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# Detection of Dysplastic Liver Nodules in Patients with Cirrhosis Using the Multi-Arterial CAIPIRINHA-Dixon-TWIST-Volume-Interpolated Breath-Hold Examination (MA-CDT-VIBE) Technique in Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Authors' Contribution:

Study Design A

Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

Literature Search F

Funds Collection G

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**Background:** The multi-arterial CAIPIRINHA-Dixon-TWIST-volume-interpolated breath-hold examination (MA-CDT-VIBE) sequence has the advantage of detecting hypervascular lesions during the arterial phase of magnetic resonance imaging (MRI) of the liver. Liver cirrhosis may be associated with dysplastic nodules. This study aimed to compare the use of routine liver MRI sequences with the MA-CDT-VIBE sequence to identify dysplastic liver nodules in patients with liver cirrhosis.


**Material/Methods:** Between February 2016 and March 2017, there were 21 patients with liver cirrhosis who had 33 dysplastic liver nodules, which were detected by comprehensive multisequence MRI as the reference standard for nodule imaging. Liver MRI using edge sharpness assessment by parametric (ESAP) modeling was compared with five dynamic arterial subphases that were included in the MA-CDT-VIBE sequence with a temporal resolution of 2.8 s and an acquisition time of 20 s during one breath-hold.

**Results:** In the 21 patients included in the study, the MA-CDT-VIBE technique (30/33 for the first reading and 33/33 for the second reading) showed an improved lesion detection rate compared with the ESAP technique (27/33 for the first reading and 29/33 for the second reading), and for 73% of the patients, MA-CDT-VIBE imaging showed improved arterial parenchyma contrast. There was a high degree of interobserver agreement between the two reads ( $\kappa$ : 0.68–0.91;  $P < 0.001$ ).

**Conclusions:** The MA-CDT-VIBE sequence of MRI liver imaging improved the detection of dysplastic nodules in cirrhosis of the liver compared with routine liver MRI sequences.

**MeSH Keywords:** **Contrast Media • Liver Abscess • Magnetic Resonance Imaging**

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## Background

Liver cirrhosis is a late-stage development in various chronic liver diseases. There is a significantly increased risk of hepatocellular carcinoma (HCC) in patients with liver cirrhosis [1,2]. Cirrhotic livers commonly develop a series of changes, including regenerative nodules, atypical hyperplastic nodules, dysplastic nodules associated with HCC. The blood supply of nodules in different stages of liver cirrhosis changes gradually [3,4]. The portal vein mainly supplies regenerative nodules and dysplastic nodules. However, high-grade dysplastic nodules (HGDNs) can be supplied by more arteries, and the abnormal blood supply from arteries increases for lesions less than 3 cm. With increasing nodular dysplasia, the proportion of the hepatic artery blood supply gradually increases. Therefore, accurate assessment and prediction of nodules in a patient with liver cirrhosis have important clinical significance for improving patient prognosis [5].

Commonly used imaging assessment methods for the liver include ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Ultrasound has a wide range of applications due to its convenience and low cost. Ultrasound contrast can be dynamic for continuous observation of the whole enhanced process, but its application is limited by the ultrasound diagnostician [6]. Enhanced computed tomography (CT) is widely used to detect benign and malignant tumors in the liver because the CT coverage area is relatively large, and the subjective impact of the observers and the effect of the gas on the CT results are small [7]. MRI is superior to CT for the follow-up of liver lesions, especially after the intervention, because of its ability to display anatomical structures and tissue resolution [8]. MRI enhancement, especially the thin-slice dynamic enhancement sequence, can reflect morphological and hemodynamic changes in benign and malignant hepatic tumors, especially hypervascular lesions, demonstrating significant advantages for the discovery and diagnosis of tumors.

The commonly used enhanced sequence of MRI is the 3D gradient echo (GRE) sequence, which is thin in thickness and can be scanned in 20 s. However, the sequence cannot provide high temporal resolution and spatial resolution at the same time. The multi-arterial CAIPIRINHA-Dixon-TWIST-volume-interpolated breath-hold examination (MA-CDT-VIBE) uses controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA), and Dixon time-resolved imaging with interleaved stochastic trajectories (TWIST) technology has a very fast scanning speed and high spatial resolution. Multiple scans can be completed in a single breath-hold [9]. The MA-CDT-VIBE sequence has an advantage in detecting the pathology of hypervascular lesions during the arterial phase. In this study, the MA-CDT-VIBE technique was applied to detect dysplastic nodules in patients with liver cirrhosis [10].

Therefore, this study aimed to compare the use of routine liver MRI sequences with the MA-CDT-VIBE sequence to identify dysplastic liver nodules in patients with liver cirrhosis.

## Material and Methods

### Patients studied

The Institutional Ethics Review Board approved this study. All subjects signed an informed consent form. Magnetic resonance imaging (MRI) scans were performed in 34 patients who were initially diagnosed with cirrhosis by continuous ultrasound. The patients were recruited between February 2016 to March 2017.

The study inclusion criteria included patients with MRI findings of cirrhosis who had non-diffuse enhanced dysplastic nodules in the cirrhotic liver observed on at least one intensified scan. The maximum diameter of a single lesion was <2 cm. Patients were excluded from the study who were pregnant or who had claustrophobia or discomfort on MRI. According to the above selection criteria, following MRI, four patients showed no positive liver lesions, three patients had maximum lesion diameters of approximately 2 cm, two patients with hemangioma, two patients with metastatic tumors, and two patients had cholangiocarcinoma, and they were excluded from the study. Finally, 21 patients (15 men and six women) with 33 lesions were included in the study, with an average age of  $61 \pm 5.79$  years (range, 41–79 years).

