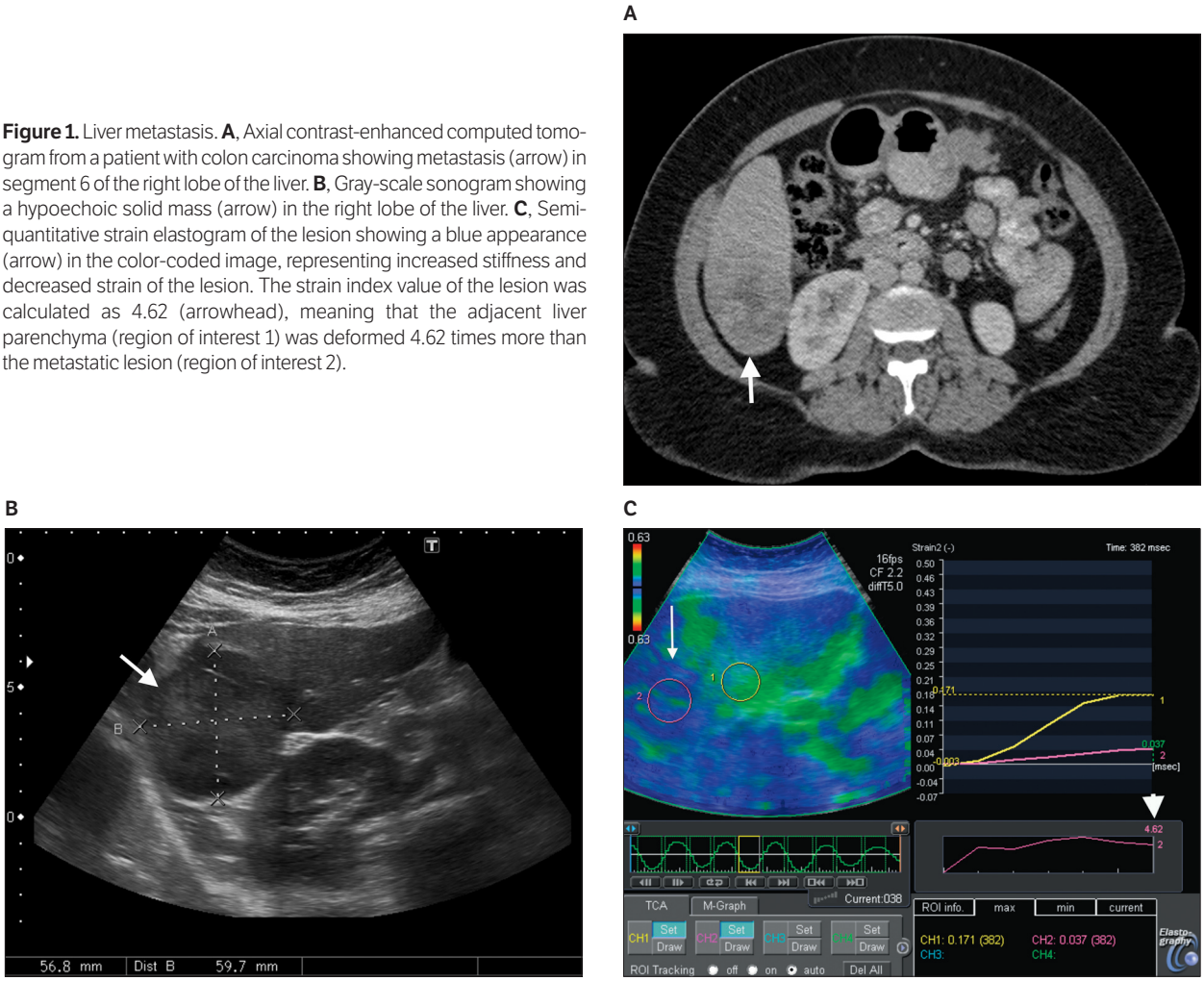


Figure 1. Liver metastasis. **A**, Axial contrast-enhanced computed tomogram from a patient with colon carcinoma showing metastasis (arrow) in segment 6 of the right lobe of the liver. **B**, Gray-scale sonogram showing a hypoechoic solid mass (arrow) in the right lobe of the liver. **C**, Semiquantitative strain elastogram of the lesion showing a blue appearance (arrow) in the color-coded image, representing increased stiffness and decreased strain of the lesion. The strain index value of the lesion was calculated as 4.62 (arrowhead), meaning that the adjacent liver parenchyma (region of interest 1) was deformed 4.62 times more than the metastatic lesion (region of interest 2).

