Oncology

Oncology 2011;81(suppl 1):86–99
DOI: 10.1159/000333267

Published online: December 22, 2011

Ultrasonography, Computed Tomography and Magnetic Resonance Imaging of Hepatocellular Carcinoma: Toward Improved Treatment Decisions

Takamichi Murakami[a] Yasuharu Imai[b] Masahiro Okada[a] Tomoko Hyodo[a]
Won-Jae Lee[d] Myeong-Jin Kim[e] Tonsok Kim[c] Byung Ihn Choi[f]

[a]Department of Radiology, Faculty of Medicine, Kinki University, Osakasayama, [b]Department of Gastroenterology, Ikeda Municipal Hospital, Ikeda, and [c]Department of Radiology, Osaka University Graduate School of Medicine, Osaka, Japan; [d]Department of Radiology, Samsung Medical Center, [e]Department of Radiology, Yonsei University Medical School and [f]Department of Radiology, Seoul National University College of Medicine, Seoul, Korea

Key Words
Liver neoplasms · Ultrasound · Computed tomography · Magnetic resonance imaging · Microbubbles · Contrast media · Hepatocellular carcinoma · Dysplastic nodule

Abstract
Detection, characterization, staging, and treatment monitoring are major roles in imaging diagnosis in liver cancers. Contrast-enhanced ultrasonography (CEUS) using microbubble contrast agents has expanded the role of US in the detection and diagnosis of liver nodules in patients at high risk of hepatocellular carcinoma (HCC). CEUS provides an accurate differentiation between benign and malignant liver nodules, which is critical for adequate management of HCC and is also useful for guidance of percutaneous local therapy of HCC and postprocedure monitoring of the therapeutic response. The technology of multidetector-row computed tomography (MDCT) has increased spatial and temporal resolutions of computed tomography (CT). It has made possible a more precise evaluation of the hemodynamics of liver tumor, and the diagnostic accuracy of dynamic MDCT has improved. Perfusion CT can measure tissue perfusion parameters quantitatively and can assess segmental hepatic function. Dynamic MDCT with high spatial and temporal resolution enables us to reconstruct 3- and 4-dimensional imaging, which is very useful for pretreatment evaluation. Dual-energy CT makes possible the differentiation of materials and tissues in images obtained based on the differences in iodine and water densities. Monochromatic images, which can be reconstructed by dual-energy CT data, provide some improvement in contrast and show a higher contrast-to-noise ratio for hypervascular HCCs. Dynamic magnetic resonance imaging with fast imaging sequence of 3-dimensional Fourier transformation T_1-weighted gradient echo and nonspecific contrast medium can show high detection sensitivity of hypervascular HCC. However, the hepatic tissue-specific contrast medium, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid, has become an essential contrast medium for liver imaging because of its higher diagnostic ability. It may replace CT during hepatic arteriography and during arterioportography.

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0030–2414/11/0817–0086$38.00/0

Accessible online at:
www.karger.com/ocl

Byung Ihn Choi, MD
Department of Radiology
Seoul National University Hospital
101, Daehak-ro, Jongno-gu, Seoul 110-744 (Korea)
Tel. +82 2 2072 2515, E-Mail bichoi@snu.ac.kr

Introduction

For the imaging diagnosis of liver tumor, detection, characterization, and staging of the tumor are very important. Moreover, the evaluation of anatomical information before treatment and the treatment response determination are also very important. Recently, less invasive imaging examination, such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) have developed dramatically. To understand these imaging modalities and to diagnose the lesion correctly by combining them optimally is very important.

Recently developed contrast-enhanced (CE) US (CEUS) technologies have been used in various clinical indications. CEUS provides an accurate differentiation between benign and malignant liver tumors, which is critical for adequate management of these patients. CEUS is now recognized as a useful imaging modality for the noninvasive diagnosis of small newly detected liver nodules during hepatocellular carcinoma (HCC) surveillance and is also useful for guidance and follow-up of locoregional therapy of HCC [1].

Recently, as multidetector-row CT (MDCT) with more than 16 channels is widely available, dynamic MDCT with high spatial and temporal resolution has been employed for liver imaging. CT imaging has developed from 2-dimensional imaging to 3-dimensional (3D) imaging, and recently, the addition of the time axis to the 3D imaging, so-called 4-dimensional (4D) imaging, has become possible [2, 3]. Moreover, research of functional imaging, such as tissue blood flow analysis by perfusion CT, is developing [4].

On the other hand, fast imaging techniques also have developed in MRI, and the usefulness of dynamic MRI with 3D Fourier transformation (3DFT) T_1-weighted gradient echo sequence and nonspecific contrast medium, such as gadopentetate dimeglumine (Gd-DTPA), was reported [5]. Moreover, on liver MRI, tissue-specific MR contrast media accumulated in Kupffer cells due to phagocytosis or in hepatic cells due to hepatocyte function are clinically available, and an improvement of tumor detection sensitivity has been reported [6–8]. In particular, hepatic tissue-specific contrast medium, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), which was clinically available recently, has become an essential contrast medium for liver imaging because of its high diagnostic ability [7–11]. However, CT during hepatic arteriography (CTHA) and CT during arterioportography (CTAP) are still believed to be reliable imaging techniques due to its high detection sensitivity in identifying HCC, though those are more invasive techniques.

In this review, we describe a recent advancement of US, CT and MRI techniques for HCC with the focus on US contrast agents, the recent role of CTHA and CTAP, and MR contrast agents.