### Instrument and scanning position

A Siemens MAGNETOM Amira 1.5 T MRI scanner (Siemens Healthcare, Erlangen, Germany) was used in this study, and a 16-channel phased-array coil was used. To prevent the coil from sliding, the coil was fixed to the upper abdomen of the patient using a band. The patient was placed in the supine position, and the head was scanned first.

### Plain scan and dynamic enhanced scan using multi-arterial CAIPIRINHA-Dixon-TWIST-volume-interpolated breath-hold examination (MA-CDT-VIBE)

A T2-weighted image (T2WI) half-Fourier single shot turbo-spin echo (HASTE) scan, fat suppression (fs) T2WI scan, diffusion-weighted imaging sequence, positive and negative phase sequences, and T1WI VIBE sequences were performed in order.

Intravenous access was established by inserting an indwelling needle into an antecubital vein of the patient, and gadolinium-diethylenetriaminepentaacetate (GD-DTPA) contrast agent (Sigma-Aldrich, St. Louis, MO, USA) was injected at a dose of

**Table 1.** The scanning parameters of routine sequences and multi-arterial CAIPIRINHA-Dixon-TWIST-volume-interpolated breath-hold examination (MA-CDT-VIBE).

Parameters	T2 WI	DWI	Positive/negative phase*	Before contrast CD-VIBE	MA-CDT-VIBE	Portal venous phase CD-VIBE	Delayed phase CD-VIBE
Orientation	COR	TRA	TRA	TRA	TRA	TRA	TRA/SAG/COR
Sub-phase (No.)	1	1	1	1	5	1	1
TR/TE (ms)	3500/87	4800/64	244/2.38	6.75/3.39	6.59/2.39	6.75/3.39	6.75/3.39
Flip angle (degree)	160	–	70	10	10	10	10
FOV (mm)	380	380	380	380	400	380	380
Basis resolution	256	134	256	320	256	320	320
Spatial Resolution	1.5×1.5×6.0	1.4×1.4×6.0	0.7×0.7×6.0	1.2×1.2×3.0	0.8×0.8×3.0	1.2×1.2×3.0	1.2×1.2×3.0
Temporal resolution	–	–	–	–	2.8 s	–	–
Slice number	26	26	30	72	72	72	72
Slice thickness (mm)	6	6	6	3	3	3	3
Slice gap (%)	20%	20%	20%	20%	20%	20%	20%
Acquisition time	135	179	20	18	20	18	18
Breathe patterns	Free breath	Free breath	Hold breath	Hold breath	Hold breath	Hold breath	Hold breath
K space A/B (%)	–	–	–	–	20/25	–	–

TR – repetition time; TE – echo time; FOV – field of view. A – the center of the imaging region. B – the periphery of the imaging region. \* Indicates that after a positive/negative phase sequence was scanned, it acquired the positive phase image and negative phase image, including 30 image in each atlas.

0.2 mmol/kg of body weight at a rate of 3 ml/s using a high-pressure syringe. After injection of the contrast medium, 20 ml of saline was immediately injected at the same speed. The arterial phase was initiated 15 s after the start of the injection of the contrast agent. The dynamic enhanced scan included the MA-CDT-VIBE sequence with five arterial subphases at the horizontal axis during the arterial phase, the CD-VIBE sequence in the portal vein phase (60 s after contrast agent injection) and the CD-VIBE sequence in the delayed phase (scanned 90 s after injection of the contrast agent), coronal CD-VIBE sequences, and sagittal CD-VIBE sequences. Table 1 shows the details of the imaging parameters.

### Selection of the equivalent standard arterial phase

The temporal resolution of the MA-CDT-VIBE sequence was 2.8 s in the arterial phase. The scanned image consisted of five subphases. The arterial phase MA-CDT-VIBE sequence commenced 15 s after the injection of the Gd-DTPA contrast agent. The fourth subphase of the five subphases (at 23.4 s after contrast agent injection) was considered equivalent to the standard hepatic artery phase of the equivalent standard arterial phase (ESAP).

### Image evaluation methods

For image evaluation in this study, two independent image interpretation groups were established. Two MRI diagnosticians with more than five years of diagnostic experience separately reviewed all five subphases of the dynamic enhanced MA-CDT-VIBE sequence in the arterial phase to diagnose the nodules' images comparison with a single ESAP image. The two diagnostic groups were blind to the other's diagnosis. Only the water image was evaluated in several resulting sets of images (a water image, lipid image, positive phase image, and inverse phase image), only the water image was evaluated. The number of lesions detected by a set of integrated, multi sequential MRI scans, including multiple sequences, was used as a diagnostic criterion. If the diagnosticians could identify abnormal lesions in any subphase of the five sub arterial phases, all subphases, or the ESAP, the result was recorded as (yes, 1); if abnormal lesions were not found, the result was recorded as (no, 2). The MA-CDT-VIBE technique was considered to have higher diagnostic value than the standard arterial phase technique if lesions undetected during the ESAP were found in at least one of the remaining four subphases. Also, sequences yielding the best visualization/liver parenchyma enhancement

in the five subphases of the MA-CDT-VIBE sequence, and the dynamic enhancement sequences were identified. Finally, whether the MA-CDT-VIBE sequence had an advantage in the diagnosis of enhanced dysplastic nodule in patients diagnosed with cirrhosis was determined (yes, 1; no, 2).

### Statistical analysis

Data were analyzed using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The consistency between the two diagnostic groups was analyzed using kappa statistics. The kappa values represented the degree of agreement between the two groups as follows: <0.20, very low consistency; 0.21–0.40, general consistency; 0.41–0.60, moderate consistency; 0.61–0.80, high consistency; and 0.81–1.00, complete consistency [8].