The sizes of the regions of interest were determined as large enough to place within the confines of the lesion to represent elasticity of the lesion appropriately. The radiologist who performed the strain measurements was not aware of the histopathologic types of the lesions during elastography and strain measurement. After the strain measurements were obtained, the strain index values of the lesions were compared. In addition, comparison of mean strain index values in the benign lesion group (hemangiomas, focal nodular hyperplasia, and nodular regenerative hyperplasia) and the malignant lesion group (metastases, hepatocellular carcinomas, and cholangiocarcinomas) was performed. All diagnoses were made by a pathologist (I.H.Ö.) who had 20 years of experience in the pathologic analysis of benign and malignant liver lesion samples obtained by core biopsy.

Statistical Analysis

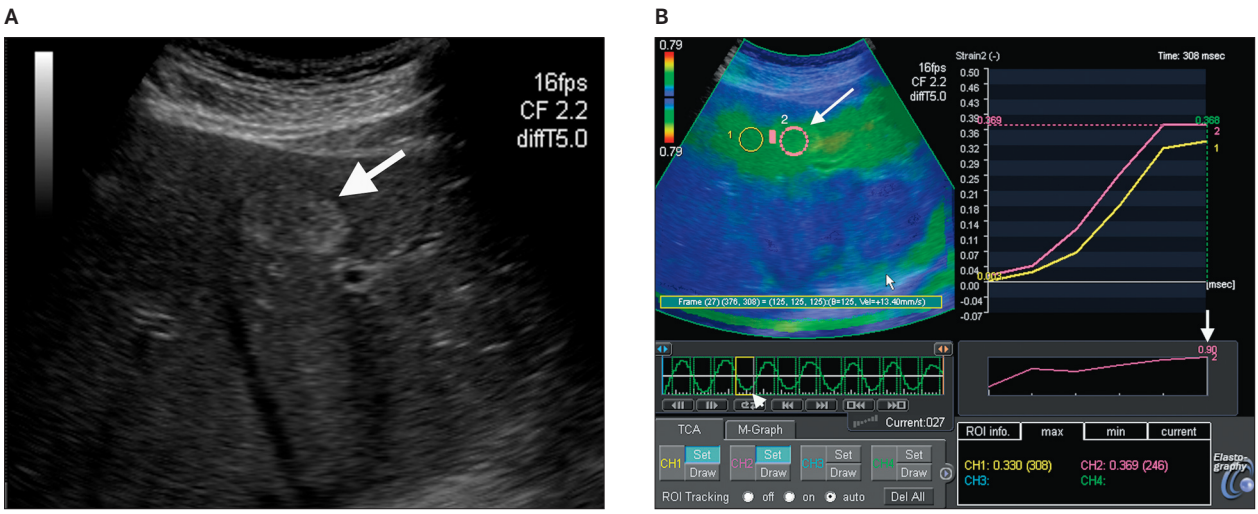
Strain values were expressed as mean ± standard deviation and analyzed using GraphPad Prism 4 (GraphPad Software, Inc, San Diego, CA). We used an unpaired *t* test for comparisons between strain index values of different types of focal solid liver lesions and benign and malignant lesions. Differences were considered statistically significant at $P < .05$. Receiver operating characteristic analysis was performed to obtain cutoff strain index values for differentiation between benign and malignant lesions.

