Feasibility of the T2 ratio technique and diffusion-weighted imaging to differentiate between hepatic hemangiomas and focal malignant hepatic tumors.

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Aims and objectives

Hemangiomas are the most common focal liver lesion and are present in 4% to 20% of the population (1). Consequently, these tumors are often incidentally detected in asymptomatic patients undergoing radiologic imaging tests of the abdomen for other reasons. This unexpected discovery prompts dynamic contrast-enhanced imaging examination using CT or MRI to ascertain the characteristics of the hepatic lesion. Modalities involving dynamic contrast-enhanced imaging after intravenous administration of a contrast agent have been the mainstay in diagnosis of focal liver lesions since they provide comprehensive hemodynamic information about the lesion. However, there are growing concerns about the association between gadolinium-based contrast agents and nephrogenic systemic fibrosis (NSF) (2) as well as radiation hazards and contrast-induced nephropathy during CT examinations (3, 4). Moreover, the use of those contrast agents increases medical costs due to the relatively high prevalence of hepatic hemangiomas in the population. Therefore, much research has been done to determine whether various unenhanced MR imaging sequences could be used to differentiate hepatic hemangiomas from malignant hepatic lesions.

T2-weighted imaging (T2WI) plays an important role in differentiating hepatic hemangiomas from malignant hepatic lesions because typical hepatic hemangiomas show very high signal intensity (SI). Although hepatic hemangiomas show significantly higher quantitative SI on T2WI compared with malignant hepatic lesions (lesion to liver SI value: lesion SI \times liver SI), quantitative measurements of hepatic hemangiomas and malignant hepatic lesions may overlap somewhat.

Diffusion-weighted imaging can also help in characterizing focal hepatic lesions and it is commonly acknowledged that benign focal liver lesions such as hemangiomas have greater apparent diffusion coefficient (ADC) values than malignant ones (5-7). However, there is marked overlap between them.

To our knowledge, the usefulness of a combination of the T2 ratio (the SI of the hepatic lesion relative to that of the psoas muscle) and ADC in differentiating hepatic hemangiomas from malignant hepatic lesions has not yet been described. Therefore, we conducted this study to determine the feasibility of using the T2 ratio and/or ADC at 1.5 T in differentiating hepatic hemangiomas from malignant hepatic lesions including hepatocellular carcinoma (HCC) and hepatic metastases.
Methods and materials

Subjects

The requirement for institutional review board approval was waived because of the retrospective nature of the study. The MR results of 34 patients with malignant tumors of the liver and 22 patients with hepatic cavernous hemangiomas who were examined from August 2012 through March 2014 were retrospectively reviewed. This study included 29 men and 27 women aged 33 to 81 years (mean: 65 years). All patients were referred for MRI examination because they had a focal liver lesion previously depicted on computed tomography (CT) or a sonographic examination. There was a total of 51 visible malignant hepatic tumors and their size (defined as the greatest diameter on the axial image) ranged from 5 to 81 mm (mean: 23 mm).

There were 51 malignant masses: 29 hepatomas and 22 metastases. Metastases were from colon cancer (n = 15), rectal cancer (n = 5), and gastric cancer (n = 1). Twenty-eight patients had a single malignant tumor visible on respiratory-triggered fat-suppressed T2-weighted turbo spin-echo imaging (T2WI), 2 patients had 2 malignant tumors, 2 patients had 3 malignant tumors, 1 patient had 6 malignant tumors, and 1 patient had 7 malignant tumors.

The final diagnosis was based on histological examination for all metastases, operation for 12 hepatomas, and percutaneous biopsy for 1 hepatoma. The other 17 hepatomas were diagnosed noninvasively on the basis of results of Gd-EOB-DTPA-enhanced imaging. All of them showed typical enhancement patterns of HCC, with increased arterial enhancement on arterial phase images followed by washout in late phase images and hepatobiliary phase images.

The 22 patients with hepatic cavernous hemangioma collectively had 49 cavernous hemangiomas that were identified on respiratory-triggered fat-suppressed T2-weighted fast spin-echo imaging. Fourteen patients had a single hepatic cavernous hemangioma, 2 patients had 2 hemangiomas, 3 patients had 3 hemangiomas, and 3 patients had more than 5 hemangiomas (6, 7, and 8 hemangiomas; one case each). The size of the hepatic cavernous hemangiomas ranged from 6 to 44 mm (mean: 14 mm). Thirty-four hemangiomas had been already known as hemangiomas for more than 2 years (from imaging-based diagnosis) and their size and morphology had not changed during this period. The other 15 hemangiomas were diagnosed on the basis of results of established imaging techniques (slightly irregular or globular peripheral enhancement after intravenous administration of contrast material followed by gradual filling of the center of the lesion on dynamic CT or dynamic Gd-EOB-DTPA-enhanced MRI) and the
absence of change in morphology and size of the lesions over more than 1 year of follow-up.

