Test-Bolus Injection for Optimization of Arterial Phase Imaging during Contrast-Enhanced Hepatic MR Imaging

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──── Abstract ────

Contrast enhancement during the dynamic MR imaging is important for the detection and characterization of focal liver lesions. The purpose of this study was to determine whether or not a timing examination with a injection of a 1.0-mL bolus of gadopentetate dimeglumine into the antecubital vein followed by rapid dynamic scanning and measurement of signal intensity of the aorta could help to obtain proper arterial-dominant phase images for the characterization of focal hepatic lesions during subsequent multiphase dynamic MR imaging. The imaging delay to acquisition of the first gadolinium-enhanced image for multiphase dynamic MR imaging was set to equal the time to peak aortic enhancement during the test examination. The first contrast-enhanced images of 80 patients with 160 focal liver lesions (hepatocellular carcinoma, n=79; cavernous hemangioma, n=51; metastatic tumor, n=30) were then retrospectively reviewed. Peak aortic enhancement occurred between 10 and 28 seconds (mean, 16.5 seconds ± 3.1) after starting the infusion of contrast material in 80 patients during the test-examination. Depending on the findings of intrahepatic vascular enhancement on the full-scale dynamic images, hepatic arterial phase (n=11, 14%) or sinusoid phase (n=65, 81%) imaging was obtained during the first gadolinium-enhanced acquisition in 76 (95%) of 80 patients. Three different lesions were well characterized and easily distinguished from each other (p < .0001) on the first-phase images depending on their enhancement pattern. In the majority of patients, timing examination with test-bolus injection was helpful in obtaining qualified images for the characterization of various focal lesions.

Key Words: Liver MR, liver neoplasms, contrast enhancement MR

INTRODUCTION

MR imaging including dynamic contrast-enhanced imaging is widely used as an important method for the assessment of hepatic lesions. Contrast enhancement during the arterial phase is important for the detection and characterization of hypervascular tumors in the liver.[1-8] However, depending on variable body status, cardiac output and/or cirrhotic changes of the liver, a dynamic MR imaging protocol with a single fixed time delay for imaging of the arterial

phase is often suboptimal.[7,8] Since the sensitivity for recognition of hypervascularity and enhancement-pattern may be impaired if the arterial enhancement window is missed, an optimally-timed arterial phase is desirable and essential for intravenous contrast-enhanced dynamic MR imaging. Earls et al. described a technical aspect of a timing examination using a small amount of contrast material just before dynamic MR imaging to obtain the proper arterial phase images.[9] To our knowledge, however, there have been no prior reports regarding the clinical utility of Earls' technique for assessing focal lesions in the liver. The objective of this study was to determine whether or not a timing examination with a 1.0-mL timing bolus of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) could help overcome individual variations of circulation time and achieve imaging during the proper arterial phase. We also tried to document the usefulness of "state-of-the-art" dynamic MR imaging using an individually-adjusted delay-time for the characterization of various focal hepatic

lesions, with the emphasis on first-phase images.