Results

Mean diameters of the benign and malignant liver lesions were 3.32 and 4.52 cm, respectively. The mean lesion depth from the ultrasound probe was 6.7 cm (range, 2.8–7.6 cm). Mean strain index values of the focal solid liver lesions are summarized in Table 1. Twenty of 24 patients with hepatocellular carcinomas had cirrhotic livers confirmed by biopsy. The liver parenchyma of patients with other lesions was not cirrhotic in appearance, and the patients revealed no history of cirrhosis. The malignant lesions appeared stiffer than benign lesions, with a blue appearance, in contrast to the benign lesions, which had a green appearance on color-coded elastography (Figures 1 and 2). The mean strain index value of all malignant lesions (2.82 ± 1.82) was significantly higher than the mean value of the benign lesions (1.45 ± 1.28; $P > .05$; Figure 3). The distribution of strain index values for the benign and malignant lesions is shown in Figure 4. The highest and lowest mean strain index values of the solid liver lesions were detected in the metastasis (3.22 ± 0.47) and hemangioma (0.92 ± 0.14) groups (Figures 1 and 2).

The mean strain index value of hemangiomas was significantly lower than the mean values of adenoma–focal nodular hyperplasia–nodular regenerative hyperplasia ($P = .0034$), hepatocellular carcinomas ($P < .0001$), and

Figure 2. Hemangioma. **A**, Gray-scale sonogram of the liver showing a hyperechoic hemangioma in the left lobe of the liver (arrow). **B**, Corresponding semiquantitative strain elastogram from the same patient. The top left part shows region of interest 1 in the liver parenchyma and region of interest 2 in the hemangioma (long arrow). Below the color-coded image, compression-relaxation waveforms are shown. Strain measurement was performed from the relaxation wave (arrowhead). Time-strain curves of regions of interest 1 and 2 are shown in the top right part. The strain index value of the hemangioma, which represents the strain ratio of the liver parenchyma (0.330) and hemangioma (0.369), appears at the bottom right as 0.90 (short arrow), meaning that the hemangioma was displaced more than the liver parenchyma in response to induced pressure during the relaxation (decompression) phase.



metastases ($P < .0001$). The mean strain index value of the adenoma–focal nodular hyperplasia–nodular regenerative hyperplasia complex was significantly lower than the mean values of hepatocellular carcinomas ($P < .02$) and metastases ($P = .0083$). The comparison between mean strain index values of hepatocellular carcinomas and metastases did not reveal a statistically significant difference ($P = .56$).

Receiver operating characteristic analysis of the strain index values yielded a cutoff value as 1.28 for differentiating benign and malignant solid liver lesions, with sensitivity and specificity of 78% and 65%, respectively (area under the curve, 0.79).

Discussion

Differentiation of focal solid liver lesions remains a major concern on imaging studies. Sonography, CT, and MRI have been used for this purpose. Gray-scale, color, and spectral Doppler sonography have limited value in differential diagnosis of these lesions.[9]

Imaging studies of focal solid liver lesions are usually required first to define the lesions as benign or malignant. Hemangiomas represent most frequently detected focal solid liver lesions in clinical practice and appear as hyperechoic solid lesions without vascularity on color flow Doppler sonography. A centripetal enhancement pattern on dynamic CT and MRI is a characteristic imaging finding of hemangiomas. However, atypical hemangiomas may present as hypoechoic masses on gray-scale sonography with atypical contrast enhancement patterns on dynamic CT and MRI. Other types of focal solid liver lesions are usually diagnosed by dynamic CT and MRI or percutaneous liver biopsy.[10]

The basic principle of elastography is to assess the degree of compression and, as a result, distortion (strain) of the tissue, which provide images representative of underlying tissue stiffness. In our study, we used semiquantitative strain elastography as a technique to investigate the relative stiffness of the liver parenchyma and liver lesions. In semiquantitative strain elastography, images are produced by estimation of the tissue recovery response to the induced pressure on the tissue. The ratio of displacement (strain) of the normal tissue and lesion in response to the induced pressure is defined as the strain index value. The stiffness of lesions is compared by the strain index values. Other elastographic techniques include measuring tissue stiffness using a mechanical push from a small piston to launch a compression wave into the tissue and to use the acoustic radiation force of the ultrasound (acoustic radiation force impulse) wave as a push pulse.[11]

Direct mechanical measurements of resected liver samples have indicated that elastic contrast exists for many tumors in the liver.[12] Elastography with the acoustic radiation force impulse technique was reported to be effective in differentiation of liver lesions from each other.[3,8] The acoustic radiation force impulse technique differs from semiquantitative strain elastography by using a high-

Figure 3. Mean strain index values of focal solid liver lesions.