US Imaging

Detection and characterization of HCC is one of the major roles of imaging diagnosis in patients at high risk of HCC. Grayscale US is a screening or surveillance technique for HCC [12], and sometimes useful for the diagnosis of liver tumors, particularly with characteristic findings. If the lesion shows peripheral halo, mosaic pattern and lateral shadowing, these findings are indicative of HCC, but, in many cases, findings of grayscale US are not specific (fig. 1). In these cases, CEUS is helpful to make a correct diagnosis of HCC.

CE CT or MR has been widely used for the diagnosis, differential diagnosis, anatomic mapping and treatment monitoring of malignant liver tumors. Likewise, US needs contrast agents for the diagnosis, differential diagnosis, anatomic mapping and treatment monitoring of liver cancers. US contrast agents are gas-filled microbubbles with an acoustic impedance different from the blood and relatively permeable shell. These microbubbles are smaller than 7 μm, remain within the vascular compartment, cross the capillary beds and survive the passage through the cardiopulmonary circulation. The microbubbles cannot move through the vascular endothelium into the interstitium; therefore, they are true blood pool agents [13].

A variety of microbubble-based contrast agents are now available for clinical use in many European, Asian, and South American countries as well as Canada [13]. Among commonly used contrast agents, Levovist (Schering AG, Berlin, Germany) is a first-generation contrast agent, but is not commercially available. SonoVue (Bracco Imaging, Milan, Italy), Definity (Lantheus Medical Imaging, Boston, Mass., USA), and Sonazoid (Daiichi Sankyo, Tokyo, Japan) are second-generation contrast agents. The first-generation contrast agent is useful for high mechanical index imaging and the second-generation contrast agent is useful for low mechanical index imaging and vascularity assessment.

Microbubbles work by resonating in a US beam, rapidly contracting and expanding in resonance to the pres-

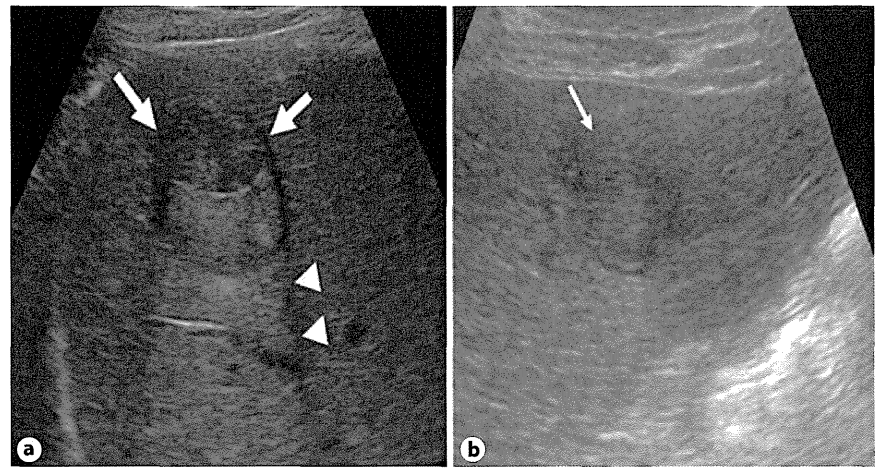


Fig. 1. Grayscale US for HCC. **a** A round mass (two arrows) shows peripheral halo, mosaic pattern and lateral shadowing (arrowheads). These characteristic findings are indicative of HCC. **b** Findings of grayscale US are, however, not specific. An ovoid mass (arrow) shows low echo without characteristic findings of HCC.

sure changes of the sound wave. If the transmitted acoustic pressure is weak, microbubbles are vibrating symmetrically and there is a conventional linear response, but, if the transmitted acoustic pressure is strong, microbubbles are vibrating asymmetrically, and there is a harmonic nonlinear response. The right dose of contrast agent for a bolus injection depends on the US device, the contrast imaging mode, the individual scanning conditions, and clinical indications. Typically, a bolus of 1.2–2.4 ml of SonoVue is injected manually through a three-way stopcock, followed by a 10-ml saline flush. The microbubbles gradually disappear as the gas diffuses through the thin shell, with a typical half-life of a few minutes in blood. The first injection usually includes a stationary field of view to include the lesion of interest and adjacent liver, both observed continuously for 4–5 min. CEUS using microbubble contrast agents has expanded the role of US in the diagnosis of liver nodules in patients at high risk of HCC [1, 14].

Presently the evaluation of the blood supply in a hepatocellular nodule is the most important imaging parameter to characterize various nodules in liver cirrhosis, because there are sequential changes in the supplying vessels and hemodynamic state during hepatocarcinogenesis [15]. Advanced HCCs are typically supplied by abnormal arteries alone, whereas regenerative nodules usually contain normal hepatic arteries and portal veins within the lesion. As dysplastic nodules have more histological atypia and malignant changes, abnormal arterial supply increases and normal arterial and portal supply decreases. Early HCCs or well-differentiated HCCs have variable degrees of arterial and portal venous supply making the diagnosis difficult [16]. Therefore, the diagnosis of HCC with CEUS, CT or MR is based on the enhancing pattern according to the time sequence or phase after injection of contrast media including the hepatic arterial phase (HAP), the portal venous phase (PVP), and the equilibrium phase. Classic HCCs are supplied by abnormal arteries alone and show positive enhancement (hypervascularity) during the HAP and negative enhancement (washout) during the PVP or equilibrium phase (fig. 2). Detection of hypervascularity in HAP is crucial to make a diagnosis of HCC as it is one of the most reliable characteristics of HCC. However, there is a small subset of HCC with no hypervascularity, including particularly those that are well differentiated [1, 17]. Negative enhancement or 'washout' during the PVP is also an important characteristic of HCC as typical tumors lack a portal venous supply. Washout of HCC in the PVP, however, is often not obvious until late (>90 s) and is generally slower and milder than that of liver metastasis [18]. Benign nodules such as regenerative nodules or dysplastic nodules are usually isoechoic or slightly hypoechoic in the HAP and PVP. However, there are occasional cases with overlap of imaging features between benign and malignant nodules, including hypovascular HCC and hypervascular HCC without washout. CEUS is helpful to characterize potential mimickers of HCC on imaging such as nontumorous arterioportal shunt or hemangioma. CEUS is also useful for a guidance of percutaneous local therapy of HCC and postprocedure monitoring of therapeutic response. CEUS can be effectively used in the diagnostic algorithm of small newly detected nodules during HCC surveillance [1].