## Results

### Imaging identification of liver nodules

All magnetic resonance imaging (MRI) sequences for each patient from plain to enhanced images were taken as the reference standard. Of the 33 lesions observed in 21 patients, nine of the patients with primary liver cirrhosis had 17 lesions after microwave ablation, four of which were solitary nodular or irregular lesions, two abnormal lesions were observed in the livers of three patients, three abnormal lesions were observed in the liver of one patient, and one lesion was observed in the liver of one patient. A total of 16 lesions in the livers of the remaining 12 patients had MRI findings of cirrhotic nodules or hepatocellular carcinoma (HCC). One patient had three lesions in the liver, two patients each had two lesions in the liver, and nine patients each had a single lesion in the liver.

### The multi-arterial CAIPIRINHA-Dixon-TWIST-volume-interpolated breath-hold examination (MA-CDT-VIBE) sequence imaging results

Of the 33 lesions in 21 patients, 91% (30/33) of the lesions were identified in a single reading of the MA-CDT-VIBE sequence, and 100% (33/33) were identified in two readings. A single reading using the ESAP showed 81% (27/33) of the lesions, and two readings showed 88% (29/33) of the lesions. Thus, the MA-CDT-VIBE sequence enabled the identification of 9% (single reading) and 12% (two readings) more lesions than the ESAP reading. High consistency was observed between the physicians reading the images. In the analysis of the MA-CDT-VIBE sequence, the diagnostic advantage was ( $\kappa=0.84$ ;  $P<0.001$ ), and in the comprehensive analysis of the multisequence examinations, the diagnostic advantage was ( $\kappa=0.68$ – $0.91$ ;  $P<0.001$ ) (Table 2). Figures 1 and 2 show the imaging samples.

### Lesions and liver parenchymal enhancement

Among the 33 lesions, no cases of best lesion visualization and parenchyma contrast enhancement occurred in the first subphase of the five subphases of the MA-CDT-VIBE sequence, 2 (6.1%) cases occurred in the second subphase, 6 (18.1%) cases occurred in the third subphase, 9 (27.3%) cases occurred in the fourth subphase, and 16 (48.5%) cases occurred in the fifth subphase.

## Discussion

The aim of this study was to compare the use of routine liver magnetic resonance imaging (MRI) sequences with the multi-arterial CAIPIRINHA-Dixon-TWIST-volume-interpolated breath-hold examination (MA-CDT-VIBE) sequence to identify dysplastic liver nodules in patients with liver cirrhosis. The MA-CDT-VIBE imaging method is a combination of three techniques or phases that include controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA), Dixon, and time-resolved imaging with interleaved stochastic trajectories (TWIST) [12]. A new, contrast-enhanced, T1-weighted, three-dimensional, saturated spoiled gradient echo (T1W-3D-fs-GRE) sequence allows multiple sub arterial subphases to be obtained in a single breath-hold scan [13,14]. In this study, the sequence contained five arterial phase subtypes. The MA-CDT-VIBE sequence can be used to obtain more dynamic enhancement information and diagnostic details using the other arterial phase [15]. The MA-CDT-VIBE sequence showed higher lesion detection rates than the standard arterial phase.

This study identified the best arterial phase and configuration of the best time in the arterial phase. Of the 33 lesions found in 21 patients using all MRI sequence images as the standard, 91% of the lesions were observed in a single reading of the MA-CDT-VIBE sequence, and 100% of the lesions were identified in two readings. In contrast, 81% of the lesions were identified in a single reading of the ESAP, and 88% of the lesions were identified in two readings. The results showed that the MA-CDT-VIBE sequence enabled the identification of 9% (one reading) and 12% (two readings) more lesions than the ESAP. The MA-CDT-VIBE sequence had a very high detection rate for enhanced dysplastic nodules in cirrhotic livers, whereas the single-stage ESAP can cause missed lesions. Also, approximately 73% of the best lesions visualized and the liver parenchyma contrast enhancement cases were not observed in the ESAP. This finding indicated that the MA-CDT-VIBE sequence is more conducive for lesion display than a single standard arterial phase image and that the MA-CDT-VIBE sequence facilitates optimization of arterial phase time allocation even if a fixed delay exists in each subphase.

