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# Application of Single Voxel <sup>1</sup>H Magnetic Resonance Spectroscopy in Hepatic Benign and Malignant Lesions

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Data Collection B  
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Data Interpretation D  
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Literature Search F  
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**Background:** To quantify the metabolite changes in hepatic tumors by single-voxel <sup>1</sup>H magnetic resonance spectroscopy (MRS) at 3.0 T and explore the application value of <sup>1</sup>HMRS in the diagnosis of hepatic benign and malignant lesions.

**Material/Methods:** A total of 45 patients (55 lesions) diagnosed with hepatic lesions by ultrasound and/or computer topography (CT) from November 2006 to March 2007 were included in this study. All patients underwent 3D-dynamic enhanced scan with liver acquisition with acceleration volume acquisition (LAVA) sequence and single-voxel <sup>1</sup>HMRS imaging with PRESS (point-resolved spectroscopy) sequence. The metabolite concentrations such as choline (Cho) and lipids (Lip) were measured.

**Results:** There was significant difference regarding the occurrence rate of the obvious elevated Cho peaks between benign and malignant tumors (7/27 vs. 21/28,  $p=0.000$ ). There was statistical significant differences regarding the Cho/Lip ratios in hepatic benign ( $0.0686\pm 0.0283$ , 95% CI: 0.0134–0.1245) and malignant ( $0.1266\pm 0.1124$ , 95% CI: 0.0937–0.2203) lesions ( $p<0.05$ ). When compared with the pathological results, the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were 85.7% (24/28), 92.6% (25/27), 92.3% (24/26), 86.2% (25/29), and 89.1% (49/55) respectively for the MRI assessment, and 92.6% (26/28), 88.9% (24/27), 89.7% (26/29), 92.3% (24/26), and 90.9% (50/55) respectively for <sup>1</sup>HMRS combined with MRI assessment.

**Conclusions:** Single Cho peaks or Lip peaks cannot be used for the diagnosis of hepatic benign and malignant lesions. Combined use of <sup>1</sup>HMRS and MRI can greatly improve the application value of MRI assessment in the diagnosis of hepatic benign and malignant lesions with a higher sensitivity, negative predictive value, and overall accuracy.

**MeSH Keywords:** **Liver Diseases • Liver Neoplasms • Magnetic Resonance Spectroscopy**

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## Background

Magnetic resonance spectroscopy (MRS), a powerful noninvasive technique, is being increasingly applied to delineate biochemical changes of the liver [1–5]. It can identify metabolite profiles *in vivo*, providing quantitative or semiquantitative measures of some metabolites. It is a key tool especially for lesion characterization, tumor grading, and assessment of local extension, as well as for treatment monitoring. MRS can study different endogenous metabolites, such as phosphorus (<sup>31</sup>P), carbon (<sup>13</sup>C), sodium (<sup>23</sup>Na), fluor (<sup>19</sup>F), or hydrogen (<sup>1</sup>H) protons. However, because <sup>1</sup>H is one of the main elements in the human body, and the absence of need for additional hardware, <sup>1</sup>H has been regarded as the preferred MRS option for most clinical applications [6]. <sup>1</sup>H MRS has been used successfully in the evaluation of brain diseases, particularly with respect to brain tumors [7–9]. It has also been used to distinguish between malignant and benign diseases in tissues such as the prostate [10], breast [11,12], and the musculoskeletal system [13,14]. In the area of liver research, <sup>1</sup>H MRS not only has been applied to evaluate liver function and diffuse hepatic disease, such as liver steatosis, hepatitis, and cirrhosis [15–19], but also used in the diagnosis of benign and malignancies.