A second-generation sonographic contrast agent, Sonazoid (Daiichi Sankyo), which consists of microbubbles

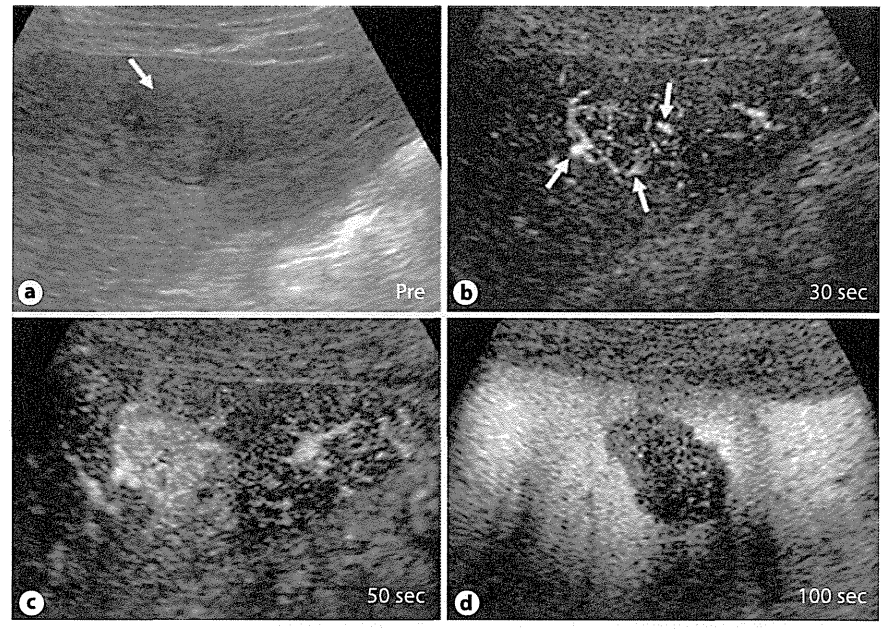


Fig. 2. CEUS for HCC. **a** Grayscale US shows well-defined mass (arrow) with hypoechoic halo. **b** Hepatic arterial phase image (30 s after injection of microbubbles) shows hypervascular mass with neovascularity (three arrows). **c** Portal venous phase image (50 s) shows high echo mass with rapid washin pattern. **d** Delayed phase image (100 s) shows rapid washout pattern, suggesting HCC.

of perfluorobutane gas with phospholipid monolayer shells (a median diameter of 2–3 μm), has been available in Japan since 2007 [19–22]. Sonazoid has been shown to be phagocytosed by reticuloendothelial cells in the liver, i.e. Kupffer cells, 5 min to at least 2 h after administration [23]. Accordingly, a persistent and very stable enhancement of the liver parenchyma can be obtained in the low-power acoustic field (a low mechanical index of 0.2–0.3), which minimizes the destruction of the microbubbles, in the postvascular phase (Kupffer phase). In the postvascular phase, hepatic lesions that contain few or no Kupffer cells are depicted as a clear perfusion defect (fig. 3). Sonazoid also allows a real-time fine vascular image of hepatic tumors in the vascular phase, being very sensitive to detecting an early stain of HCC (fig. 3, 4).

The detection of focal liver lesions by Sonazoid-enhanced US has been reported to be better than that of MDCT (fig. 4) [19]. Sonazoid-enhanced US is also useful for the characterization of hepatic tumors including HCCs (fig. 3), metastatic liver tumors, hemangiomas and focal nodular hyperplasias (fig. 5) [19, 20]. Moreover, stable Kupffer phase imaging can be used for the surveillance of HCC in cirrhotic patients. Kudo et al. [21] developed the technique of defect reperfusion imaging by using the properties of Kupffer phase images and real-time fine blood flow images of Sonazoid-enhanced US for the diagnosis of a hypervascular HCC which cannot be detected by B-mode US (fig. 6). This novel dual-phase fu-

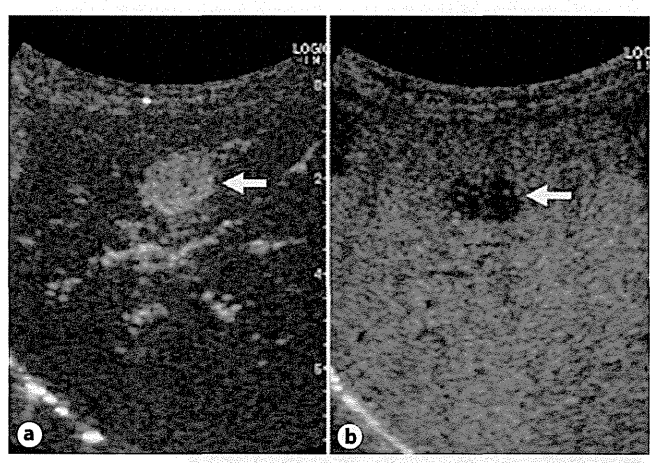


Fig. 3. Sonazoid-enhanced US image of a typical hypervascular HCC vascular phase (**a**) and a postvascular phase (Kupffer phase) (**b**). **a** In the vascular phase of Sonazoid-enhanced US using the amplitude modulation mode, clear early enhancement (arrow) of the tumor can be seen. **b** The Kupffer phase image of Sonazoid-enhanced US was obtained at 30 min after intravenous injection of Sonazoid, by scanning the tumor at a high mechanical index (0.7–1.0) which destroys microbubbles within and around it. The Kupffer phase image shows a very clear perfusion defect (arrow), indicating a lack of Kupffer cells in the tumor.