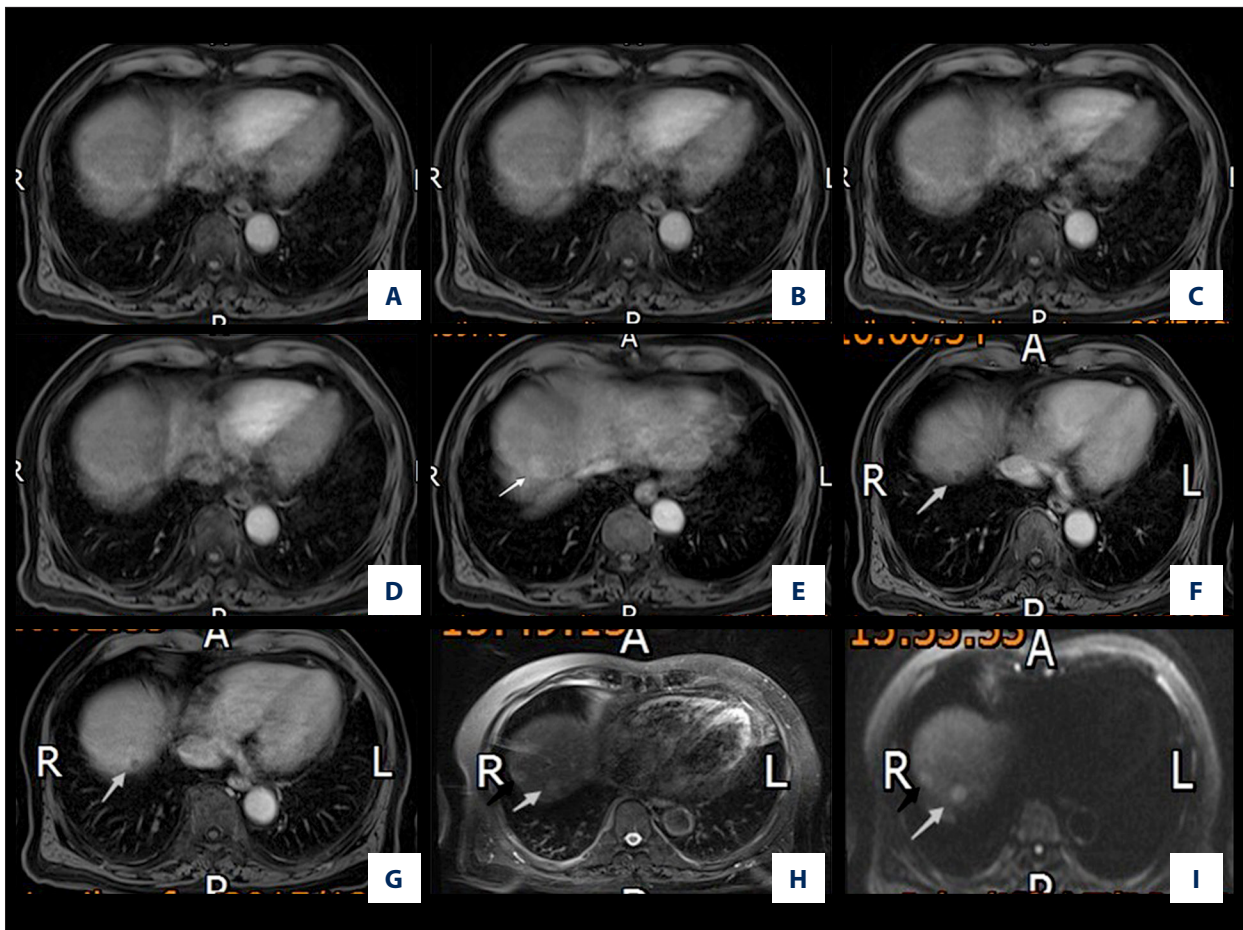
**Table 2.** The display of 33 lesions in 21 patients using the full set of imaging methods.

Patient code	Lesion code	T2WI	DWI	PV	DL	ESAP	The best phase in MA-CDT-VIBE	The best sequence in DCE	The advantage of MA-CDT-VIBE
1	1	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
	1*	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
	2	1	1	1	1	2	1 (5/5)	MA-CDT-VIBE	1
	2*	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
	3	1	1	1	1	1	1 (4/5)	DL	1
	3*	1	1	1	1	1	1 (4/5)	DL	1
	4	1	2	1	1	1	1 (2/5)	MA-CDT-VIBE	1
	4*	1	1	1	1	1	1 (2/5)	MA-CDT-VIBE	1
2	5	1	1	2	1	2	1 (5/5)	DL	1
	5*	1	1	1	1	2	1 (5/5)	DL	1
	6	2	1	1	1	1	1 (4/5)	DL	1
	6*	1	1	1	1	1	1 (4/5)	DL	1
	7	1	1	2	1	2	1 (5/5)	DL	2
	7*	1	1	1	1	2	1 (5/5)	DL	1
3	8	2	1	1	1	1	1 (3/5)	MA-CDT-VIBE	1
	8*	1	1	1	1	1	1 (3/5)	MA-CDT-VIBE	1
	9	1	1	1	1	1	1 (5/5)	PV	1
	9*	1	1	1	1	1	1 (5/5)	PV	1
	10	2	2	1	1	1	1 (2/5)	DL	1
	10*	1	1	1	1	1	1 (2/5)	DL	1
4	11	1	1	2	1	2	2 (-)	DL	2
	11*	1	1	1	1	2	1 (5/5)	DL	2
	12	1	1	1	1	1	1 (3/5)	MA-CDT-VIBE	1
	12*	1	1	1	1	1	1 (3/5)	PV	1
5	13	2	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1
	13*	1	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1
	14	1	1	2	1	1	1 (5/5)	DL	1
	14*	1	1	1	1	1	1 (4/5)	DL	1
6	15	2	1	2	2	2	1 (5/5)	DL	2
	15*	2	1	2	1	2	1 (5/5)	DL	2
	16	2	1	1	1	1	1 (3/5)	MA-CDT-VIBE	1
	16*	1	1	1	1	1	1 (3/5)	DL	1
7	17	1	1	2	1	1	1 (4/5)	DL	2
	17*	1	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1