Soper et al. [20] tested the potential of *in vitro* <sup>1</sup>H MRS with the addition of a statistical classification strategy to discriminate between normal liver, cirrhotic nodules, and nodules of hepatocellular carcinoma. They found that normal liver and cirrhotic liver could be discriminated from hepatocellular carcinoma (HCC) with accuracies of 100% and 98%, respectively. These findings were consistent with a previous report by Wang et al. [21]. To date, there have only been a few studies regarding *in vivo* <sup>1</sup>H MRS. Kuo et al. [5] suggested that *in vivo* <sup>1</sup>H MRS at 3.0 T is technically feasible for the evaluation of focal hepatic lesions, but there are limitations in distinguishing between normal liver, benign tumors, and malignant tumors. Fischbach et al. [22] suggested that there was only a tendency towards increased choline-containing compound (CCC) levels in the spectra of HCC lesions. Zhang et al. [23] suggested a significant increase in mean CCC peak area in malignant tumors. Overall, the use of MRS in the liver is relatively understudied, and there is some controversy as to its ability to quantify metabolite levels in liver lesions. In this study, we investigated the metabolite changes in hepatic benign and malignant lesions. In addition, we also assessed the application value of <sup>1</sup>H MRS in discriminating hepatic benign and malignant lesions.

## Material and Methods

### Patients

The study was approved by the institutional review board of Jining No.1 People's Hospital and in accordance with the

**Table 1.** Pathological results.

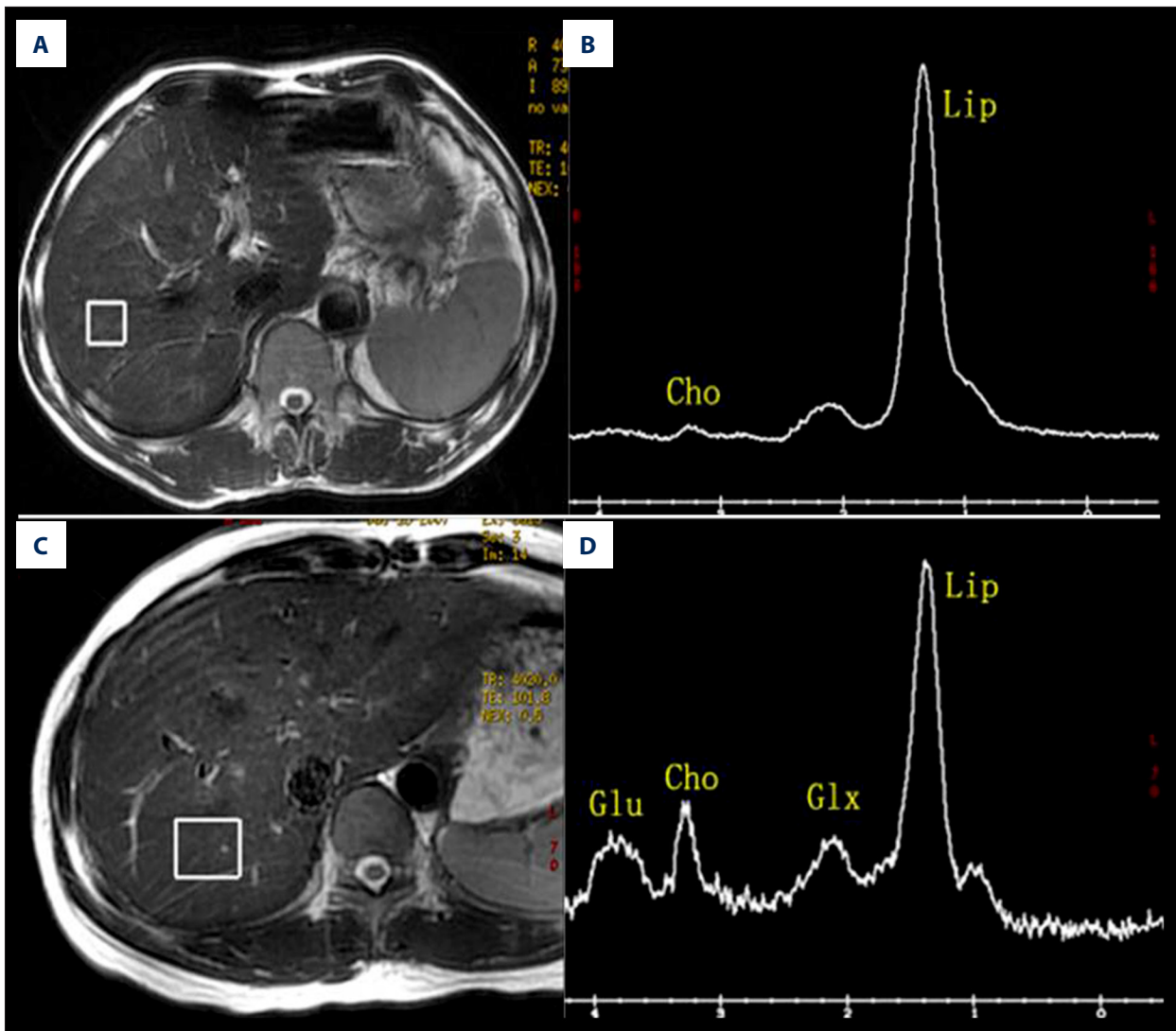
Pathological results	Case number	Lesions number
Benign	21	27
Cavernous hemangioma	10	15
Cirrhosis associated with nodule formation	5	6
IPT	1	1
Focal hepatitis	1	1
FNH	2	2
Mesenchymal hamartoma	1	1
BCS associated with intrahepatic single nodule formation	1	1
Malignant	24	28
Hepatocellular carcinoma	16	16
Metastatic tumor	6	10
Cholangiocarcinoma	2	2