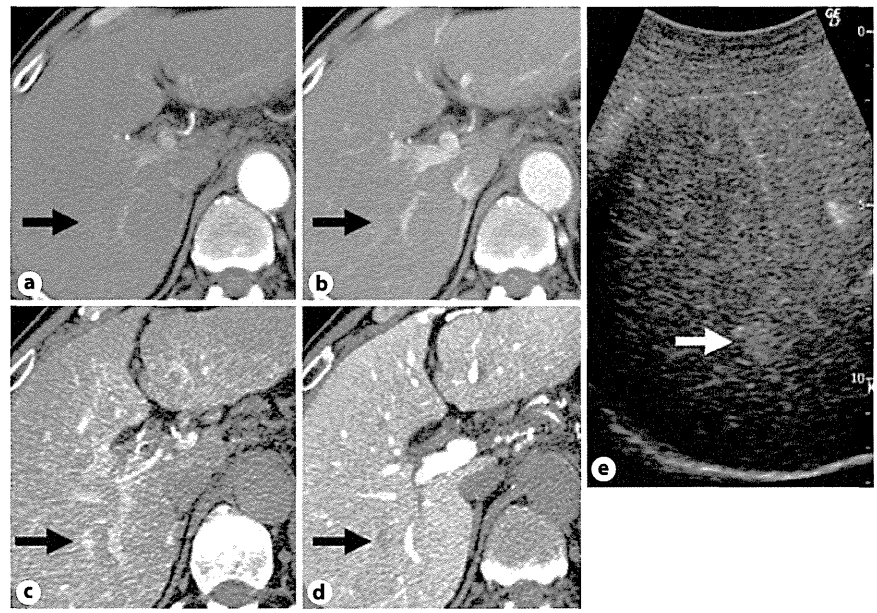


Fig. 4. A small hypervascular HCC: arterial phase of MDCT (**a**), PVP of MDCT (**b**), CTHA (**c**), CTAP (**d**) and vascular phase of Sonazoid-enhanced US (**e**). Arrows show HCC. A small early stain and a perfusion defect of HCC are seen on CTHA (**c**) and on CTAP (**d**), respectively. While MDCT could not detect the tumor at all, Sonazoid-enhanced US clearly shows early enhancement (**e**).

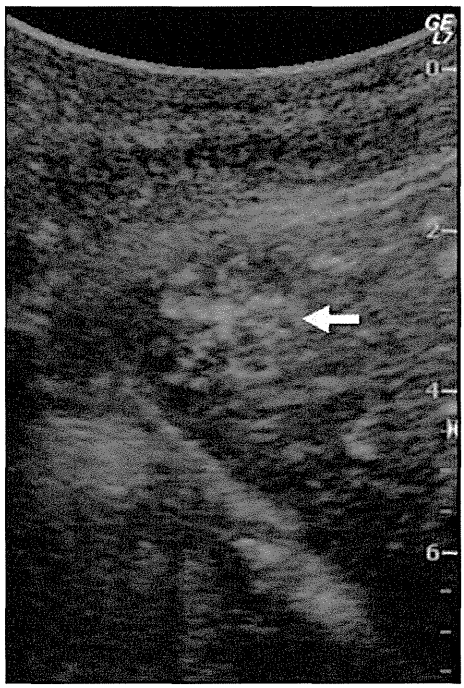


Fig. 5. Sonazoid-enhanced US image of a focal nodular hyperplasia. The vascular phase reveals a typical spoke-wheel pattern (arrow).

sion imaging is also utilized for the guidance of needle insertion in ablative therapy and for the evaluation of the ablation area [22].

The Volume Navigation system of the LOGIQ E9 (GE Healthcare, Milwaukee, Wisc., USA), an ultrasound fusion imaging [24], has recently been developed. To work the Volume Navigation system, the transmitter generating a magnetic field, two sensors for the probe and the other sensor unit in the US console are needed. The CT or MRI volume DICOM data are loaded onto the US through the navigation network and processed by the image fusion software. The ultrasound and CT/MRI cross-sectional images are coregistered through a 3-point registration procedure. Then, the side-by-side or fusion images of US and CT/MRI begin to synchronize. This ultrasound fusion imaging technology has many advantages in the diagnosis and treatment of HCC. Lesions which are seen on CT/MRI but not on B-mode US can be identified by the Volume Navigation system. Recently, we have encountered hypovascular nodules showing hypointensity on the hepatocyte phase of Gd-EOB-DTPA-enhanced MRI in the cirrhotic liver, which are often invisible on B-mode US. A successful core needle biopsy leading to a diagnosis of HCC of such a nodule under the Volume Navigation system is presented in figure 7. The ultrasound fusion imaging is also useful for the guidance of needle insertion during radiofrequency ablation, providing accurate targeting with safety [24].