MRI

MRI was performed with a 1.5 T superconducting magnet (Signa HDxt 1.5 T or Signa Excite HD 1.5T; GE Healthcare, Milwaukee WI, USA) using a phased array surface body coil. All patients underwent respiratory-triggered fat-suppressed T2-weighted fast spin echo imaging, diffusion-weighted single-shot echo-planar imaging (DWI) and dynamic Gd-EOB-DTPA-enhanced MR imaging.

For the respiratory-triggered fat-suppressed T2 weighted fast spin echo imaging, scanning parameters were as follows: TR range/TE range, 6,000/106; slice thickness, 6 mm; interslice gap, 2 mm; matrix, 256 × 192 mm; FOV, 36 cm. Respiratory-triggered diffusion-weighted (DW) images were acquired in the axial plane using the single-shot echo-planar technique. The scanning parameters at b values of 0 and 800 s/mm² were as follows: TR range/TE range, 13,636 (TR may change depending on the respiratory rate)/69; slice thickness, 5 mm; interslice gap, 0 mm; matrix, 128 × 192 mm; FOV, 40 cm; NEX, 4. Diffusion-encoding gradients were applied along the three orthogonal directions of motion-probing gradients.

For gadoxetic acid-enhanced MRI, a 0.025 mmol/kg body weight dose of Gd-EOB-DTPA was administered intravenously using a power injector at a rate of 1.0 ml/s, followed by a 20-ml saline flush. Unenhanced, arterial phase (30 s), portal phase (80 s), equilibrium (120 s), and hepatobiliary phase (20-min delayed) images were obtained using a fat-suppressed T1-weighted 3D sequence (liver acquisition with volume acceleration [LAVA], GE Healthcare: 5/-2.5; flip angle, 12°; matrix, 192 × 320 mm) and the SPECIAL (spectral inversion at lipid) technique with a field of 40 cm.

Image Analysis

All annotations were made using an Advantage Workstation 4.4 (GE Healthcare).

Circular regions of interest (ROIs) were manually drawn to encompass as much of each liver lesion as possible to calculate its SI on respiratory-triggered fat-suppressed T2WI. The T2 ratio (SI of the lesion / SI of the ipsilateral erector spinales muscles at
the same level) was measured to assess relative SI among tumors. Equal-sized ROIs corresponding to T2WI were drawn on ADC maps and median ADC values ($\times 10^{-3}$ mm$^2$/s) were calculated.

Statistical Analysis

SPSS (IBM SPSS Statistics, version 17.0; IBM Corp., Armonk NY, USA) was used for statistical analysis. The Wilcoxon rank-sum test was used to assess differences in ADC and the T2 ratio between hepatic hemangiomas and malignant hepatic lesions. Binary logistic regression was used to evaluate the predictive power of (1) the T2 ratio, (2) ADC, and (3) a combination of the T2 ratio and ADC (T2r + ADC) for the differentiation of hepatic hemangiomas from malignant hepatic lesions. The formula of the regression model is as follows:

Equation A: $z = C + #_{ADC}ADC_L + #_{T2}T2r_L$

Equation B: $p = e^z / (1 + e^z)$

C = regression constant

The $p$ indicates the probability that the lesion is a hepatic hemangioma. ADC$_L$ and T2r$_L$ indicate the ADC and T2 ratio of the corresponding ROI of the lesion respectively. The terms #$_{ADC}$ and #$_{T2}$ are the regression coefficients corresponding to these variables. Equation (B) represents the conversion from $z$ to the probability $p$.

Linear logistic regression results in values for #$_{ADC}$ and #$_{T2}$ and the significance of these variables in the regression model. Receiver operating characteristic curves (ROCs) were calculated to compare the diagnostic performance of these methods using the probability $p$. A $p$-value of less than 0.05 was regarded as statistically significant.
Results

The mean T2 ratio was 6.45 ± 2.21 (standard deviation) for hepatic hemangioma and 3.21 ± 1.35 for malignant hepatic lesions; respective ADC values were $1.75 \times 10^{-3} \text{mm}^2/\text{sec} \pm 1.11$ and $1.24 \times 10^{-3} \text{mm}^2/\text{sec} \pm 0.34$. Both ADC and the T2 ratio differed significantly between hepatic hemangiomas and malignant hepatic lesions ($P< 0.001$ for both) (Fig. 1).