IPT – inflammatory pseudotumor; FNH – focal nodular hyperplasia; BCS – Budd-Chiari syndrome.

Declaration of Helsinki. Written informed consent was obtained from all patients. Between November 2006 and March 2007, 45 patients (55 lesions) diagnosed with hepatic lesions by ultrasound and/or computer topography (CT) were included in the study. Patients with renal failure or who had metallic foreign bodies were excluded. None of the study participants received biopsies or treatment before the MRI examination. There were 38 males and 7 females with a mean age of 45.7 years (range 43–75 years). The 55 lesions were verified with needle biopsy or surgical pathology (27 benign, 28 malignant). The pathological results are summarized in Table 1.

### Abdominal MRI examination

MRI and proton MRS were performed on a 3.0 T body scanner (GE Signa Excite HD; GE Medical Systems, Milwaukee, WI, United States) using an eight channel phased-array body coil. In order to reduce motion artifacts, an elastic belt of 30-cm width was wrapped around the phased-array coil. For patients with severe ascites or obese patients, a shielding cushion was utilized to eliminate shielding artifacts. Prior to the MRI examination, all patients fasted for three to four hours. Breathing instructions were explained to the patients and breathing exercises was performed before entering the MRI machine, and patients entered head first in a supine position.

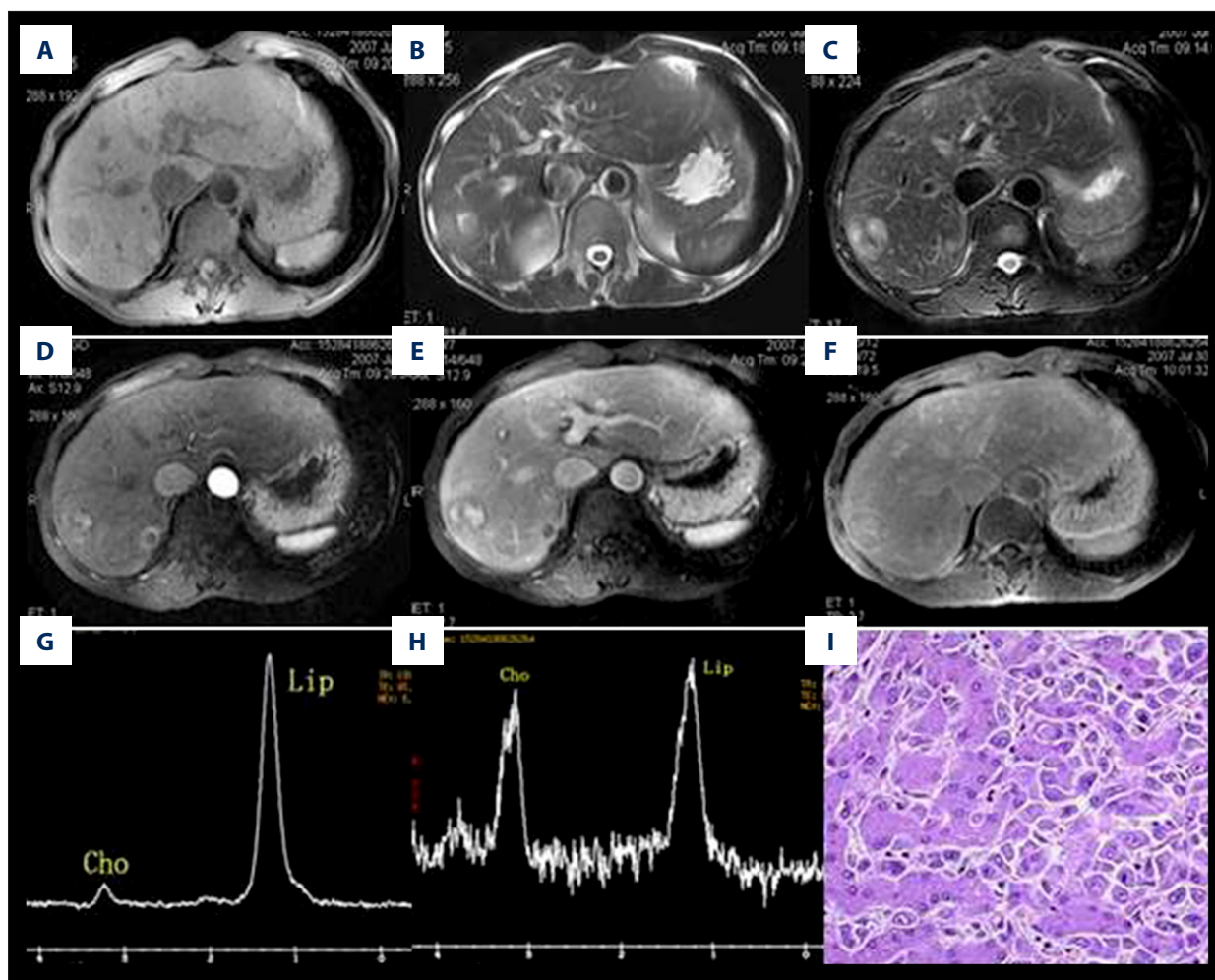


