Appendix E1

1. Detailed MR Imaging Protocol

All patients fasted for at least 8 hours prior to undergoing MR examination. MR images were obtained from the level of the liver dome to the tip at axial imaging and from the liver dome to the iliac crest at coronal imaging. MR images were acquired with a respiratory-triggered T2-weighted fast spin-echo sequence, a T2-weighted single-shot fast spin-echo sequence, a breath-hold T1-weighted, dual-echo (in-phase and opposed-phase) spoiled gradient-recalled echo sequence, and a T2*-weighted gradient-recalled-echo sequence. Fat-saturated 3D spoiled gradient-echo sequences (liver acquisition with volume acceleration [LAVA]; GE Medical Systems, Milwaukee, Wis) were performed both before and after intravenous bolus administration of gadoxetic acid (Primovist; Bayer Schering Pharma, Berlin, Germany) at a dose of 0.025 mmol/kg (0.1 mL/kg body weight) at a rate of 1 mL/sec, immediately followed by a 30-mL saline flush through an antecubital venous catheter by using a power injector (Spectris Solaris EP; MEDRAD, Warrendale, Pa). Dynamic MR imaging included the following phases: hepatic arterial phase, portal venous phase, delayed phase, and hepatobiliary phase. Imaging delay times after contrast material injection determined with real-time MR imaging fluoroscopic monitoring were as follows: arterial phase, 7 seconds after contrast media arrival at a distal thoracic aorta; portal venous phase, 60 seconds after contrast material injection; delayed phase, 3 minutes after contrast material injection; and hepatobiliary phase, 10 and 20 minutes after contrast medium injection.

2. MR Sequence Parameters

MR Sequence	Repetition Time (msec)/Echo Time (msec)	Flip Angle (degrees)	Echo Train Length	Field of View	Matrix	Section Thickness (mm)	Intersection Gap (mm)
Respiratory-triggered T2-weighted fast spin echo	8000–10 000/103	90	16	380 × 380	448 × 256	7	0
Breath-hold T2-weighted single-shot fast spin echo	850/160	90	1	380 × 380	320 × 192	7	0
Breath-hold T1-weighted spoiled gradient-recalled echo	In-phase, 6.6/4.4; opposed-phase, 6.6/2.1	12	1	380 × 380	320 × 224	4.8	1.2
T2*-weighted gradient recalled echo	100/15	30	1	380 × 380	320 × 288	7	0
Breath-hold T1-weighted 3D LAVA	4.6/2.3	12	1	380 × 380	320 × 224	4.8	1.2

Note.—LAVA = liver acquisition with volume acceleration (GE Medical Systems).

3. Techniques of MR Elastography

The MR elastography parameters were as follows: 1.5-T Signa Excite imaging software version 16M4 (GE Healthcare); 1333.8/51.2; excitation flip angle, 90°; refocusing flip angle, 180°; field of view, 380 × 380 mm; acquisition matrix size, 72 × 72; section thickness, 3.5 mm; no intersection gap; Array Spatial Sensitivity Encoding Technique parallel imaging factor, three;

three phase offsets; and a 6.45-msec, 3.2-T/cm, bipolar, trapezoidal, motion-encoding gradient on each side of the refocusing pulse.

To obtain a consistent position of the liver for each phase offset, patients were instructed to hold their breath at the end of expiration. A stiffness map (elastogram) for each MR elastography section was generated automatically by processing the acquired images of propagating shear waves by using a previously described 3D local frequency estimation inversion algorithm (1). Elastograms were generated both in grayscale and as a color bitmap with a scale corresponding to the stiffness values. The motion-encoding gradients were applied sequentially in three orthogonal directions to measure the vector displacement field throughout the volume. Three-dimensional, three-axis MR elastography provides theoretical advantages of enhanced accuracy of elastograms over two-dimensional MR elastography, as it allows for the removal of longitudinal wave propagation with curl filtering, and 3D processing reduces artifacts from through-plane wave propagation. Multisection acquisitions can sometimes have small intersection phase shifts, independent of the desired phase, due to the tissue vibrations that, if left in the data, can adversely affect 3D processing because these phase variations do not reflect the actual tissue motion. This artifact appears as a high-frequency striping pattern in the section direction because of the interleaved section acquisition. To remove this artifact, a one-dimensional low pass filter was applied in the section direction of each complex-valued image volume before calculating the curl of the wave field and performing the local frequency estimation. The filter was designed as a fourth-order Butterworth low pass filter with a cutoff frequency of 0.357 cm^{-1}. Spatial presaturation bands were applied on each side of the imaging volume to reduce motion artifacts derived from blood flow. To prevent chemical shift artifacts, spatial spectral pulses were used to generate the initial 90° radiofrequency pulse. Like in other liver and spleen MR elastography studies, susceptibility artifacts normally associated with echo-planar–based sequences were not a problem in our study (2).