MATERIALS AND METHODS

Subjects

Among the 161 patients examined by hepatic MR imaging during a 12-month period (from December, 1997 to November, 1998), 80 patients (45 men and 35 women, 32–81 years old) with the 3 most common focal liver lesions, including hepatocellular carcinoma, cavernous hemangioma and liver metastasis from malignancy of extrahepatic organs, were included in this study. Simple cysts can be easily detected and characterized by other imaging studies including sonography, CT as well as unenhanced T1- and T2-weighted MR imaging, and were excluded in this study. Seventy-nine hepatocellular carcinomas (0.6–9 cm in the longest dimension; mean, 1.9 cm) were diagnosed in 42 patients (liver cirrhosis, n=31; chronic viral hepatitis, n=8; unknown risk factor, n=3) without any evidence of extrahepatic primary malignancy. A high level of serum alpha-fetoprotein was reported in 25 patients. Of these 42 patients, 15 had histologically-proven hepatocellular carcinomas verified by biopsy (n=10), or hepatic resection (n=5). A biopsy of just one lesion was typically performed for 5 patients with multiple lesions, and they were presumed to have multifocal hepatocellular carcinomas when the other lesions (n=8 in 5 patients) had the same appearance on MR imaging as those of the biopsy-confirmed lesions. Other 56 hepatocellular carcinomas in 27 patients were highly suggested on the basis of characteristic angiographic findings (n=48), including those seen at one or more follow-up iodized-oil CT scans at 3-week intervals (n=46) or those showing tumor growth during subsequent follow-up periods (n=10). Diagnosis of hemangiomas (n=51; 0.6–11 cm in the longest dimension; mean, 2.8 cm) in 33 patients was established by means of additional confirmatory radiologic findings, including angiograms (n=10) or technetium-99m red blood cell scintigrams (n=11), classic contrast enhancement patterns on dynamic CT and/or MR images associated with markedly high signal intensities on heavily T2-weighted images (n=48). Hemangiomas were also accompanied by a noncystic appearance on sonograms that showed no change in the size or number of lesions for 6 months or more at serial imaging (n=26). Nine patients had 30 liver metastases, with the following primary tumors: stomach (n=2), colorectal (n=4), breast (n=1), pancreas (n=1), and lung (n=1). The presence of liver metastases (n=27; 0.6–7 cm in the longest dimension; mean, 2.0 cm) was diagnosed in 6 cases on the basis of clinical history and progression in size in serial radiographic examinations. Diagnosis in the remaining 3 patients was proved by sonography-guided biopsy. Three patients had liver metastases and hemangiomas coincidentally. One patient had a hepatocellular carcinoma and a hemangioma. Four patients with hemangiomas had liver cirrhosis, and there was no chronic liver disease for the patients with metastatic tumors in the liver.

MR imaging

MR imaging was performed on a 1.5-T whole body imager (Magnetom Vision; Siemens, Erlangen, Germany). T2-weighted images were obtained by multishot turbo spin-echo sequences (TR range/effective TE =3,540–4,000/138, echo train length=29) with and without fat-suppression by chemical saturation prepulse. A multisection fast low-angle shot (FLASH) sequence (TR/TE=160.8/4.1, flip angle=80) with fat-suppression by chemical saturation pre-pulse was used for unenhanced and contrast-enhanced T1-weighted imaging during the first 6 months of this study. During the following 6 months, however, simultaneous acquisition of an in-phase and an opposed phase image (SINOP) on the basis of FLASH sequence (TR/TE=140/2.7 for opposed phase and TR/TE=140/5.3 for in-phase, flip angle=90°) was substituted for unenhanced and contrast-enhanced T1-weighted imaging. A timing examination was performed using a MR power injector (Spectris MR Injector, model SBT 200; MedRad, Pittsburgh Pa, USA). The examination included injection of a 1.0-mL bolus gadopentetate dimeglumine into the antecubital vein followed by injection of 12-mL saline, both infused at 3 mL/sec. Multiple, sequential, single-level, axial turbo FLASH images (TR/TE/inversion time=11/4.2/300, flip angle=15) were obtained every 2 seconds for 40 seconds. The images were all obtained at a level that included the proximal abdominal aorta near the porta hepatis. User-defined regions of interest were drawn over the central portion of the aorta on timing examination imaging, and

a signal-intensity vs. time-curve was plotted to determine the optimum timing for maximum contrast enhancement of intraaortic blood. The imaging delay from the start of infusion to peak aortic enhancement was recorded. For dynamic MR imaging, multisection FLASH or SINOP sequences were employed using the same parameters as for unenhanced T1-weighted imaging. Gadopentetate dimeglumine (0.1 mmol/kg of body weight) was administered before the dynamic phase of the examination. A power injector was used to administer the contrast material, followed by a 12-mL saline flush, both at 3 mL/sec. The imaging delay to acquisition of the first gadolinium-enhanced image was set to equal the time to peak aortic enhancement, followed by additional contrast-enhanced imaging at 30 seconds and 5 minutes after start of the first gadolinium-enhanced acquisition. Contrast-enhanced images of the entire liver could be imaged in all patients with a single acquisition. Time of acquisition was $19-21$ sec in each examination, and all MR imaging could be acquired during a single breath-holding period.