**Figure 1.** Voxel localization (FSE-T2WI) images and <sup>1</sup>H magnetic resonance spectrum (MRS) of the uninvolved liver tissues (normal self-control area). In the <sup>1</sup>H MRS spectra of liver tissues in the self-control area, Cho and Lip peaks were identified at 3.20 ppm and 1.30 ppm (A, B). In some patients, Glx (glutamine and glutamate complex) and Glu (glycogen and glucose complex) peaks were also identified at 2.25 ppm and 3.70 ppm (C, D).

Routine MRI protocols consisted of axial T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), and fat saturated T1WI and T2WI. Multi-phases dynamic enhanced scanning was performed with a 3D gradient-echo pulse liver acquisition with volume acceleration (LAVA) sequence after the administration of gadopentetate dimeglumine (GD-DTPA; Beilu Pharmaceutical, Beijing, China) into the elbow vein at a dose of 0.1 mmol/kg with a rate of 1.5–3 mL/s by high-pressure syringe. The contrast agent was followed by using an intravenous bolus administration of 15 mL of saline at a rate of 2 mL/s. Scanning parameters were as follows: TR=4.5 ms, TE=2.2 ms, matrix size=288×160, slice thickness=4–5 mm, overlap=50%, flip angle (FA)=12°, the layer number of scanning ranged from 76–84, and breath holding time=17–22 s. The arterial, portal

venous, and delayed phase scans were performed three times; the first began at 15–20 s, then 60 s and 180 s after contrast injection, respectively.