**Table 2 continued.** The display of 33 lesions in 21 patients using the full set of imaging methods.

Patient code	Lesion code	T2WI	DWI	PV	DL	ESAP	The best phase in MA-CDT-VIBE	The best sequence in DCE	The advantage of MA-CDT-VIBE
	18	1	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1
	18*	1	1	1	1	1	1 (5/5)	PV	1
8	19	2	2	1	1	1	1 (5/5)	MA-CDT-VIBE	1
	19*	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
	20	1	1	2	1	2	2 (--)	DL	2
	20*	1	1	2	1	2	1 (5/5)	DL	2
9	21	1	1	2	1	1	1 (4/5)	MA-CDT-VIBE	1
	21*	1	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1
10	22	1	1	2	1	1	1 (5/5)	MA-CDT-VIBE	2
	22*	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
11	23	2	1	1	1	1	1 (5/5)	DL	1
	23*	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
12	24	1	1	1	1	1	1 (3/5)	MA-CDT-VIBE	1
	24*	1	1	1	1	1	1 (3/5)	MA-CDT-VIBE	1
13	25	1	1	2	1	1	1 (4/5)	MA-CDT-VIBE	1
	25*	1	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1
14	26	1	1	1	2	1	2 (5/5)	DL	2
	26*	1	1	1	1	1	1 (5/5)	DL	2
15	27	2	1	2	1	1	1 (4/5)	MA-CDT-VIBE	1
	27*	1	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1
16	28	1	2	1	1	1	1 (4/5)	DL	2
	28*	1	1	1	1	1	1 (4/5)	MA-CDT-VIBE	1
17	29	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
	29*	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
18	30	2	1	2	2	1	1 (5/5)	MA-CDT-VIBE	1
	30*	2	1	2	1	1	1 (5/5)	MA-CDT-VIBE	1
19	31	1	2	1	1	1	1 (5/5)	MA-CDT-VIBE	1
	31*	1	1	1	1	1	1 (5/5)	MA-CDT-VIBE	1
20	32	1	1	1	1	1	1 (3/5)	PL	2
	32*	1	1	1	1	1	1 (3/5)	PL	2
21	33	1	1	1	1	1	1 (3/5)	DL	1
	33*	1	1	1	1	1	1 (3/5)	MA-CDT-VIBE	1
$\kappa$ p<0.001		0.81	0.91	0.83	0.76	0.77	0.85 (0.74)	0.68	0.87

In each sequence, 1 indicates yes, 2 indicates no; \* indicates the result of the second review. PV – portovenous phase; DL – late dynamic phase; ESAP – equivalent standard arterial phase.

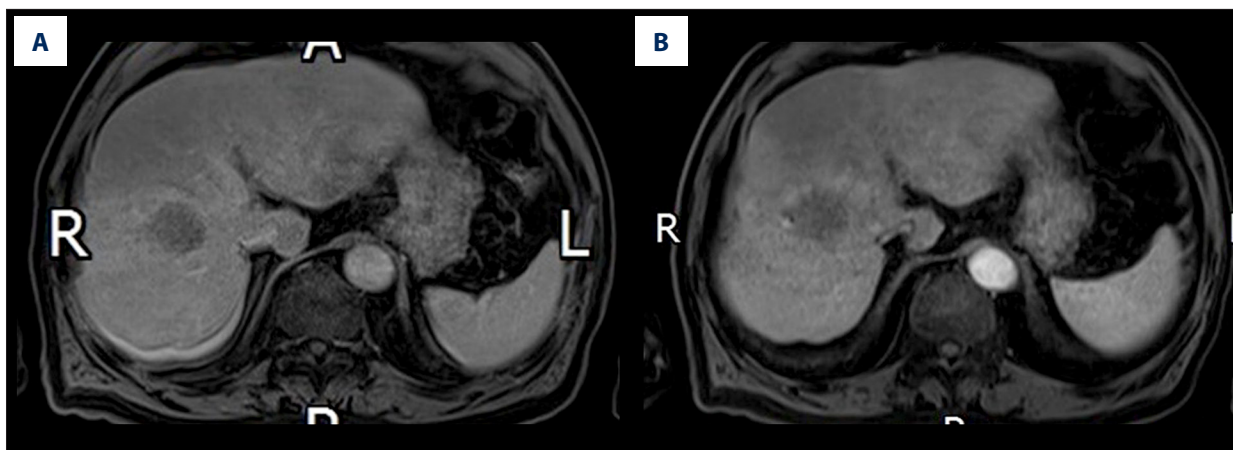


**Figure 1.** Multi-Arterial CAIPIRINHA-Dixon-TWIST-Volume-Interpolated Breath-Hold Examination (MA-CDT-VIBE) of a 73-year-old male patient with a history of chronic hepatitis B virus (HBV) infection for more than ten years and ultrasound diagnosis of liver cirrhosis. Two round nodules are shown in the right posterior lobe (VII) (black and white arrows). **Panel A–E** show the first, second, third, fourth, and fifth arterial subphases of the MA-CDT-VIBE sequence, respectively. **Panel D** (fourth arterial subphase) is an equivalent standard arterial phase (ESAP) image. **Panel F** is a portal vein phase image. **Panel G** is a delayed phase image. **Panel H** is an image obtained by T2-weighted imaging (T2WI). **Panel I** is an image obtained by diffusion-weighted imaging (DWI) ( $b = 800$ ). The images show that the two enhanced nodules were not clearly shown in the first through fourth subphases. However, significantly enhanced lesions were observed in the fifth arterial phase. White arrows indicate nodules with decreased signals in the portal vein phase (**Panel F**) and delayed phase (**Panel G**) exhibiting a ‘fast in and fast out’ type. The black arrows indicate nodules with a nonsignificant decrease in the signals in the portal vein phase and delayed phase. The two enhanced lesions show high signals on T2WI. The diffusion of the signals was limited on DWI ( $b=800$ ), which shows high signals.

Plain MRI images can generally detect lesions, but enhanced images can reveal more non-cystic lesions [16]. As the blood supply of regenerative nodules, dysplastic nodules, and HCC gradually change from the portal system to the hepatic artery system and the enhancement performance exhibits significant overlap. This finding reflects complex enhancement, and images scanned too early or too late in the arterial phase may lead to unclear lesion enhancement or even no lesion enhancement. Accordingly, the best arterial phase to display lesions can be missed, resulting in difficulty in diagnosing lesions. For example, in a conventional MRI scan, due to the presence of a single arterial phase, the dynamic display of a lesion will be

directly affected if the contrast agent’s peak value is missed. The MA-CDT-VIBE sequence can clearly and accurately capture the characteristics of early and late arterial enhancement of liver nodule signal changes, including the timing and intensity of nodular enhancement, and simultaneously reflect the lesion differentiation status to a certain extent.