Image analysis

To evaluate the ability of tumor characterization on arterial dominant phases, a case analysis was undertaken on the first images after gadolinium injection. For the first contrast-enhanced images, we defined three phases of enhancement based on the location of gadolinium enhancement within the various hepatic vessels.[10] The early arterial phase was the phase in which contrast material was present in the hepatic arteries and not in portal veins. The late arterial phase or sinusoid phase showed contrast material in the hepatic arteries and portal veins, but not in hepatic veins. The early non-equilibrium phase or portal phase was defined as a phase of maximum hepatic parenchymal enhancement recognized as the earliest phase of contrast material in all hepatic vessels. Drawing on our experience with dynamic MR imaging, we regarded not only the hepatic arterial phase, but also the sinusoid phase as the arterial-dominant phase because hypervascular lesions supplied by hepatic arteries could be enhanced preferentially to a greater extent than the background liver, even in the sinusoid phase. At the time of retrospective review by 4 observers (J.S.Y., K.W.K., B.J.J., J.K.K., and all unaware of the findings of other imaging data), the

number of times that the first and second contrast-enhanced images were obtained in the arterial-dominant phase was recorded in conference. The patterns of contrast enhancement were also analyzed for each lesion on first-phase images as follows: homogeneous enhancement, diffuse-heterogeneous enhancement, peripherally circumferential rim/rind-like enhancement, and focal-eccentric/globular enhancement. To determine the differential ability for each focal lesion during first-phase imaging, statistical analyses of the results were generated by chi-square test. A p value of less than .05 was considered to indicate a statistically significant difference.

RESULTS

Peak aortic enhancement at the level of the porta hepatis occurred between 10 and 28 seconds (mean, 16.5 seconds ± 3.1) after starting the infusion of contrast material in 80 patients during the test-examination (Fig. 1). Peak aortic enhancement of 39 patients with cirrhosis or chronic hepatitis occurred between 10 and 28 seconds (mean, 16.3 seconds $\pm$ 3.3), and peak aortic enhancement of the other 41 patients occurred between 12 and 24 seconds (mean,
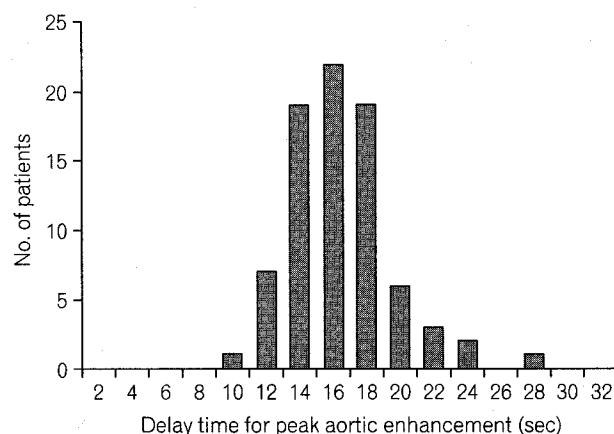

Fig. 1. Results of the timing examination in 80 patients. The horizontal axis represent the timing of peak aortic enhancement after the start of test-bolus injection and the vertical axis represents the number of the patients. The timing of peak aortic enhancement was used as the delay-time for acquisition of the first phase images after contrast agent injection during the full-scale dynamic MR imaging in each patient.