MRS was performed after the conventional MRI scans and before the enhanced scans. The fast spin-echo (FSE) respiratory triggering fat-saturated T2W axial sequence was used for localizing image. The single-voxel MRS was done using a point resolved spectroscopy sequence (PRESS, Probe-P in GE Medical Systems) in all patients. The scanning parameters were as follows: repetition time, 1,300 msec; echo time, 35 msec; number of excitations, 8; and FOV, 24×24 cm. The region of interest (ROI) of 25×25×25 mm was positioned in the hepatic lesions, avoiding the inclusion of the areas of cystic change, bleeding,



**Figure 2.** A 55-year old male with hepatic pain for about one month. A 3×2.9 cm abnormal signal can be detected in the right posterior liver lobe. FS-T1WI shows low signal (A), T2WI (B), and FS-T2WI (C) show a slightly heterogeneous high signal. The arterial (D), portal venous (E), and delayed phase (F) scans shows slightly enhanced signal, obvious enhanced signal and slight low signal. Compared with the self-controlled areas, the <sup>1</sup>H MRS spectra of liver tissues in the involved area (lesion area) shows obvious elevated Cho peaks (25301.8890), slight decreased Lip peaks (282100.6221), and obvious elevated Cho/Lip. Pathological examination shows hepatocellular carcinoma.

and necrosis. An uninvolved area of the liver was chosen for comparison, avoiding the inclusion of the hepatic fissure as well as the vascular and biliary structures. The location of ROI was determined by a single experienced radiologist specialized in gastrointestinal and hepatobiliary MRI. Shallow and regular breathing was taught before the imaging test and maintained during MRS data acquisition. Prior to the acquisition of MRS data, the automatic shimming and water suppression were performed using GE 3.0T PRESS. The MRS data were acquired when the full-width half-maximum (FWHM) were below 15 Hz, while the effectiveness of water suppression was over 90%.

### MRI and spectra analysis

After acquisition, data were processed on the ADW4.3 workstation using MR spectroscopic analysis package (SAGE 7.0; GE Medical Systems). After selecting the raw image with the highest signal noise ratio (SNR), the raw data were then zero-filled once, apodized with a 5-Hz Gaussian filter, Fourier transformed, and phase and baseline corrected. We performed Marquardt curve fitting using a Gaussian line shape to calculate the area under the peak. MRS spectroscopic data were analyzed by two MR radiologists who were experienced in MRI and MRS analysis and blinded to clinical data and surgical or pathological findings.



**Table 2.** The mean Cho and Lip peak height at 3.0T <sup>1</sup>H MRS in hepatic benign and malignant lesions.

	Benign lesions (n=27)	Malignant lesions (n=28)	P values
Cho peak height	22355.7450±20624.2371	32585.1650±24063.8876	0.073
Lip peak height	326133.6278±339024.2253	257403.0021±223153.9800	0.086

### Statistical analysis

Statistical analyses were performed with SPSS software (version 12.0; SPSS, Chicago, IL, USA). Quantitative data were expressed as means standard deviation (SD) and compared using Student's *t*-test. Qualitative data were expressed as number or percentage and compared using chi-square test. For all tests, a *p* value of less than 0.05 was considered statistically significant different.

### Results

Forty-five <sup>1</sup>HMRS spectra (100%) were successfully obtained from uninvolved liver tissues (normal self-control area) of 45 patients. Forty-three spectra were successfully obtained once from 43 of the 55 lesions. Nine spectra were successfully obtained twice from the other 12 lesions after shimming and voxel reposition. No ideal spectra were obtained from the remaining three lesions. Among these three lesions, one failed to obtain ideal spectra due to its small size (14.01 mm), the remaining two failed to obtain ideal spectra due to large noise. In this study, the mean value of maximum tumor diameter 52.24±19.31 mm (range 26.8–108.6 mm).

In the <sup>1</sup>HMRS spectra of liver tissues in the uninvolved area (self-control area), Cho and Lip peaks were identified at 3.20 ppm and 1.30 ppm (Figure 1A, 1B). In some patients, Glx (glutamine and glutamate complex) and Glu (glycogen and glucose complex) peaks were also identified at 2.25 ppm and 3.70 ppm, respectively (Figure 1C, 1D). The mean Cho and Lip peak height of self-control areas were 22971.6603±22583.3862 and 310843.7138 ± 3076170.2453, respectively. The occurrence rate of Cho peaks and Lip peaks in self-control areas was 94.55% (53/55) and 100% (55/55). In the <sup>1</sup>HMRS spectra of liver tissues in the involved area (lesion area), tumor spectra showed Cho peaks at 3.10–3.34 ppm and Lip peaks at 1.20–1.35 ppm. A representative case of <sup>1</sup>HMRS was shown in Figure 2. The *t*-test showed that no statistically significant difference regarding the mean Cho and Lip peak height was identified between the hepatic benign and malignant lesions (all *p*>0.05) (Table 2).