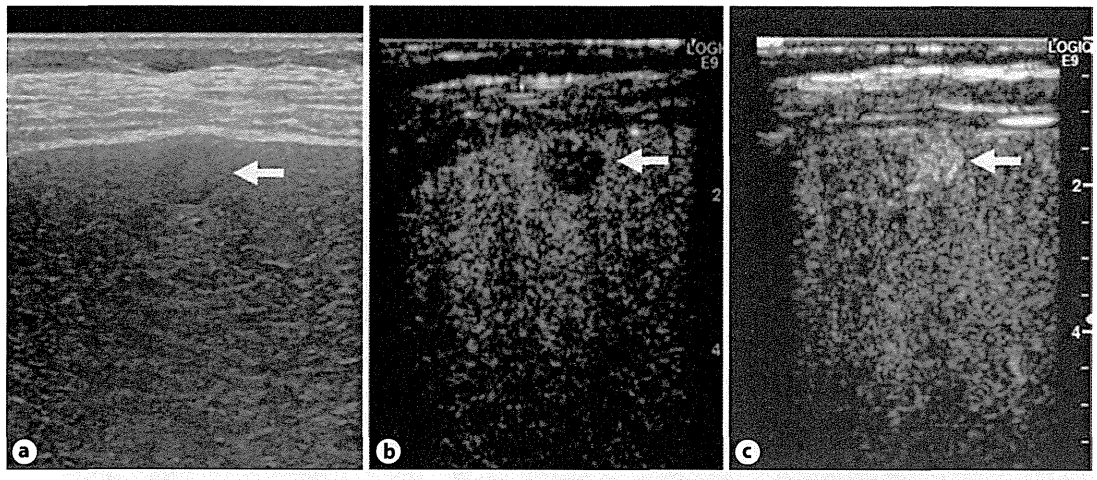


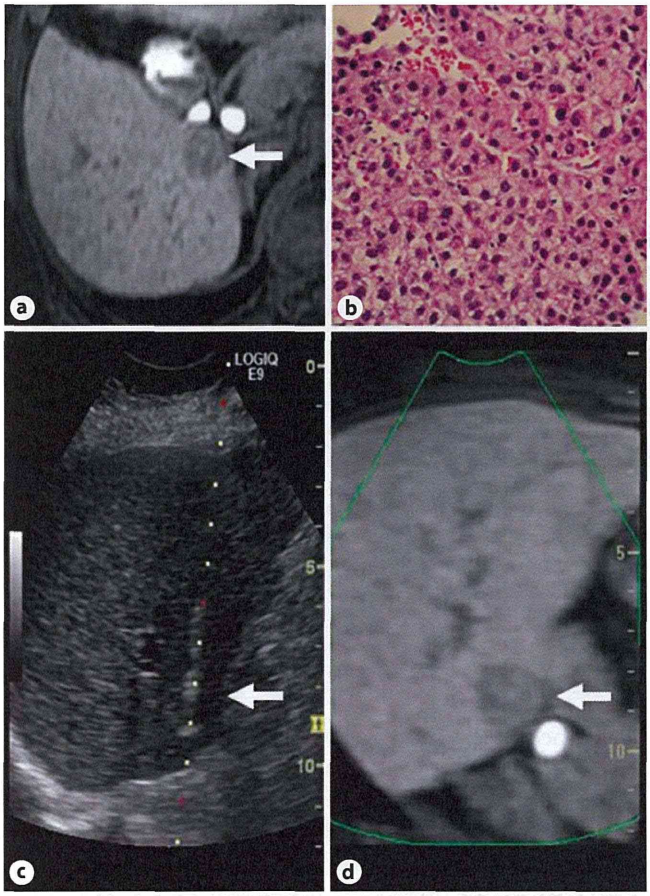
Fig. 6. The dual-phase fusion imaging of Sonazoid-enhanced US of a small hypervascular HCC located in the liver surface: B-mode US (**a**), post-vascular phase (Kupffer phase) (**b**), and arterial enhancement of the tumor after reinjection of Sonazoid (**c**). **a** In this case, it is difficult to detect the tumor (arrow) by B-mode US. **b** In the Kupffer phase, the tumor becomes detectable as a clear hypoechoic nodule (arrow). Reinjection of Sonazoid shows a clear early enhancement (**c**; arrow), resulting in the diagnosis of HCC.

CT Imaging

Dynamic MDCT with a bolus injection of contrast medium is essential for diagnosis of liver tumor [2, 5]. In MDCT, progressively higher spatial and temporal resolutions have been achieved by increasing gantry rotation speed and the number of detector rows. The developed technology of MDCT has brought more precise evaluation of hemodynamics of liver tumor, and diagnostic accuracy has improved.

On dynamic MDCT for the liver, the arterial, portal venous, and equilibrium phase images are usually obtained. The arterial phase imaging is useful to detect hypervascular HCC. The portal venous and equilibrium phase imaging are useful for the differential diagnosis of HCC, because the washout of contrast medium from the tumor in these phases is a typical finding of hypervascular HCC (fig. 8). However, arterial parenchyma enhancement due to arterioportal venous (AP) shunt may become a false-positive lesion on dynamic MDCT that evaluates hemodynamics of liver tumor, and it may sometimes reduce specificity. The washout pattern is useful to distinguish nontumorous AP shunt from hypervascular HCC. Both show focal arterial enhancement, but the corresponding washout in the portal and equilibrium phases indicates HCC. However, the differentiation is sometimes difficult because some HCCs do not demonstrate washout. Scanning through the upper abdomen can be performed in less than 3 s by MDCT scanners with more than 64 channels, even though a spatial resolution of 0.6 mm is employed for both longitudinal and short axis of the body (transverse slice thickness), so-called isotropic voxel volume imaging. From the isotropic voxel imaging data, high quality 3D images can be reconstructed by using multiplanar reconstruction, volume rendering and maximum intensity projection techniques (fig. 9). These 3D images are useful for preoperative anatomical evaluation for surgeons and preoperative explanations for patients [3].