Table 1. Enhancement Patterns of Focal Liver Lesions at the Individually-Adjusted First Phase Images during the Multiphase Dynamic MR Imaging

Enhancement pattern	Hepatocellular carcinoma (n=79)			Cavernous hemangioma (n=51)			Liver metastasis (n=30)		
	P1	P2	P3	P1	P2	P3	P1	P2	P3
Homogeneous	46	12	2		7	21	1	2	
Diffuse-heterogeneous	28	17	6		5	7	3	3	5
Peripheral rim/rind-like	2	17	23	2	0	1	23	20	15
Eccentric or globular	1	1	0	40	36	22	0	0	0
No or hypointense enhancement	2	32	48	7	3	0	3	5	6

Note. - P1, P2, P3 mean the first phase (acquired after the individually-adjusted delay time calculated by a test-examination just before the dynamic MR imaging), second phase (acquired at 30 sec after the initiation of first phase imaging), third phase (acquired at 5 min after the initiation of first phase imaging) images of contrast enhancement respectively.
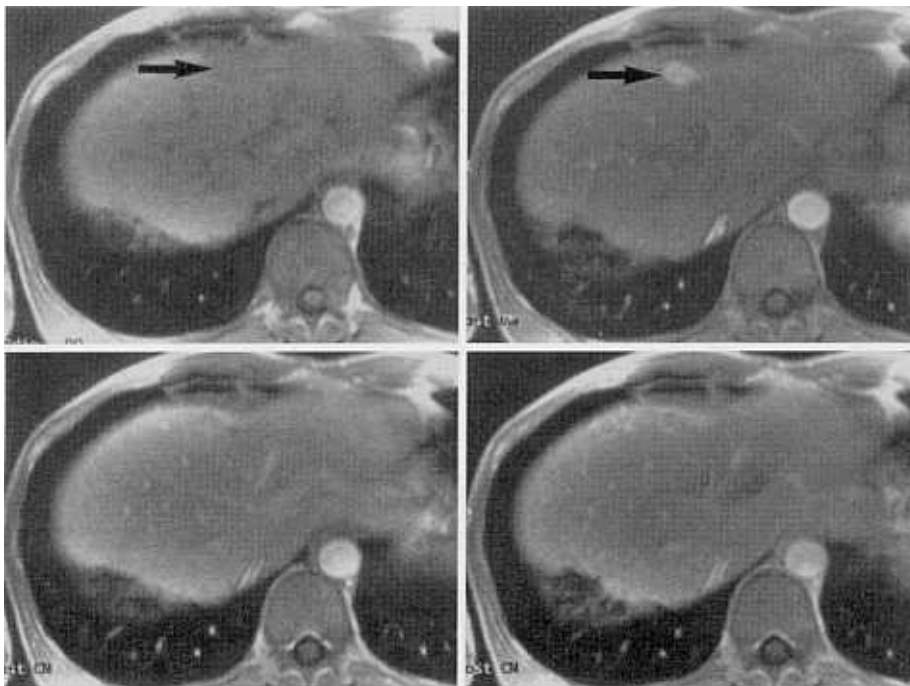

Fig. 2. Homogeneous enhancement of hepatocellular carcinoma on first phase of dynamic MR imaging with multisecton FLASH sequence (160.8/4.1, 80° flip angle) with fat-suppression. Precontrast image (upper left) shows a low intensity nodule (arrow) which is homogeneously enhanced on first phase contrast-enhanced image (upper right) obtained at 14 sec after administration of contrast injection was initiated. Slightly heterogeneous and peripheral-rim enhancement are seen on second phase (lower left) and third phase (lower right) images obtained at 44 sec and 5 min after administration of contrast injection.

16.6 seconds ±2.9). Depending on the findings of intrahepatic vascular enhancement on the full-scale dynamic images, hepatic arterial phase (n=11, 14%) or sinusoid phase (n=65, 81%) imaging was obtained during the first gadolinium-enhanced acquisition in 76 (95%) of 80 patients. In 4 patients (5%), the first-phase images were acquired during non-equilibrium phase. Second-phase images were obtained during sinusoid phase in four patients (5%) or during non-equilibrium phases in 76 patients (95%). Among the 43 patients with liver cirrhosis or chronic hepatitis

(n=5), hepatic arterial-phase and sinusoid-phase imaging were obtained in 7 (16%) and 32 patients (74%), respectively. However, non-equilibrium phase images were obtained during first-phase imaging in 4 patients (9.3%). For the 37 patients without cirrhosis or chronic hepatitis, arterial-dominant phase imaging (hepatic arterial phase, n=4; sinusoid phase, n=33) always proved successful during the first phase.