Compared to the self-control areas, 28 of the 55 lesions existed the obvious elevated Cho peaks (Table 3). Among 27 benign tumors, obvious elevated Cho peaks were identified in seven lesions. Among 28 malignant tumors, obvious elevated Cho

**Table 3.** The obvious elevated Cho peaks detected by <sup>1</sup>H MRS in hepatic benign and malignant lesions compared to self-control areas.

Pathological results	Obvious elevated Cho peaks (n,%)	P values
Benign lesions (n=27)		0.000
Yes	7 (25.9%)	
No	20 (74.1%)	
Malignant lesions (n=28)		
Yes	21 (75.0%)	
No	7 (25.0%)	

peaks were identified in 21 lesions. Chi square test showed a significantly difference regarding the occurrence rate of the obvious elevated Cho peaks between benign and malignant tumors ( $\chi^2=13.2453$ , *p*=0.000). If the obvious elevated Cho peaks were chosen as the criteria for discriminating benign and malignant lesions with <sup>1</sup>HMRS, the sensitivity, specificity, and accuracy for malignant tumors using our criteria were 75% (21/28), 74.1% (20/27), and 74.5% (41/55), respectively.

In addition, there was statistical significant difference regarding the Cho/Lip ratios in hepatic benign (0.0686±0.0283, 95% CI 0.0134–0.1245) and malignant (0.1266±0.1124, 95% CI 0.0937–0.2203) lesions (*p*<0.05) (Table 4). If 0.093 was chosen as the threshold value for discriminating benign and malignant tumor with <sup>1</sup>HMRS, the sensitivity, specificity, and accuracy for malignant tumors using our criteria were 61.9% (13/21), 71.4% (5/7), and 64.2% (18/28), respectively.

The examination was regarded as positive if the definite hepatic malignant tumor could be seen by MRI and/or <sup>1</sup>HMRS. When compared with the pathological results, the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were 75.0% (21/28), 74.1%(20/27), 80.8% (21/26), 69.0% (20/29), and 74.5% (41/55) respectively for the <sup>1</sup>HMRS assessment; 85.7% (24/28), 92.6% (25/27), 92.3% (24/26), 86.2%(25/29), and 89.1% (49/55) respectively for the MRI assessment; and 92.6% (26/28), 88.9% (24/27),

**Table 4.** The mean Cho/Lip ratios at 3.0 T <sup>1</sup>H MRS in hepatic benign and malignant lesions.

	Mean values	95% CI	P values
Benign lesions	0.0686±0.0283	0.0134–0.1245	0.023
Malignant lesions	0.1266±0.1124	0.0937–0.2203	

**Table 5.** The accuracy of <sup>1</sup>H MRS, MRI and <sup>1</sup>H MRS combined with MRI in differentiating between benign and malignant lesions (n=55).

Methods	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
<sup>1</sup> H MRS	21/28 (75.0%)	20/27 (74.1%)	21/26 (80.8%)	20/29 (69.0)	41/55 (74.5%)
MRI	24/28 (85.7%)	25/27 (92.6%)	24/26 (92.3%)	25/29 (86.2%)	49/55 (89.1%)
<sup>1</sup> H MRS+MRI	26/28 (92.6%)	24/27 (88.9%)	26/29 (89.7%)	24/26 (92.3%)	50/55 (90.9%)

89.7 (26/29), 92.3(24/26), and 90.9% (50/55) respectively for the <sup>1</sup>H MRS combined with MRI assessment. <sup>1</sup>H MRS combined with MRI assessment was significantly higher than <sup>1</sup>H MRS or MRI assessment in terms of sensitivity, negative predictive value, and overall accuracy (Table 5).