MDCT can be used not only to image anatomical structures, but also to analyze liver function. As an example, perfusion CT is performed by the acquisition of serial images of the same slice level after a bolus administration of 30–40 ml of iodinated contrast medium, enabling detailed analysis of liver hemodynamics [25, 26]. The perfusion parameters coming from CT perfusion data are as follows: tissue blood flow (ml/min/100 g), tissue blood volume (ml/100 g), mean transit time (s), which is the average time for blood elements to traverse the vasculature from an arterial inlet to a venous outlet (proportional to perfusion pressure), and hepatic arterial fraction (%), which is the ratio of arterial perfusion to total liver perfusion (fig. 10). Thus, the analysis of the microcirculation by perfusion CT can be useful in the clinical situation including evaluation of treatment response. Perfusion CT can be used for detection of tumor angiogenesis and in



Color version available online

Fig. 7. Core needle biopsy of a hypovascular well-differentiated HCC, which was undetectable by B-mode US, under the Volume Navigation system using hepatocyte phase image of Gd-EOB-DTPA-enhanced MRI as a reference. **a** Hepatocyte phase of Gd-EOB-DTPA-enhanced MRI. **b** HE staining. **c** B-mode US image, Volume Navigation system. **d** Multiplanar reconstruction image of hepatocyte phase of Gd-EOB-DTPA-enhanced MRI. **a**, **d** A tumor with a diameter of 19 mm (arrow) is detected by the hepatocyte phase of Gd-EOB-DTPA-enhanced MRI. However, it is not detectable by B-mode US (**c**; arrow), Sonazoid-enhanced US or MDCT. A 21-gauge needle biopsy of the tumor could be performed under the Volume Navigation system using a Gd-EOB-DTPA-enhanced image as a reference (**c**, **d**). The histological diagnosis of the tumor was a well-differentiated HCC. Radiofrequency ablation therapy was also conducted under the Volume Navigation system.

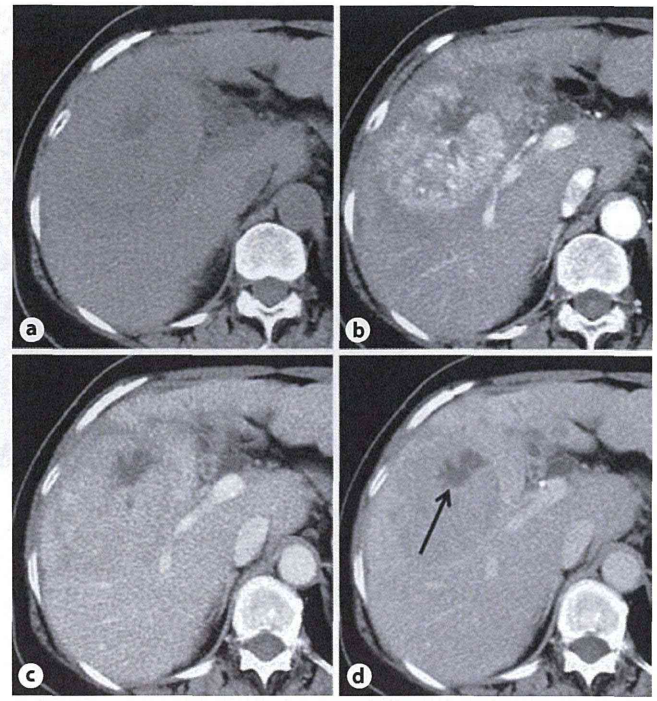
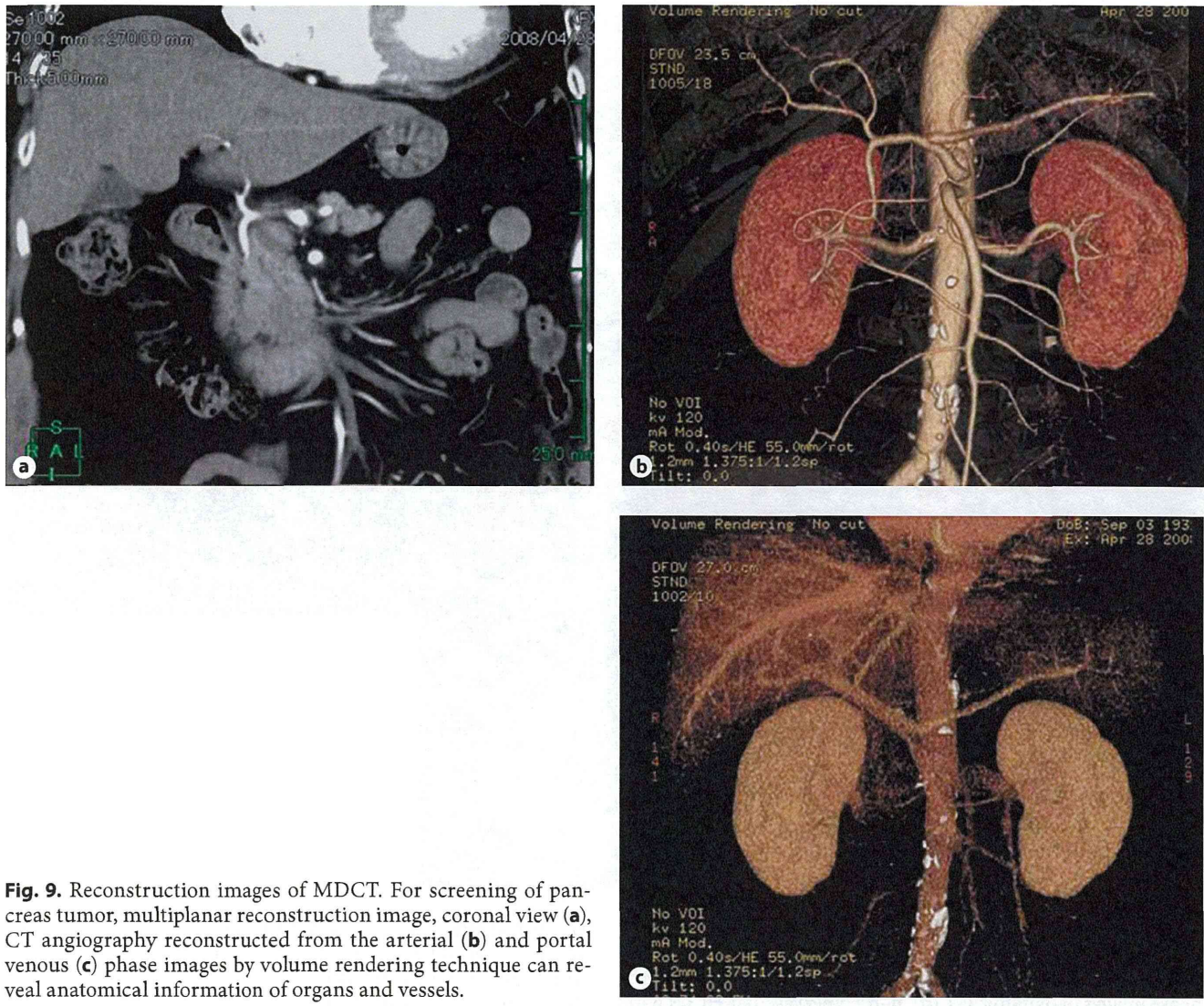