The enhancement patterns of various focal lesions during the three-phase dynamic images are summarized in Table 1. Seventy-four of 79 hepatocellular
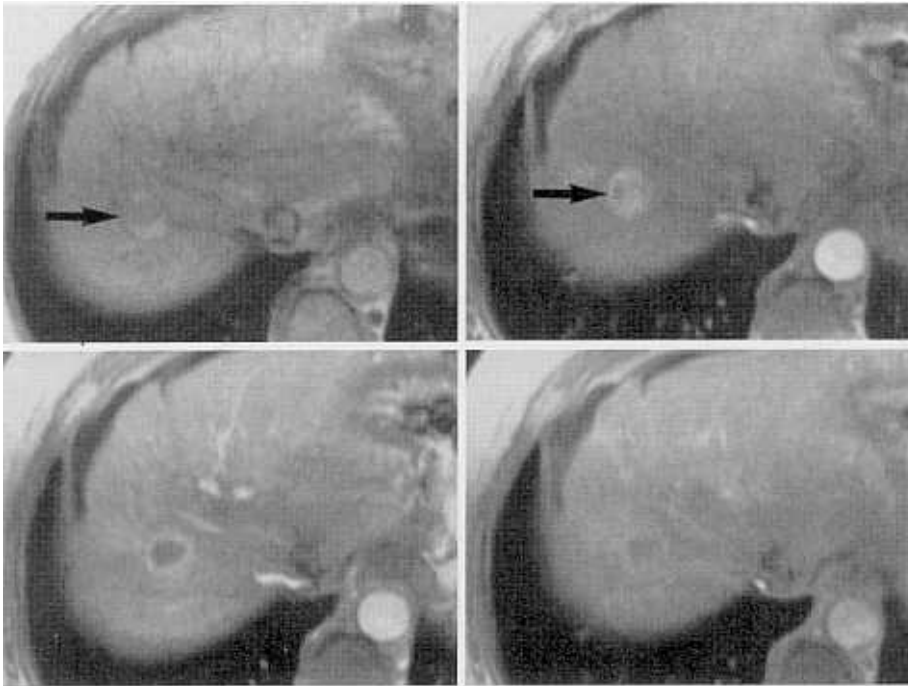
Fig. 3. Diffuse-heterogeneous enhancement of hepatocellular carcinoma on first phase of dynamic MR imaging with multisecton FLASH sequence (160.8/4.1, 80° flip angle) with fat-suppression. Precontrast image (upper left) shows a focal lesion with nodule-in-nodule appearance (arrow) which is heterogeneously enhanced on first phase contrast-enhanced image (upper right) obtained at 18 sec after administration of contrast injection was initiated. Peripheral rim enhancement is prominently seen on second phase image (48 sec, lower left). At the third phase image (5 min, lower right), enhancement of the tumor is no longer well distinguished from the surrounding hepatic parenchyma.
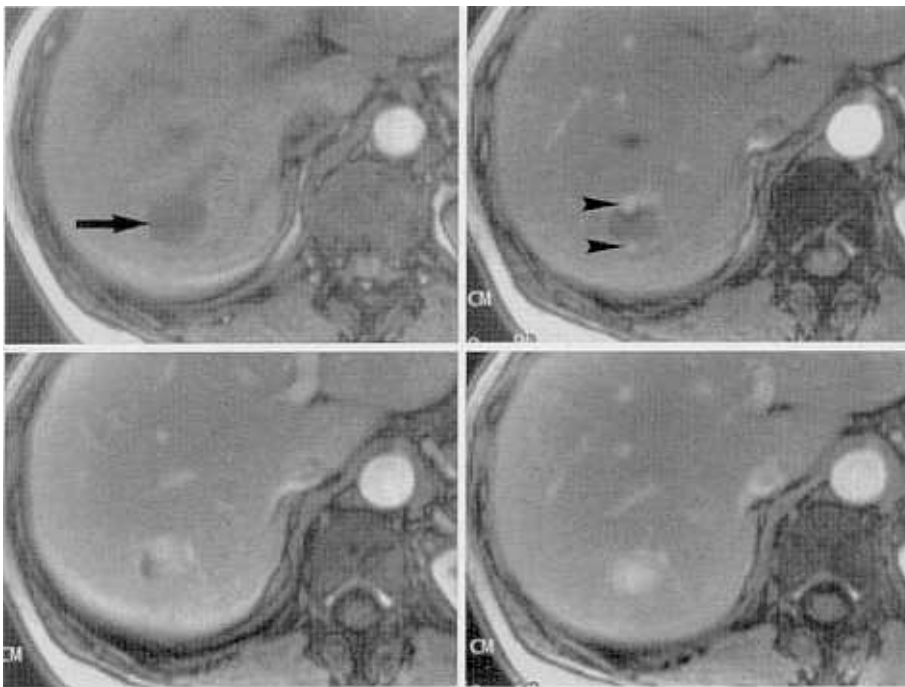

