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Usefulness of new subtraction algorithm in estimating degree of liver fibrosis by calculating extracellular volume fraction obtained from routine liver CT protocol equilibrium phase data: Preliminary experience

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ABSTRACT

Objectives: To assess whether extracellular volume fraction (ECV) obtained from routine liver CT equilibrium phase data utilizing new subtraction algorithm is useful in estimating the degree of liver fibrosis.

Materials and methods: Consecutive 41 patients, 21 men and 20 women, with chronic liver diseases who underwent quadri-phase liver CT and MR elastography within 3 months were retrospectively enrolled. Subtraction image of unenhanced from equilibrium phase (240 s) images using conventional and new algorithms were made. We firstly assessed the quality of these subtraction algorithms using patients in whom anatomical misregistration between the two image sets were prominent. Then, ECVs were calculated using both subtraction data sets (ECV-convSub, and ECV-newSub, respectively). ECV were also calculated by traditional manual method (ECV-man). Correlation coefficients of 3 types of ECV were compared using liver stiffness (kPa) as measured by MR elastography and pathologically proven fibrosis grades as reference standards.

Results: For eleven patients with prominent anatomical misregistration between the unenhanced and equilibrium phases, new algorithm provided significantly better subtraction images than the conventional one ($p = 0.001$, Wilcoxon's signed rank test). As for correlation with liver stiffness, R^2 for ECV-man, ECV-convSub, and ECV-newSub, were 0.57, 0.59, and 0.66, respectively (all $p < 0.0001$, Pearson's correlation). Histological assessment for fibrosis grades were available in 20 patients, and rho values for these three ECVs were 0.66, 0.61, and 0.71, respectively (all $p < 0.01$, Spearman's rank correlation).

Conclusion: ECV-newSub showed better correlation to liver stiffness and pathological fibrosis grades than ECV-convSub and ECV-man, which could be a reliable biomarker of liver fibrosis obtained from routine clinical diagnostic imaging data, where equilibrium phase delay time was set at 240 s.

1. Introduction

Assessment of the degree of liver fibrosis is important in the management of patients with chronic liver diseases, because it has been shown to be related to the prognosis of these patients directly or indirectly via hepatocarcinogenesis [1–4]. Several imaging approaches have been reported to be useful as tools for non-invasive assessment of liver fibrosis, including shearwave or strain ultrasonographic elastography, or magnetic resonance (MR) elastography (MRE) [3,4]. Among these, MRE may be the most reliable and accurate, according to the recently accumulated evidences [3–5]. However, all these methods are additional examination to the routine clinical follow up, or requires specific hardware and/or software.

Assessment of liver fibrosis degree by estimating extracellular volume fraction (ECV) has been attempted utilizing the equilibrium phase of contrast enhanced computed tomography (CT) [6–9]. ECV in% is simply expressed as (100- hematocrit) * Δ liver/Δ blood pool, where Δ represents the difference in the CT values between at the unenhanced and equilibrium phase, because the concentration of iodine is considered the same for both intra- and extra-vascular spaces at the equilibrium phase [6–9]. ECV is the sum of extracellular extravascular space and intravascular space of a tissue; the former is the place where fibrosis occurs, whereas the latter is not [6,7]. In spite of the unknown factor of intravascular space included, initial animal study showed very high correlation between ECV and quantitatively assessed pathological fibrosis volume [6], followed by several clinical studies with promising

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results [7–9].

ECV was originally calculated by manually placed region-of-interests (ROI) both on the unenhanced and equilibrium phase images [6–8], but if accurate subtraction is possible after adequate anatomical correction between the two image sets, detailed ECV may be assessed on voxel-basis for any parts of the whole liver. For this purpose, sophisticated non-linear non-rigid anatomical correction algorithm is required, because the liver is a soft organ which may be deformed by respiration or by intestinal peristalsis. Recently new subtraction algorithm (SURE SUBTRACTION Iodine Mapping, Canon Medical Systems, Tokyo, Japan: SSIM) was introduced which is specifically designed for soft tissue density organs in the abdomen [10], in contrast to the conventional algorithm (Lung Subtraction ALL mode, Canon Medical Systems, Tokyo, Japan: LSAM), which had been originally designed for the lung tissue of air density [11].

The purpose of this study is to elucidate whether ECV obtained from routine liver CT equilibrium phase image data utilizing new subtraction algorithm is useful in estimating the degree of liver fibrosis, as compared to those calculated from data obtained by conventional subtraction algorithm or by traditional manual ROI method.

2. Materials and methods

2.1. Patients

Our institutional review board approved this study, and waivered the requirements to obtain written informed consents from the patients because of its retrospective nature.

Between 2016 April and 2017 March, consecutive 41 patients who underwent both quadri-phase CT and MR elastography within three month were retrospectively recruited. The flowchart of patient enrollment is shown in Fig. 1. There were 21 men and 20 women, with age ranging from 19 to 91 years (average 65.6), all of whom had suspected liver masses on ultrasonography. The demographic data of these patients are shown in Table 1.