A recent study performed liver scans using the CAIPIRINHA-Dixon-VIBE sequence without the TWIST technique with a temporal resolution of 7.5 s, resulting in an arterial phase with three subphases [17]. Another study with three subphases of the hepatic artery was conducted using a 1.5 T MRI



**Figure 2.** Multi-Arterial CAIPIRINHA-Dixon-TWIST-Volume-Interpolated Breath-Hold Examination (MA-CDT-VIBE) of a 71-year-old male approximately six months after microwave ablation of primary liver cancer. **Panel A.** Standard VIBE image. **Panel B.** Water image in the MA-CDT-VIBE image. As shown in **Panel A** and **Panel B**, the parallel acquired noise (PAT artifact) is mainly located in the right lobe of the liver. The granular noise in Panel b is more evident than that in **Panel A**. The PAT artifacts in **Panel B** do not affect the local structure display or the diagnosis of the lesions.

scanner [18]. This study confirmed that the middle subphase (the subphase when scanning 8.4 s after the peak of the contrast agent in the aorta) of the three subphases was the best subphase to detect HCC. Compared with the 3-mm thickness in the MA-CDT-VIBE sequence used in our study, the thickness of the CAIPIRINHA-Dixon-VIBE sequence without the TWIST technique of approximately 8–9 mm will affect the display and diagnosis of lesions, especially small lesions, due to the partial volume effect [19,20]. The 3-mm-thick MA-CDT-VIBE sequence had a higher spatial resolution and provided a clearer picture of the edges and details of the hypervascular lesions.

To optimize the timing of the arterial phase, one solution would be to scan at a fixed time point, but no defined standard exists for this fixed time point. In general, after contrast agent injection through an antecubital vein, approximately 17 s is required for the contrast agent to reach the abdominal aorta, and approximately 20 s is required for the contrast agent to reach the hepatic artery [21,22]. However, some studies have shown that the hepatic arterial phase enhancement time varies considerably among different patients [23,24]. For example, studies have shown that the contrast agent reached the celiac trunk of the abdominal aorta at  $18.2 \pm 4.1$  s, with a fluctuation range of approximately 12–13 s [23]. This finding is also consistent with a study by Van Beers et al., in which enhanced MRI scans of 47 patients with hypervascular lesions and found that the largest lesion-to-noise ratio occurred 26.5 s after contrast agent injection [24]. Because this time point varies greatly among patients, the optimal hepatic arterial phase with a single standard arterial phase is difficult to accurately determine using a fixed time point, thus affecting the display of lesions.

Another method is to develop different scanning protocols according to different individuals, such as determining the arterial phase scan time by pre-scanning the contrast agent or real-time tracking of the contrast agent [23]. However, a consensus has not yet been reached on which vessel to use as a reference. For example, some criteria require a breath-hold command when the contrast agent reaches the aortic arch, while some criteria require that the breath-hold begins when the contrast agent reaches the descending aorta or abdominal aorta [19,20,23]. Also, real-time tracking of contrast agents requires specialized training for the radiology technician, which cannot be achieved in all institutions, which limits the use of this technology [16].

The above techniques emphasize the clinical importance of the optimal arterial phase. Compared to other techniques, MA-CDT-VIBE sequences with multiple arterial phases with high temporal resolution can be used for multiphase scans with a fixed time delay. The specific fixed scan time point does not limit this technique and the specific vascular reference point. The requirements for the radiation technician are not very high, and the probability of capturing the best arterial phase is increased by obtaining multiple sub arterial phases. This sequence also has a very thin thickness, which is conducive to the display of small lesions.

Among the 33 liver lesions that underwent imaging in this study, no best lesion visualization to parenchyma contrast enhancement cases occurred in the first subphase of the five subphases of the MA-CDT-VIBE sequence. There were 6.1% of such cases that occurred in the second subphase, 18.1% of these cases occurred in the third subphase, 27.3% of the cases occurred in the fourth subphase (ESAP), and 48.5% of the cases occurred in the fifth subphase. Therefore, increased proximity



to the later subphases corresponded with better lesion display. In the images obtained by our MA-CDT-VIBE sequence, some of the images showed significant respiratory artifacts, and greater proximity to the later subphases corresponded to more severe respiratory artifacts. The CD-VIBE technique, which does not include the TWIST (view-sharing strategy) technique, has been shown to have a relatively low temporal resolution and spatial resolution. However, this technique shows smaller respiratory artifacts than those shown using the CDT-VIBE technique [17]. Reading the complete K-space information only during the first data acquisition is a key technology of the TWIST sequence [25]. Therefore, if breathing motion occurs at the time of the first data acquisition, subsequent data acquisition will be affected, and the overall image quality will be reduced. As a result, the view-sharing technique does not apply to patients who do not cooperate with the radiation technician's instructions in terms of breathing.