Fig. 4. Eccentric and globular enhancement of cavernous hemangioma on first phase of dynamic MR imaging with opposed-phase image of SINOP sequence (140/2.7, 90° flip angle). Precontrast image (upper left) shows a low intensity nodule (arrow) which is partially enhanced at the periphery (arrowheads) on first phase contrast-enhanced image (upper right) obtained at 14 sec after administration of contrast injection was initiated. The enhancement pattern on the second phase image (44 sec) was categorized as diffuse-heterogeneous enhancement resulted from progressive fill-in of contrast agent into the vascular spaces of cavernous hemangioma (lower left). The lesion shows homogeneous enhancement on 5 min delayed image after contrast agent injection (lower right).

carcinomas (94%) showed homogeneous or diffuse-heterogeneous enhancement patterns in first-phase images (Fig. 2 and 3), which was significantly greater (p<.0001) than those of hemangiomas (4%) or liver metastases (13%). The majority of hemangiomas showed eccentric/globular enhancement patterns in first phase images (Fig. 4) in 40 of 51 cases (78%), they were well distinguished from liver metastases which showed no such pattern of enhancement, as well as hepatocellular carcinoma (1.3%, p<.0001).
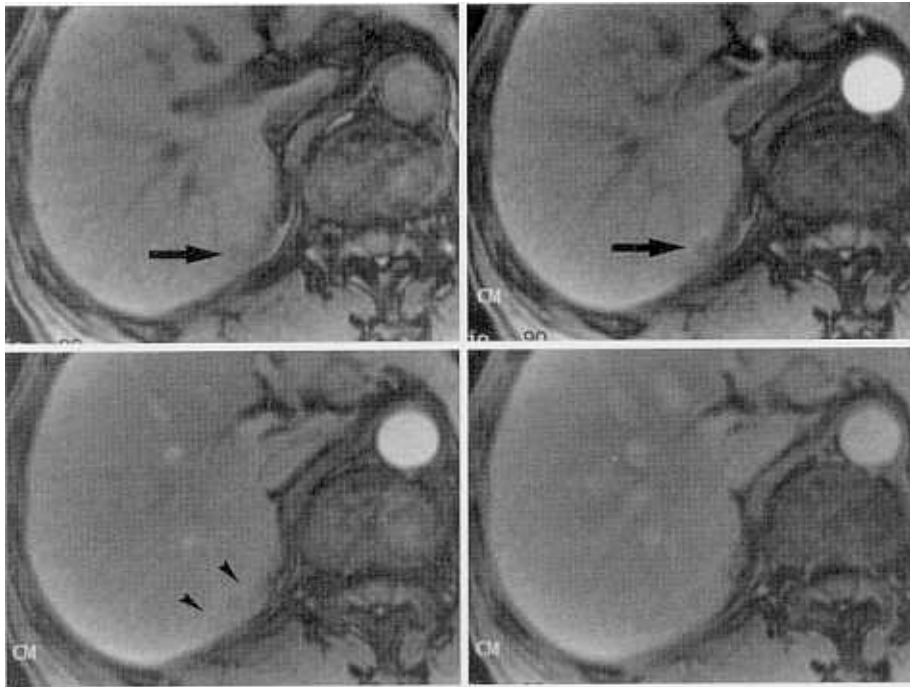
Fig. 5. Peripheral rind-like enhancement of metastatic tumor from stomach cancer on first phase of dynamic MR imaging with multisection FLASH sequence (160.8/4.1, 80° flip angle) with fat-suppression. Precontrast image (upper left) shows a low intensity nodule (arrow) which shows ring-like peripheral enhancement on first phase contrast-enhanced image (upper right) obtained at 22 sec after administration of contrast injection was initiated. On second phase (lower left) and third phase (lower right) images obtained at 52 sec and 5 min after administration of contrast injection, the tumoral enhancement is not well distinguished from the ill-defined subsegmental enhancement (arrowheads) of the surrounding hepatic parenchyma.