4. Details of the Statistical Analyses

The two subject groups were compared by using the Student *t* test (for age) or χ^2 test (for subject sex). The relationship between MR elastography values and variceal grade was assessed by using Spearman correlation analysis. The correlation between spleen length and variceal grade was evaluated by using the Pearson correlation coefficient. To identify significant independent predictors of the presence of varices, high-grade varices, and variceal bleeding, multivariate logistic regression analysis with the stepwise selection method was performed; a significance level of $P_{in} < .05$ (where P_{in} represents the probability of F-to-enter) and $P_{out} > .10$ (where P_{out} represents the probability of F-to-remove) was established. Variables of age, sex, hepatitis B virus, HS, SS, and spleen length were used as variables in the analysis. To evaluate the diagnostic accuracy for the prediction of the presence of varices (regardless of grade) or high-risk varices (grade ≥ 2), the mean AUC, sensitivity, and specificity were calculated for HS, SS, spleen length, and DCE MR imaging. We looked for cutoff values of HS and SS, which maximized the accuracy for predicting the presence of varices and high-risk varices. Accuracy of MR elastography and spleen length was further assessed by means of the leave-one-out cross-validation method to make up for the lack of an independent test set. To perform the leave-one-out cross-validation analysis, the total study population was divided into two groups at random. After a cutoff value was calculated in one group, that cutoff value was applied to the other group, and sensitivity and specificity were calculated. The same analysis was then performed after

switching groups, and two values were obtained. The weighted mean of these two values of sensitivity and specificity were then calculated.

To evaluate the added value of MR elastography, the readers were provided with the stiffness values of the liver and spleen and were then requested to assess the presence of varices and high-grade varices by using DCE MR imaging. The AUC, sensitivity, and specificity of a combined technique by using MR elastography and DCE MR imaging were compared with those of DCE MR imaging alone. Differences between AUC values were compared by using the method described by DeLong et al (3). Sensitivities and specificities were compared by using the McNemar test.

The mean values of HS and SS were compared between patients with and without variceal bleeding in the high-grade group. The diagnostic performance of HS, SS, spleen length, and DCE MR imaging were assessed for the association with unprotected variceal bleeding in patients with high-risk varices who did not undergo prophylactic variceal ligation by using AUC, sensitivity, and specificity. Additional ROC analysis was performed by using HS as a binary variable.

The reproducibility of *(a)* mean HS and SS over three sections and *(b)* maximum HS and SS over three sections was evaluated by using a one-way random model of intraclass correlation coefficients and Bland-Altman analysis. All statistical analyses except ROC curves were performed by using the SPSS software package (SPSS version 19.0; SPSS, Chicago, Ill). Results from ROC curves were obtained by using MedCalc software (MedCalc Software, Mariakerke, Belgium). A *P* value of less than .05 was considered to indicate a significant difference.

References

1. Manduca A, Oliphant TE, Dresner MA, et al. Magnetic resonance elastography: non-invasive mapping of tissue elasticity. Med Image Analysis 2001;5(4):237–254.

2. Nedredal GI, Yin M, McKenzie T, et al. Portal hypertension correlates with splenic stiffness as measured with MR elastography. J Magn Reson Imaging 2011;34(1):79–87.

3. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(3):837–45.