The results of the present study showed that the MA-CDT-VIBE sequence enabled the identification of 9% (one reading) and 12% (two readings) more lesions than the ESAP sequence. The best visualization of the arterial phase/hepatic parenchyma contrast enhancement was observed in all subphases except for the first arterial subphase. The extra arterial subphase of the MA-CDT-VIBE sequence allows its superior performance over the standard arterial phase sequence in capturing the optimal contrast phase in the display of the enhancement foci. Also, more lesions can be displayed in multiple consecutive phases compared to a single arterial phase. The MA-CDT-VIBE sequence used in this study had a scan time of 20 s and a time resolution of 2.8 s with five subphases. Although we can obtain more arterial subphases by increasing the breath-hold time, as in a previous study [12], the MA-CDT-VIBE sequence used had a temporal resolution of 2.1 s, resulting in 14 arterial subphases. However, increasing the breath-hold time can lead to respiratory motion artifacts in the following arterial subphase and even in the following portal arterial phase and delayed phase, affecting the image quality of each sequence of the dynamic contrast-enhanced scan and possibly reducing the diagnostic rate of the whole MRI scan sequence. Considering that most patients with primary liver cancer have a lower breath-holding capacity after microwave ablation compared to healthy people, these results suggest that the MA-CDT-VIBE sequence with a scan time of 20 s, a time resolution of 2.8 s, and five subphases was a reasonable, effective sequence for the detection and diagnosis of enhanced nodules in cirrhotic livers (Figures 1, 2).

According to the modified Response Evaluation Criteria in Solid Tumors (m RECIST), the precise timing of the arterial phase is more important than adequate evaluation of treatment efficacy [26]. Conventional dynamic contrast-enhanced methods lack the display of images 25–30 s before the inflow of blood

containing the contrast agent, which prevents observation of the dominant phase of the hepatic arteries. At present, the status of some hepatic arterial lesions can be obtained by fluorescence detection. In contrast, the MA-CDT-VIBE technique, a noninvasive method with multiple subtypes of arteries, provides more arterial information, especially for smaller cirrhotic nodules, HCC, and residual and recurrent lesions after surgery [27,28]. By applying the MA-CDT-VIBE sequence to the detection of focal liver lesions, Kazmierczak et al. showed that the MA-CDT-VIBE sequence could detect more lesions than the standard arterial phase, especially hypervascular lesions such as HCC, small foci of HCC, and liver metastases [16]. The use of the MA-CDT-VIBE sequence also facilitates detection of liver metastases without continuous enhancement, which may help influence and guide the choice of treatment regimens [29], because the enhancement of a lesion can be compared across multiple temporal subtypes of the arterial phase, resulting in a dynamic display of the arterial phase sequence images. This explanation is also consistent with the observations in this study. In this study, the MA-CDT-VIBE sequence was used to detect and diagnose enhanced cirrhotic nodules and small foci of HCC, and the results showed that more lesions were identified in this sequence than in a single standard arterial phase.

This study had several limitations. First, we treated the fourth subphase of the arterial phase of the MA-CDT-VIBE sequence as a single standard arterial phase and evaluated the application of the MA-CDT-VIBE sequence in enhanced cirrhotic nodules and small foci of HCC using an internal validation method. However, the fourth subphase is not strictly consistent with the standard arterial phase. As previously mentioned, more obvious parallel acquired noise (PAT artifacts), and respiratory movement artifacts occur in this subphase. However, if we want to compare the MA-CDT-VIBE sequence with a real single arterial phase, a patient must undergo two enhanced MRI scans in a short period and receive two contrast agent injections, which is neither feasible nor in line with ethical principles. Second, because the objective of the present study was to determine whether more lesions were found in the MA-CDT-VIBE sequence than in the standard single-phase arterial scan, the nodules were not all histologically confirmed, and only a complete set of MRI scans were used as the standard. Third, this study did not strictly limit the type of lesions. Future studies should focus on one type of lesion to further accurately investigate the diagnostic advantages and clinical applications of the MA-CDT-VIBE sequence.

## Conclusions

This study aimed to compare the use of routine liver magnetic resonance imaging (MRI) sequences with the multi-arterial CAIPRINHA-Dixon-TWIST-volume-interpolated breath-hold

examination (MA-CDT-VIBE) sequence to identify dysplastic liver nodules in patients with liver cirrhosis. The MA-CDT-VIBE sequence of MRI liver imaging improved the detection of dysplastic nodules in cirrhosis of the liver compared with routine liver MRI sequences. The MA-CDT-VIBE sequence with five arterial subphases in one breath-hold had high temporal and spatial resolution, and had a technical advantage in the detection of

enhanced dysplastic nodules in cirrhotic livers. The sequence has a higher detection rate than that of the standard arterial phase and provided a more optimized time configuration for the display of lesions. The MA-CDT-VIBE sequence captured a more accurate contrast enhancement phase, and several adjacent arterial subphases could be observed continuously for a dynamic enhancement comparison during an arterial phase.