Twenty-three of 30 metastases (77%) showed a peripheral rim/rind-like circumferential enhancement with varying thickness in first-phase images (Fig. 5), significantly greater (p < .0001) than those of hepatocellular carcinomas (2.5%) or cavernous hemangiomas (3.9%).

DISCUSSION

Many investigators have agreed about the important role of arterial-phase imaging during dynamic CT or MR studies for making a diagnosis for focal liver lesions.[1-12] In many of those studies, however, the arterial dominant phase was arbitrarily fixed to a certain timing and the delay time between contrast injection and the start of image acquisition varied between studies.[1-6] Actually, the timing of enhancement of liver or tumors can be affected by a patient's size, weight, cardiac output, metabolic status, and degree of hydration, as well as those factors related to the lesion such as tumor vasculature and cirrhosis of surrounding hepatic parenchyma.[9,13-15] These factors, however, have great individual variation. Meanwhile, compared with dynamic CT scan, MR imaging uses a smaller volume of contrast medium (10−15 mL) and the injection time is very short (up

to 5 sec in this study). Although MR imaging can provide better contrast resolution and better quality on well-timed arterial-phase imaging, the time window for the arterial-dominant phase is narrower.[4,5,16] These observations imply that if limited to a phase with a fixed image-acquisition time during dynamic MR imaging, the visualization of optimal arterial enhancement may fail and the diagnosis could be troublesome, depending on tumor vascularity.[8,14]

Regardless of the amount of intratumoral vascularity, or the speed of intratumoral blood flow, most hepatic tumors are exclusively supplied by the hepatic arteries and have the potential for arterial enhancement. The liver is also a hypervascular organ, but in hepatic sinusoids, the contrast material purely induced from the hepatic artery is profoundly diluted by a large amount of unenhanced portal venous flow. In this situation, depending on the tumor vasculature, the tumors preferentially enhance to a greater extent than the background liver during the arterial phase of IV contrast-enhanced dynamic imaging.[17] There should be some additional time for maximal enhancement of the tumor after contrast enhancement of the hepatic artery itself.[10] As well, tumor enhancement would be preserved for some time after the first pass of the contrast-filled arterial flow depending on the speed of intratumoral blood flow and/or capillary

permeability. Ideally, arterial-phase images should be acquired at the time when a tumor exhibits maximal liver-to-lesion contrast, but the addition of extra time for sufficient tumoral enhancement to the hepatic arterial phase inevitably leads to some inflow of contrast-filled portal venous blood.[9,13] There is also a time extension for sufficient enhancement of liver parenchyma by portal venous inflow following contrast enhancement of the portal vein itself. Meanwhile, recognition of contrast enhancement of the hepatic vein (early non-equilibrium phase or portal phase) in this study was seen as an indication that liver parenchyma was profoundly perfused by contrast-filled portal venous inflow and was no longer in the arterial-dominant phase.[13]