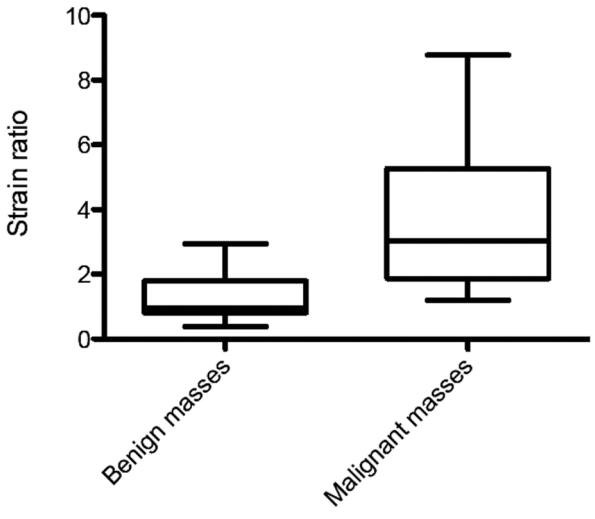
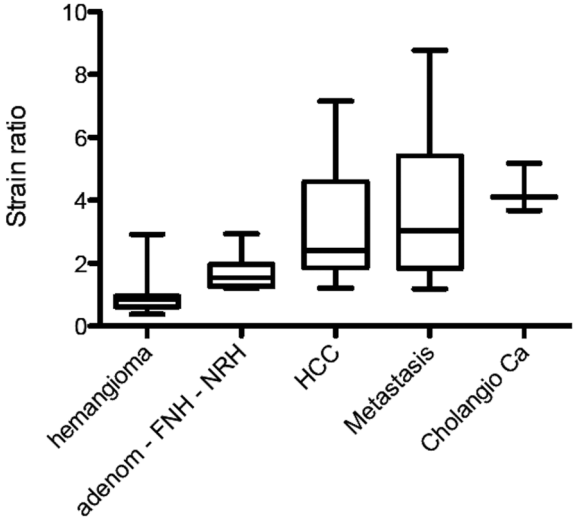


Figure 4. Significant differences between mean strain index values of benign and malignant lesions; adenom indicates adenoma; Ca, carcinoma; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; and NRH, nodular regenerative hyperplasia.



intensity focused ultrasound beam without manual or motorized compression with moving probes. Measurement of the shear wave velocity or analysis of tissue movement can be used to estimate the stiffness of the examined tissue on acoustic radiation force impulse imaging. The shear wave velocity depends on tissue elasticity because the speed of the shear wave traveling through a region of interest increases as tissue stiffness increases.[3] Acoustic radiation force impulse elastography was reported to be helpful in differentiating malignant hepatic tumors from hemangiomas and other benign liver lesions by using shear wave velocity measurements.[3,8] Yu and Wilson[13] found significant differences between quantitative acoustic radiation force impulse values of benign and malignant liver masses. In comparison to our study, a threshold acoustic radiation force impulse value of 1.9 m/s in their study yielded lower sensitivity (68% versus 78%) and higher specificity (69% versus 65%) for differentiation between benign and malignant liver masses. However, the subtypes of benign (hemangioma, focal nodular hyperplasia, focal fat sparing, focal fat deposit, and adenoma) and malignant (hepatocellular carcinoma and metastasis) masses in that study were not the same as in our study. Hepatocellular carcinomas and metastases were distinguished from benign liver lesions by acoustic radiation force impulse values.[13] Although metastases revealed more stiffness than hepatocellular carcinomas, there was no significant difference between the shear wave velocities of these lesions.[13] Those quantitative acoustic radiation force impulse results were in concordance with our semiquantitative strain index value measurements. Similar strain index values of malignant focal solid liver lesions were attributed to common histologic properties of malignant lesions that include hypercellularity and a tight tissue structure.