## Discussion

<sup>1</sup>H and <sup>31</sup>P are the two nuclei most commonly used *in vivo* MRS due to their high natural abundance. Other nuclei are not only less abundant or sensitive than the proton, but always need dedicated coil systems tuned to the specific Larmor frequency of the nucleus at the desired field strength. <sup>1</sup>H MRS, however, has the most valuable advantage in that the same hardware can be used for MRI and MRS. Moreover, its sensitivity is a factor of 7 higher than that of phosphorus, so that the volumes of interest (VOIs) of typically 4–8 cm<sup>3</sup> are applied for <sup>1</sup>H MRS instead of 30–100 cm<sup>3</sup> for <sup>31</sup>P MRS [15]. <sup>1</sup>H MRS can detect metabolite and biochemical substance changes of organ tissue such as Cho and Lip [24]. Currently, <sup>1</sup>H MRS is mainly used to: 1) diagnosis and identify hepatic lesions, 2) help qualitative diagnosis of lesions when pure routine imaging modalities are insufficient to make a definite diagnosis; 3) assess the clinical effects of tumor treatments and tumor residual and its recurrence; and 4) assess the tumor range and puncture location. <sup>1</sup>H MRS is mainly applied to evaluate liver function and diffuse hepatic disease such as liver steatosis, hepatitis, and cirrhosis [15–19]. The application of <sup>1</sup>H MRS in the diagnosis of benign and malignancies is still underdeveloped. In this study, we applied <sup>1</sup>H MRS in evaluation of hepatic lesions and found Cho and Lip peaks were at 3.20 ppm and 1.30 ppm in the uninvolved area and at 3.10–3.34 ppm and 1.20–1.35 ppm in the involved area, respectively. Overall, the Cho and Lip peaks in malignant liver tumors showed no significant differences to normal liver tissues.

Cho, one of the components of phospholipid metabolism, participated in cell membrane transport and diffusion and multiple metabolic pathways. In normal tissues, free Cho will be maintained at a low concentration. In malignant lesions, fast cell division will cause accelerated cell proliferation and cell membrane transport and thus resulting in the increase in Cho values [25]. Kuo et al. reported a significant statistical difference regarding the mean Cho/Lip ratio between malignant and benign tumors. In addition, they also found the mean Cho/Lip ratios after the transcatheter arterial chemoembolization (TACE) treatment were significantly decreased compared to before TACE [5]. These findings suggested the restriction of cell proliferation and acute toxic effects to chemotherapy. In this study, we found that the Cho values in hepatic malignant lesions were obviously increased. This finding coincides well with the degree of tumor progress and histopathologic characteristics of tumor cell.

An intro <sup>31</sup>P MRS experiment by Dixon et al. showed that Cho compounds were largely responsible for the increase in the phosphomonoester (PME) signal in hepatic lesions [26]. Another study also demonstrated that primary hepatocellular carcinoma showed obvious higher Cho values than cirrhotic and normal liver tissues and suggested that the values of Cho peaks can be used as an index of tumor cell proliferation [20]. In our study, we found a general trend of increased Cho values in hepatic malignant lesions. Our findings were consistent with the previous mentioned study [20], in which obvious elevated Cho peaks were identified in 7/27 lesions and in 21/28 lesions. There was partial overlap regarding the Cho compounds between malignant and benign lesions. Thus whether existing the Cho peaks was not the specific manifestation of malignant lesions. The reason that the Cho peaks cannot be seen in most of the benign lesions (20/27 lesions) may be due to slow growth, membrane transport, and proliferation which

may lead to low Cho values. Another reason may be associated with the limitation of MRS technique [25]. Among the seven lesions in malignant lesions with no obvious elevated Cho peaks, low Cho peaks were identified in four lesions, and no occurrence of Cho peaks was identified in the remaining three lesions. These may be due to large tumor size which may increase the possibility of necrosis. If there exists some necrotic tissues within the voxel during the voxel positioning, slow or no Cho peaks will occur. Soper et al. [20] reported that hepatocellular carcinoma had lower Lip values than normal liver tissues. However, histopathological study showed that most of the hepatocellular had local or diffused steatosis/fatty degeneration at different degrees [27]. In addition, atypical adenomatous hyperplastic nodules can progress into hepatocellular carcinoma after local cancerization, whereas steatosis is a vital sign of local cancerization. Therefore, the diagnosis of hepatocellular carcinoma cannot be excluded if there existed elevated Lip peaks within the tumors.