Fig. 8. Dynamic MDCT of the liver. Hypervascular HCC in chronic hepatitis C. The lesion shows hypoattenuation in the precontrast (**a**), hyperenhancement relative to the liver parenchyma in the arterial phase (**b**), and iso- or hypoattenuation due to washout of contrast medium in the portal venous (**c**) and equilibrium phases (**d**). **d** Capusular enhancement can also be seen. These are characteristic enhancement patterns of hypervascular HCC. Nonenhanced region within the tumor indicates necrosis (arrow).

assessing response to antiangiogenic treatment for various cancers [27, 28]. Regarding liver imaging, the greatest impact of perfusion CT has been shown in the assessment of patients with HCC, especially that of tumor response to antiangiogenic drugs, such as sorafenib (Nexavar, Bayer Schering Pharma AG, Berlin, Germany) [29, 30].

The volume helical shuttle (VHS) scan technique that we have developed with GE Healthcare can provide almost real-time hemodynamic change by shuttling the CT scanning cradle back and forth during scanning, and also enables wider coverage for complete organ imaging: >120 mm longitudinally [31]. The VHS has the potential for use in 4D imaging, that is producing a movie-like image with wide volume coverage. With VHS, the liver is repeatedly scanned in axial acquisitions, thereby providing coverage of the whole liver with reciprocating movement. Hypervascular HCC can be analyzed by using several whole liver scans, such as 12 phases in the arterial phase of dynamic CT (fig. 11). Blood flow information, such as a blood flow direction, can also be obtained by VHS scanning. The VHS technique can be used for perfusion studies of the liver and for 4D CT angiography. Liver perfusion CT has generally been performed for a single section [4, 32, 33]. However, the high temporal resolution of VHS



Color version available online

Fig. 9. Reconstruction images of MDCT. For screening of pancreas tumor, multiplanar reconstruction image, coronal view (**a**), CT angiography reconstructed from the arterial (**b**) and portal venous (**c**) phase images by volume rendering technique can reveal anatomical information of organs and vessels.

scanning enables whole liver perfusion imaging with multisections.

Perfusion CT and 4D imaging with VHS technique have the major drawback of radiation exposure, but Adaptive Statistical Iterative Reconstruction (ASiR; GE Healthcare) provides similar quality at a lower dose compared with the usual filtered back-projection algorithm. If ASiR is used at the same dose, better image quality is obtained than that using the back-projection algorithm [31].

Dual-energy CT is a promising technique used to obtain material-specific images. It enables differentiation of materials and tissues in images obtained based on the differences in iodine and water densities; the resulting CT images are reconstructed using two different energy spectra [34]. Iodine contrast agents are more conspicuous at low-voltage X-rays (such as 80 kVp) than at high tube voltage (120–140 kVp) settings [35, 36], but may result in high image noise, particularly in large patients [37]. Post-processing algorithms enable subtraction of iodine maps from dual-energy CT data (e.g. subtraction of calcification) to create a virtual noncontrast image. Moreover, monochromatic images can be reconstructed by dual-energy reconstruction. Monochromatic images provide some improvement in contrast. CT images at 80 kVp or the equivalent 55 keV (kiloelectron voltage) monochro-