## References:

- Kanda T, Goto T, Hirotsu Y et al: Molecular mechanisms driving progression of liver cirrhosis towards hepatocellular carcinoma in chronic hepatitis B and C infections: A review. *Int J Mol Sci*, 2019; 20(6): pii: E1358
- Shen J, Huang CK, Yu H et al: The role of exosomes in hepatitis, liver cirrhosis and hepatocellular carcinoma. *J Cell Mol Med*, 2017; 21(5): 986–92
- O'Rourke JM, Sagar VM, Shah T, Shetty S: Carcinogenesis on the background of liver fibrosis: Implications for the management of hepatocellular cancer. *World J Gastroenterol*, 2018; 24(39): 4436–47
- Pinter M, Trauner M, Peckradosavljevic M, Sieghart W: Cancer and liver cirrhosis: Implications on prognosis and management. *ESMO Open*, 2016; 1(2): e000042
- Marquardt JU, Nguyentat M, Galle PR, Wörns MA: Surveillance of hepatocellular carcinoma and diagnostic algorithms in patients with liver cirrhosis. *Visc Med*, 2016; 32(2): 110
- Park HS, Desser TS, Jeffrey RB, Kamaya A: Doppler ultrasound in liver cirrhosis: Correlation of hepatic artery and portal vein measurements with model for end-stage liver disease score. *J Ultrasound Med*, 2017; 36(4): 725–30
- Zhu AX, Kang Y-K, Yen C-J et al: Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased  $\alpha$ -fetoprotein concentrations (REACH-2): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*, 2019; 20(2): 282–96
- van Aerts RMM, van de Laarschot LFM, Banales JM, Drenth JPH: Clinical management of polycystic liver disease. *J Hepatol*, 2018; 68(4): 827–37
- Kazmierczak PM, Theisen D, Thierfelder KM et al: Improved detection of hypervascular liver lesions with CAIPIRINHA-Dixon-TWIST-volume-interpolated breath-hold examination. *Invest Radiol*, 2015; 50(3): 153
- Qu J, Shuai H, Zhang H et al: Arterial phase with CAIPIRINHA-Dixon-TWIST (CDT)-Volume-Interpolated Breath-Hold Examination (VIBE) in detecting hepatic metastases. *Transl Oncol*, 2017; 10(1): 46
- Altman DG (ed.): *Practical statistics for medical research*. Chapman and Hall, London, 1991
- Michaely HJ, Morelli JN, Budjan J et al: CAIPIRINHA-Dixon-TWIST (CDT)-volume-interpolated breath-hold examination (VIBE): A new technique for fast time-resolved dynamic 3-dimensional imaging of the abdomen with high spatial resolution. *Invest Radiol*, 2013; 48(8): 590–97
- Qu J, Han S, Zhang H et al: Improved detection of recurrent hepatocellular carcinomas in arterial phase with CAIPIRINHA-Dixon-TWIST-Volumetric Interpolated Breath-Hold Examination. *Invest Radiol*, 2016; 51(10): 602–8
- Budjan J, Ong M, Riffel P et al: CAIPIRINHA-Dixon-TWIST (CDT)-volume-interpolated breath-hold examination (VIBE) for dynamic liver imaging: Comparison of gadoterate meglumine, gadobutrol and gadoxetic acid. *Eur J Radiol*, 2014; 83(11): 2007–12
- Granata V, Petrillo M, Fusco R et al: Surveillance of HCC patients after liver RFA: Role of MRI with hepatospecific contrast versus three-phase CT scan-experience of high volume oncologic institute. *Gastroenterol Res Pract*, 2013; 2013: 469097
- Coulam CH, Chan FP, Li KC: Can a multiphasic contrast-enhanced three-dimensional fast spoiled gradient-recalled echo sequence be sufficient for liver MR imaging? *Am J Roentgenol*, 2002; 178(2): 335–41
- Pietryga JA, Burke LM, Marin D et al: Respiratory motion artifact affecting hepatic arterial phase imaging with gadoxetate disodium: Examination recovery with a multiple arterial phase acquisition. *Radiology*, 2014; 271(2): 131988
- Mori K, Yoshioka H, Takahashi N et al: Triple arterial phase dynamic MRI with sensitivity encoding for hypervascular hepatocellular carcinoma: Comparison of the diagnostic accuracy among the early, middle, late, and whole triple arterial phase imaging. *Am J Roentgenol*, 2012; 184(184): 63–69
- Sharma P, Bobby Kalb MD, Kitajima HD et al: Optimization of single injection liver arterial phase gadolinium enhanced MRI using bolus track real-time imaging *J Magn Reson Imaging*, 2011; 33(1): 110–18
- Park YS, Lee CH, Kim IS et al: Usefulness of controlled aliasing in parallel imaging results in higher acceleration in gadoxetic acid-enhanced liver magnetic resonance imaging to clarify the hepatic arterial phase. *Invest Radiol*, 2014; 49(3): 183–88
- Ohtomo K, Itai Y, Yoshikawa K et al: Hepatic tumors: Dynamic MR imaging. *Radiology*, 1987; 163(1): 27–31
- Earls JP, Rofsky NM, Decorato DR et al: Hepatic arterial-phase dynamic gadolinium-enhanced MR imaging: Optimization with a test examination and a power injector. *Radiology*, 1997; 202(1): 268–73
- Sharma P, Kitajima HD, Kalb B, Martin DR: Gadolinium-enhanced imaging of liver tumors and manifestations of hepatitis: Pharmacodynamic and technical considerations. *Top Magn Reson Imaging*, 2009; 20(2): 71–78
- Van Beers BE, Materne R, Lacrosse M et al: MR imaging of hypervascular liver tumors: Timing optimization during the arterial phase. *J Magn Reson Imaging*, 1999; 9(4): 562–67
- Lee SH, Kim JH, Kim KG et al: Optimal clustering of kinetic patterns on malignant breast lesions: comparison between K-means clustering and three-time-points method in dynamic contrast-enhanced MRI. *Conf Proc IEEE Eng Med Biol Soc*, 2007: 2007: 2089–93
- Kim DJ, Clark PJ, Heimbach J et al: Recurrence of hepatocellular carcinoma: Importance of mRECIST response to chemoembolization and tumor size. *Am J Transplant*, 2014; 14(6): 1383–90
- Wong RJ, Devaki P, Long N et al: Increased long-term survival among patients with hepatocellular carcinoma after implementation of model for end-stage liver disease score. *Clin Gastroenterol Hepatol*, 2014; 12(9): 1534–40
- Karaman B, Battal B, Sari S, Verim S: Hepatocellular carcinoma review: Current treatment, and evidence-based medicine. *World J Gastroenterol*, 2014; 20(47): 18059–60
- Namasivayam S, Martin DR, Saini S: Imaging of liver metastases: MRI. *Cancer Imaging*, 2007; 7(1): 2–9