The regression models for ADC alone and the T2 ratio alone can be expressed as follows.

$$z = -1.745 + 1.191 \text{ADC}$$

$$z = -4.32 + 0.95 \text{T2r}$$

The model combining ADC and T2-ratio can be expressed as:

$$z = -7.125 + 1.58 \text{ADC} + 1.071 \text{T2r}$$

The ROC for T2r + ADC using binary logistic regression yielded the highest area under the curve (AUC) (AUC = 0.92, 95% confidence interval [CI]: 0.88-0.98) compared to that for T2r alone (AUC = 0.90, CI: 0.84-0.96) and ADC alone (AUC = 0.62, CI: 0.58-0.79) (Fig. 2). The ROC for ADC + T2r was significantly better than that for T2r alone ($P < 0.001$)
Fig. 1: Box plot of (a) T2-ratio and ADC value (b) in hepatic hemangioma (HH) and malignant hepatic tumor (MHT). There were significant differences in T2 ratios (P<0.001) and ADC values (P<0.001) between HH and MHT. (the mean T2 ratio for HH, 6.45; MHT, 3.21) (mean ADC for HH, 1.75×10⁻³ mm²/sec; MHT, 1.24×10⁻³ mm²/sec). Red crosses= mean for that group, box=middle 50% of values, black line in box=group median, lines at bottom and top of error bars=minimum and maximum values, respectively. Outlier beyond this range is represented by # or #. "n" below each group indicates the number of lesions in that group. P values were calculated with Wilcoxon rank sum test.

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**Fig. 2:** Receiver operating characteristic curves of each regression model of 1) T2 ratio (T2r), 2) ADC value (ADCv) and 3) a combination of T2r and ADCv (T2r+ADCv) in differentiating hepatic hemangioma from malignant hepatic lesions. The curve for T2r +ADCv yielded the highest area under the curve (AUC= 0.92, CI: 0.88-0.98) compared to that for using T2r (AUC= 0.90, CI: 0.84-0.96) or ADC (AUC= 0.62, CI: 0.58-0.79) alone. Diagonal black line = reference line of 0.50 AUC.

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Conclusion

Estimates of the prevalence of hepatic hemangiomas have ranged from 4% to 20% of the population (8-11). Due to their high prevalence, it is not uncommon to discover hemangiomas incidentally by ultrasonography (US) during a health checkup. Although ultrasonography is a cost-effective imaging modality that can depict a hemangioma as a well circumscribed, uniformly hyperechoic mass, once such a focal hepatic lesion is detected by US, dynamic contrast-enhanced CT and/or MRI using contrast-enhanced medium may be recommended to diagnose the lesion as a hemangioma. This is because the pattern of peripheral, discontinuous, intense nodular enhancement during the arterial-dominant phase with progressive centripetal fill-in on these modalities is considered pathognomonic for hemangiomas. However, there are some issues with dynamic contrast-enhanced CT using a non-ionic water-soluble iodine-containing contrast agent. Specifically, there are concerns regarding radiation exposure and contrast media-induced renal dysfunction, gadolinium-based contrast agents for MRI have been linked to the development of NSF and nephrogenic fibrosing dermopathy (NFD), especially in patients with moderate to end-stage renal disease, and the use of a contrast medium increases medical spending.

Among imaging modalities that do not use a contrast agent, MRI is more sensitive and specific in the diagnosis of hepatic hemangiomas than US or CT because hemangiomas show marked hyperintensity on T2-weighted images. Moreover, quantitative measurement of T2 values on T2WI and ADC on DW imaging have greater utility in differentiating hepatic hemangiomas from other malignant liver lesions than subjective visual assessment, which allows for more accurate and confident differentiation (12) (Fig. 3).

Soyer et al. quantitatively analyzed hepatic lesions using SI and the contrast-to-noise ratio (C/N). The SI and C/N of hemangiomas were significantly higher than those of malignant hepatic tumors, yielding an accuracy of 97% to 98% (13). Cieszanowski et al. measured T2 relaxation times of hepatic lesions. T2 relaxation times of benign lesions including cysts and hemangiomas (155-583 ms) were significantly longer than those of malignant hepatic lesions (85 ms), generating a sensitivity of 90% and a specificity of 94% (14). Besides SI of hepatic lesions, echo time (TE) is also a crucial factor in distinguishing benign lesions like cysts and hemangiomas from malignant lesions since a heavily T2-weighted sequence (with TE > 150 ms) is considered to be better for distinguishing them (12). In our study, the sensitivity and specificity of the T2-ratio alone (84% and 83% respectively) were lower than in prior studies. Potential reasons for this result may be that the hepatic lesions (mean size: 18 mm) in our cohort were small for the slice thickness (6 mm) and we used a shorter TE (100 ms) on T2WI.
DW MR imaging is now widely used in imaging of the liver and is sensitive to microscopic motion that can be quantified by means of ADC in living tissues. The ADC values of benign lesions (cysts and hemangiomas) were significantly higher than those of malignant lesions, reflecting the higher cellularity of malignant lesions (6, 7, 15, 16) (Fig. 4).