Table 1
Demographic data of the patients.

sex	M: F = 21: 20
age	19–91 years old (mean 65.6)
background	HBV/HCV/NBNC/ALD/noLD/others[a] =7/16/7/1/8/2
height	140.0–176.0 cm (mean 158.4)
body weight	40.0–82.0 kg (mean 56.3)
body mass index	16.0–36.3 (mean 22.4)
Child-Pugh score	normal or 5/6/7/8 = 25/8/5/3
liver stiffness at MR elastography (kPa)	2.1–11.1 kPa (mean 5.0)
pathological F grades (n = 20)	F0/F1/F2/F3/F4 = 2/7/6/3/2

M/F: male/female, HBV/HVC: hepatitis B/C viral infection, NBNC: non-B non-C liver disease, ALD: alcoholic liver disease, noLD: no liver disease.
[a] One auto-immune hepatitis, one primary biliary cholangitis.

2.2. CT protocol

CT equipment used was an area-detector CT (Aquilion ONE ViSION Edition, Canon Medical Systems, Tokyo, Japan), and scanning parameters were as follows: 0.5 mm x 80 row, 120 kVp, three-dimensional auto-exposure control (Volume EC: SD12@5 mm), 0.5 s/rotation, 0.813 beam pitch, 512 × 512 matrix, 300–350 mm field-of-view, and 2 mm reconstruction. Noise reduction was achieved by a hybrid iterative reconstruction (Adaptive Iterative Dose Reduction or AIDR 3D Weak).

After obtaining unenhanced images, 600 mgI/kg iodine contrast medium (Iopamiron 370, Bayer Health Care, Osaka, Japan) was injected for 30 s at a variable injection rate, and arterial dominant phase images were obtained using bolus tracking method, followed by portal dominant phase at 60 s, and equilibrium phase images at 240 s after the commencement of CM injection.

2.3. MRE protocol

MRE was obtained with a 3.0T clinical unit (Discovery 750 W, GE, Milwaukee, USA) along with a 32-element phased-array coil. A 19-cm-diameter passive pneumatic driver was positioned over the center of the right rib cage at the level of the xiphoid process and attached to an acoustic waveform generator. A 60-Hz waveform was applied to the driver. A 2D spin-echo echo-planar MRE sequence (TR/TE = 1000/59, 66 × 64 matrix, 10 mm slice thickness, 80-Hz magnetization encoding gradient) acquired magnitude and unwrapped phase difference wave images using a 42-cm field-of-view [5,12,13]. Four slices were obtained including the level of the hepatic hilum under 16-s breath-holding. Wave images and MRE images (stiffness map) with cross-hatching marks were automatically generated on the operating console. The inversion algorithm used for stiffness map calculation was a multi-scale direct inversion. Liver stiffness was measured by one experienced radiologist (KY) using the free hand method, by placing regions of interest (ROIs) on the stiffness map, mainly in the right hepatic lobe, avoiding apparent pathologies, large vessels, areas with inadequate wave propagation and cross-hatching marks [12]. An average of the four slices was used to represent the liver stiffness of each patient. These data were recorded at the time of routine clinical practice and liver stiffness measurement was not repeated for this study.

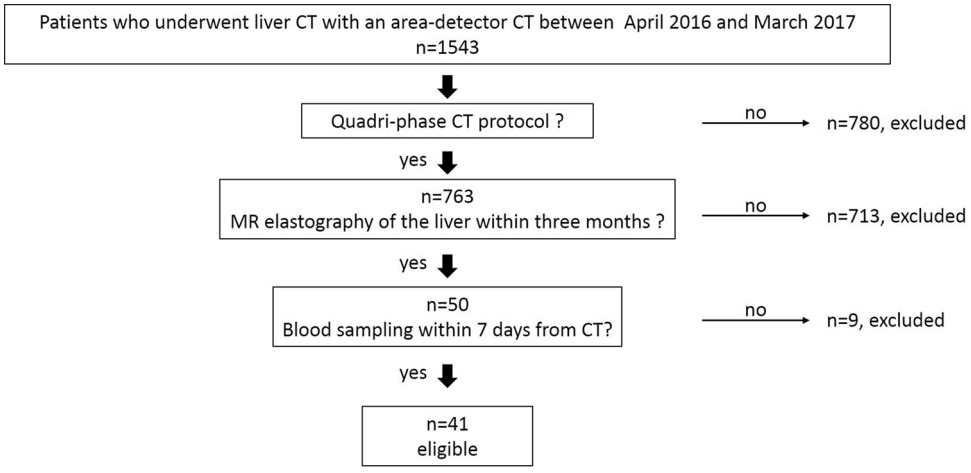

Fig. 1. Flowchart of patient enrollment.