A comparison of strain index values revealed a significant difference between hemangiomas and the adenoma–focal nodular hyperplasia–nodular regenerative hyperplasia complex that might have been due to differences between the tissue architectures of these lesions. Hemangiomas are mainly constituted of dilated venous channels, whereas non-neoplastic hypercellularity is the dominant histologic feature in the tissue architecture of the adenoma–focal nodular hyperplasia–nodular regenerative hyperplasia complex. Benign lesions other than hemangiomas (focal nodular hyperplasia, nodular regenerative hyperplasia, and adenomas) were included in the benign lesion group in this study because they are hypercellular lesions mimicking malignant lesions more frequently than hemangiomas on sonography, CT, or MRI. Although there was significant difference between the mean strain index values of benign and malignant liver lesions, there was a substantial overlap limiting the clinical usefulness of semiquantitative strain elastography (Figure 4).

In cirrhotic patients, the strain of the liver is decreased; therefore, one may expect a considerable decrease in the strain index value of focal solid liver lesions.[12] Parenchymal fibrosis in liver cirrhosis decreases the elasticity of liver parenchyma as well as hepatocellular carcinomas because hepatocellular carcinomas are usually surrounded by fibrotic parenchyma. Twenty of 24 patients with hepatocellular carcinomas also had a diagnosis of cirrhosis in our study, and the mean strain index value of hepatocellular carcinomas was found to be significantly higher than benign lesions. This result suggests the possible utility of semiquantitative strain elastography to help distinguish benign from malignant focal solid liver lesions. Additional work is needed to determine how this technique could improve diagnostic accuracy when added to conventional sonography.

The sensitivity and specificity values of conventional sonography in differentiation between benign and malignant liver lesions range from 28.1% to 58.8% and 34.6% to 50.7%, respectively.[9,14] Because we obtained higher sensitivity and specificity values on semiquantitative strain elastography in comparison to results of conventional sonography in the literature, we suggest that semiquantitative strain elastography may improve the characterization of liver lesions as benign or malignant on sonography.

Contrast-enhanced sonography is a reliable imaging technique in the characterization of liver lesions as benign or malignant, with higher sensitivity and specificity values, ranging from 85% to 90% and 80% to 99%, respectively[15,16] Although the sensitivity and specificity levels of semiquantitative strain elastography are low when compared to contrast-enhanced sonography, elastography has the advantages of noninvasiveness (it does not require any chemical administration) and rapidity.

Our study had some limitations. Considering hemangiomas as benign lesions might be suggested as a limitation because hemangiomas are formed mainly from dilated vascular channels, and this histologic structure may cause high strain values, resulting in decreased strain index values in the benign lesion group. Similarly, hemangiomas usually appear on sonography as hyperechoic solid masses that can be easily differentiated from other focal solid liver lesions. However, atypical hemangiomas may present with a hypoechoic appearance, which makes them indistinguishable from malignant focal solid liver lesions.[17] The comparison of strain index values in different patients who had liver lesions might be questioned because compression-relaxation forces by freehand elastography

may be different, which may result in varying strain index values for the same lesion types. In this study, the strain index values of all patients were measured on the relaxation waveform with a sinusoidal shape. Another limitation of elastography is that compression of the liver has always been difficult because of the surrounding ribs, the presence of ascites, and patients with the inability to hold breath. We performed elastography by subcostal scanning after having the patients take a deep breath to overcome this limitation. The compression-decompression waveforms in semiquantitative strain elastography represent probe movements. This factor may be suggested as a limitation of this technique. However, it should be kept in mind that compression-decompression waveforms in semiquantitative strain elastography represent the magnitude of the applied force, which results in tissue strain. Semiquantitative strain elastography cannot be performed in some groups of patients with solid liver lesions, which limits its clinical usefulness. In our study, we had to exclude 20.3% of patients (21 of 103) because of difficulty in detection of normal liver parenchyma (n = 9), the inability to hold breath properly (n = 6), the presence of ascites (n = 4), and deep-seated (>8-cm) lesions (n = 2).

In conclusion, strain value measurement by elastography reflects the elasticity of focal solid liver lesions. Semiquantitative strain elastography may be used as a noninvasive and easily applied complementary tool for differentiation between benign and malignant focal solid liver lesions by comparison of the strain index values of these lesions.

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