However, due to the presence of necrosis, malignant lesions do not always show low ADC (Fig. 5). It has been shown that necrotic tissues have higher ADC compared to non-necrotic portions of malignant lesions. Furthermore, there is significant heterogeneity between studies due to differences in MR machines, the maximum b factor, the number of b factors used for ADC calculation, and cohort characteristics(17, 18). Li Y et al. conducted a meta-analysis to evaluate the diagnostic accuracy of diffusion-weighted MR imaging with ADC values for differentiation between malignant and benign hepatic focal lesions. They concluded that the pooled sensitivity and specificity were 86% and 84%, respectively, although there was also significant heterogeneity between studies(19). In our study, the sensitivity and specificity of ADC alone (65% and 69%, respectively) were lower than those in the meta-analysis, but more research should be done to confirm the usefulness of ADC due to the heterogeneity of results from prior studies.

The sensitivity and specificity improved when a combination of ADC and the T2 ratio was used in our study (92% and 88%, respectively). This improvement in diagnostic accuracy was possible in part because of the weak correlation between these parameters. This improvement in diagnostic performance achieved by combining diagnostic information from different sources can be explained on theoretical grounds(20). Our results indicate that the quantitative value of the T2 ratio includes more important information for differentiating hepatic hemangiomas from malignant hepatic lesions than that of ADC does. Furthermore, the AUC of 0.92 for the combination of ADC and the T2 ratio indicates the feasibility of using this method in routine diagnosis.

Several limitations of this study were considered. First, biases could be present in the study population since this was a retrospective study. Second, some nodules were relatively small for the slice thickness on T2WI and DW imaging, and misregistration and inaccurate measurements of ADC and the T2 ratio are more likely with small lesions. Third, the low resolution of DW images with high b values made detection of small focal liver lesions difficult, especially when the ADC of the lesion was almost equal to that of normal liver tissue around it.

In conclusion, it is feasible to use a combination of the T2 ratio and ADC to differentiate between hepatic hemangiomas and focal malignant hepatic lesions. The combination of ADC and T2 ratio showed the highest diagnostic accuracy in differentiating hemangiomas from malignant focal hepatic lesions compared with the T2 ratio or ADC alone. Although prospective tests of the combination of ADC and the T2 ratio will be necessary to confirm...
our findings, this quantitative approach without a contrast agent is highly suited for computer-assisted diagnosis and thus could save time in the daily routine.
Images for this section:

**Fig. 3:** MR images in a 57-year-old woman with typical hepatic hemangioma.  
a) Respiratory-triggered fat-suppressed T2 weighted fast spin echo image shows hyperintense focal liver lesion (arrow) (T2 ratio = 11.2). According to logistic regression model using T2 ratio alone, the probability of hepatic hemangioma was 0.99.  
b) Respiratory-triggered diffusion weighted image shows the lesion as hyperintensity (arrow). The ADC was 1.81 which was much more than the mean ADC of hepatic hemangioma (1.24). According to logistic regression model using ADC alone, the probability of hepatic hemangioma was 0.6. According to binary logistic regression model using T2 ratio and ADC, the probability of hepatic hemangioma was 0.99.

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**Fig. 4:** MR images in a 57-year-old woman with known hepatic hemangioma.  
a) Respiratory-triggered fat-suppressed T2 weighted fast spin echo image shows hyperintense focal liver lesion (arrow) (T2 ratio = 8.22). According to logistic regression
model using T2 ratio alone, the probability of hepatic hemangioma was 0.97.

b) Respiratory-triggered diffusion weighted image shows the lesion as hyperintensity (arrow). The ADC was 1.23 which was almost equal to the mean ADC of malignant hepatic lesion (1.24). According to logistic regression model using ADC alone, the probability of hepatic hemangioma was 0.43. However, according to binary logistic regression model using T2 ratio and ADC, the probability of hepatic hemangioma was 0.97.

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Fig. 5: MR images in a 67-year-old man with surgically confirmed hepatoma.

a) Respiratory-triggered fat-suppressed T2 weighted fast spin echo image shows slightly hyperintense focal liver lesion (arrow) (T2 ratio=2.35). According to logistic regression model using T2 ratio alone, the probability of hepatic hemangioma was 0.11. b) Respiratory-triggered diffusion weighted image shows the lesion as slightly hyperintensity (arrow). The ADC was 1.58 which was close to the mean ADC of hepatic hemangioma (1.75). According to logistic regression model using ADC alone, the probability of hepatic hemangioma was 0.53. However, according to binary logistic regression model using T2 ratio and ADC, the probability of hepatic hemangioma was 0.06.

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References