MRI has clinical value in the examination and qualitative diagnosis of hepatic lesions, particularly in the discrimination of hepatic carcinoma from hepatic cavernous hemangioma. Compared with other imaging methods, it has unique advantages and clinical values due to its excellent tissue resolution. An enhanced scan is essential for the diagnosis of hepatic benign and malignant lesions because it cannot only display the lesions more clearly, but also can detect tumors which cannot be detected on plain scan. In this study, we adopted the 3.0 T MR apparatus which has an advanced LAVA sequence. For hepatic lesions, LAVA sequence has the advantages of qualitative identification of focal lesions. It has a higher detection rate than 2D GRE sequence particularly for the small lesions with good blood supply because it could more accurately capture the enhanced signal of lesions at the arterial phase and clearly display lesion edges [28]. In addition, it can also be used for 3D reconstruction. Multiple planar reconstruction help with the accurate judgment of location and invasion degree of lesions. Maximum intensity projection can not only depict the condition and invasion degree of adjacent vessel of lesions, but also clearly depict anatomical characteristics of hepatic artery and portal vein which can provide information for hepatectomy, interventional therapy, and liver transplantation [29,30]. Based on its specific anatomical location and increased metabolic demands, the liver is considered an ideal organ for MR spectroscopy investigation [31]. Previous animal experiments have demonstrated the positive role of <sup>1</sup>H MRS in the diagnosis of liver cancer [32,33] and fatty liver [4,34]. However, the study of MRS in the clinical diagnosis of hepatic diseases is still in the exploratory stage, and continues to be a hot topic as new findings are reported. Li et al. [35] performed experiments at

three T <sup>1</sup>H MRS in hepatic tumors and found a high sensitivity and accuracy regarding detection of CCCs such as Cho concentrations. Combined with MRI, particularly with LAVA scanning technique, <sup>1</sup>H MRS has higher sensitivity and accuracy for detection of hepatic malignant lesions. In this study, the sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were 85.7% (24/28), 92.6% (25/27), 92.3% (24/26), 86.2% (25/29), and 89.1% (49/55) respectively for the MRI assessment; and 92.6% (26/28), 88.9% (24/27), 89.7 (26/29), 92.3(24/26), and 90.9% (50/55) respectively for the <sup>1</sup>H MRS combined with MRI assessment. These findings showed that <sup>1</sup>H MRS combined with MRI assessment had significantly higher sensitivity and accuracy than <sup>1</sup>H MRS or MRI assessment. Therefore, fully understand the imaging characteristics of <sup>1</sup>H MRS and MRI and the combined use of these imaging methods will help to the diagnosis and identification of the hepatic malignant lesions.

Despite the advantages of <sup>1</sup>H MRS, its clinical applications are still affected by other factors. First, spectra imaging has a high requirement with regard to homogeneity of magnetic field. For example, a slight motion by the patient, hemoglobin and necrosis within lesions, and adipose tissue surrounding lesions will hinder the successful acquisition of <sup>1</sup>H MRS. Second, it is difficult to obtain accurate results for small tumors due to compromises among voxel size, signal to noise ratio, and scan time resulting from low spectra resolution. In addition, there was no unified standards regarding the data among different reports due to the variation of spectra analysis software and individualized manipulator experience. Furthermore, the single voxel method used in this study allowed spectra of a small quantity of tissue samples. Thus the accuracy may be affected if there exist heterogeneous distribution of lesions such as hemorrhage, necrosis, liquidation, and calcification. Further studies with a larger number of samples are warranted.

## Conclusions

Single Cho peaks or Lip peaks cannot be used for the diagnosis of hepatic benign and malignant lesions. Combined use of <sup>1</sup>H MRS and MRI can greatly improve the application value of MRI assessment in the diagnosis of hepatic benign and malignant lesions with a higher sensitivity, negative predictive value, and overall accuracy.

## Conflict of interest

The authors declare that they have no competing interest.

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