To determine the delay time for obtaining the proper arterial-dominant phase images, the concept of Earls et al was also adopted for this study.[9] The timing of peak enhancement of the abdominal aorta following IV contrast injection was measured, and the delay time for acquisition of first-phase images during the subsequent full-scale dynamic imaging was set to equal the time to peak aortic enhancement during test examination to overcome individual variation in circulation time. The FLASH sequences used in this study were fast multisection techniques acquired during a 19–21-second breath-holding period.[18,19] These sequences comprise data that are integrated over all the sections obtained in a given acquisition, and the image contrast is primarily determined by the bulk of signal data in which k space is traversed over central lines. An opportunity exists to target the central portion of data acquisition to coincide with the arterial-dominant phase. Meanwhile, the amount of contrast agent for test-examination was 1 mL, and the amount of full-scale dynamic imaging was 10 to 15 mL with the same injection speed (3 mL/sec). As a consequence, the timing of peak aortic enhancement during full-scale dynamic imaging could be delayed more than during the test-examination. Synchronization of the imaging delay for dynamic imaging with the timing of peak aortic enhancement during the test examination could create an extended time period of about 10 sec to compromise the discrepancy in the timing of peak aortic enhancement between the timing-examination and full-scale dynamic imaging, in addition to allowing sufficient arterial enhancement of the focal lesions.

As demonstrated by our results, the late arterial or sinusoid phase was more frequently imaged in the majority of patients, than in the early arterial phase. Despite the timing examination in this study, hepatic venous enhancement was observed during the first phase in 4 patients. In those cases, however, 4 hepatocellular carcinomas were highly enhanced and well distinguished from the surrounding liver parenchyma. It is our impression that there could have been decreased portal flow related to portal hypertension resulting from liver cirrhosis, and that hepatic arterial flow might be increased enough to strongly enhance the tumors and not be profoundly diluted in the hepatic sinusoids. The relatively high density of contrast material from hepatic arteries, accompanied by a small amount of unenhanced portal flow in the sinusoids could have appeared in the hepatic veins, which may have been earlier than the timing of contrast enhancement through the contrast-filled portal venous inflow. The hepatic venous enhancement during the first phase was thought to be due to the altered arterial and venous hemodynamics from cirrhosis, rather than the failure of test-examination in this study. It is our impression that test-examination and any subsequent dynamic MR imaging with individually-adjusted delay time for arterial-dominant phase imaging would be feasible for assessing focal lesions combined with cirrhosis.

Despite variations of tumor vascularity depending on cellular differentiation or intratumoral degenerative changes, hepatocellular carcinoma is a stereotypically hypervascular tumor and it is well characterized by patterns of homogeneous or diffusely heterogeneous enhancement during arterial-dominant phase imaging.[4,5,8,14] Regarding cavernous hemangiomas, the role of well-timed arterial phase imaging is not so essential for diagnosis. The typical pattern of centripetal fill-in with sustaining enhancement can be characterized in the later phases.[3,20-22] Particularly for some smaller lesions, however, there is an atypical pattern of early homogeneous enhancement which is not well distinguished from other hypervascular lesions.[23] In those cases, the arterial phases were useful to delineate the initial enhancement patterns. Among the 7 hemangiomas with homogeneous enhancement on second-phase images, 5 cases showed partially eccentric/globular enhancement patterns on first-phase images in this study. The role of arterial-dominant imaging for the diagnosis of metastatic tumors from extrahepatic malignancy is also not well

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