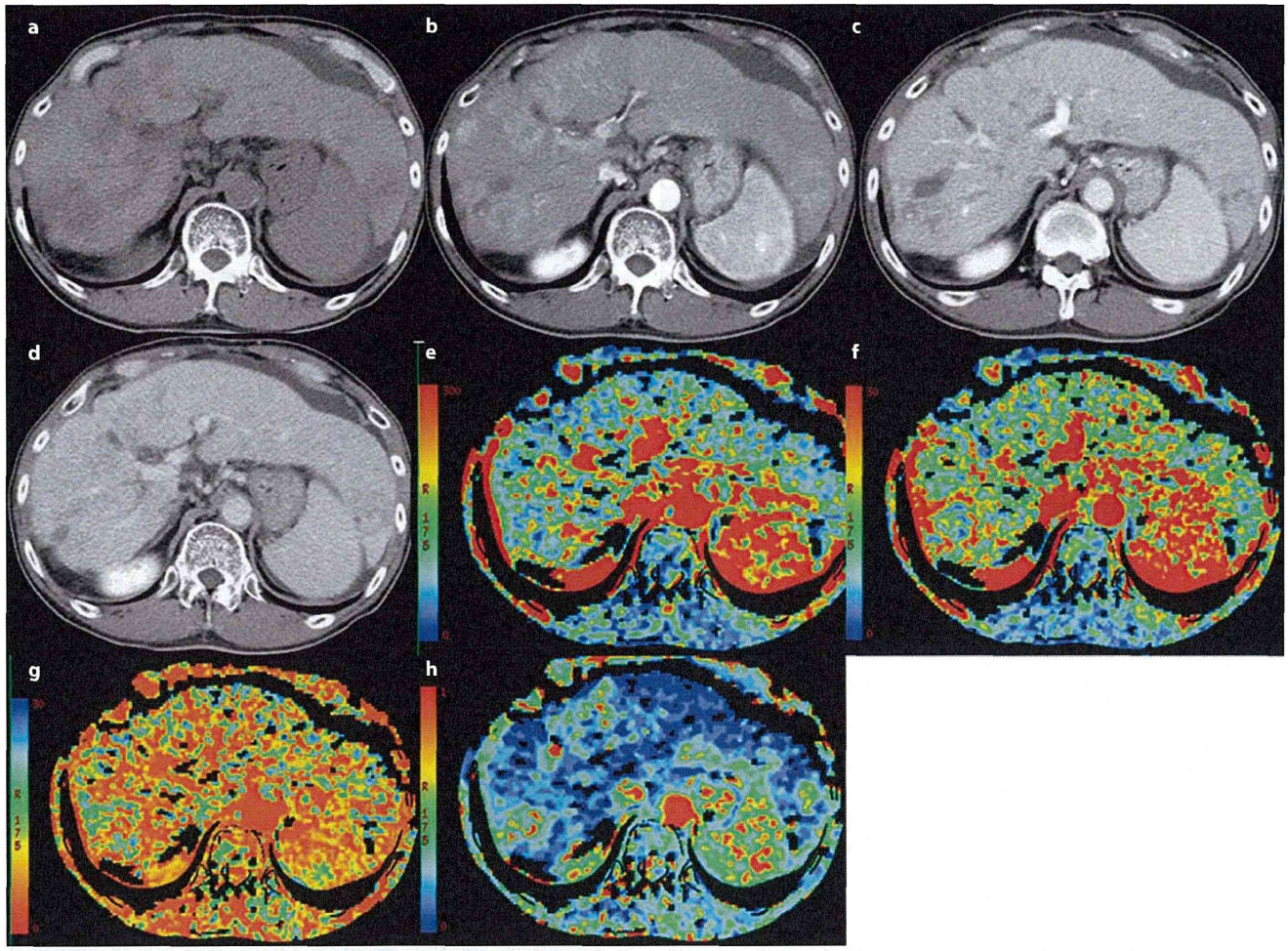


Fig. 10. Perfusion CT of HCC. Premolecular targeting chemotherapy for HCCs in the lateral segment, segment 4 and 6: precontrast (**a**), arterial phase (**b**), portal venous (**c**), and equilibrium phase images of dynamic CT (**d**). **b–d** Hypervascular HCCs with a necrotic region in the tumor can be seen. Perfusion parameters, such as hepatic blood flow (HBF) (**e**), hepatic blood volume (HBV) (**f**), mean transit time (**g**), and hepatic arterial fraction (**h**), can be shown as color mapping images. Liver perfusion parameters of each segment can be evaluated, e.g. HBF of HCC is 92 ml/min/100 g, HBV 18 ml/min/100 g, mean transit time 12.9 s, and hepatic arterial fraction 0.39 (39%).

matic images may show a higher contrast-to-noise ratio for hypervascular HCCs [38]. Pure 80 kVp data acquired from a dual-energy CT scanner produce greater differences in attenuation between hepatic lesions and surrounding liver, and potentially improve the assessment and detection of liver tumors [31], especially of hypervascular liver tumors during the arterial phase. More importantly, dual-energy CT is more effective in reducing radiation dose than single-energy CT. This advantage can be explained by the fact that the radiation dose is significantly reduced when CT images are obtained using 80 kVP as compared with 140 kVp [39].

Magnetic Resonance Imaging

As MDCT imaging, dynamic MRI is also useful for liver imaging. The nonspecific contrast medium Gd-DTPA has been widely used in dynamic MRI. Our data revealed that there was no significant difference between dynamic MDCT and dynamic MRI in detecting sensitivity of hypervascular HCC [5]. We should choose imaging modalities in consideration of cost and radiation exposure, especially for the follow-up study of HCC.

As a liver-specific contrast agent, superparamagnetic iron oxide (SPIO) has for many years been used as a fur-

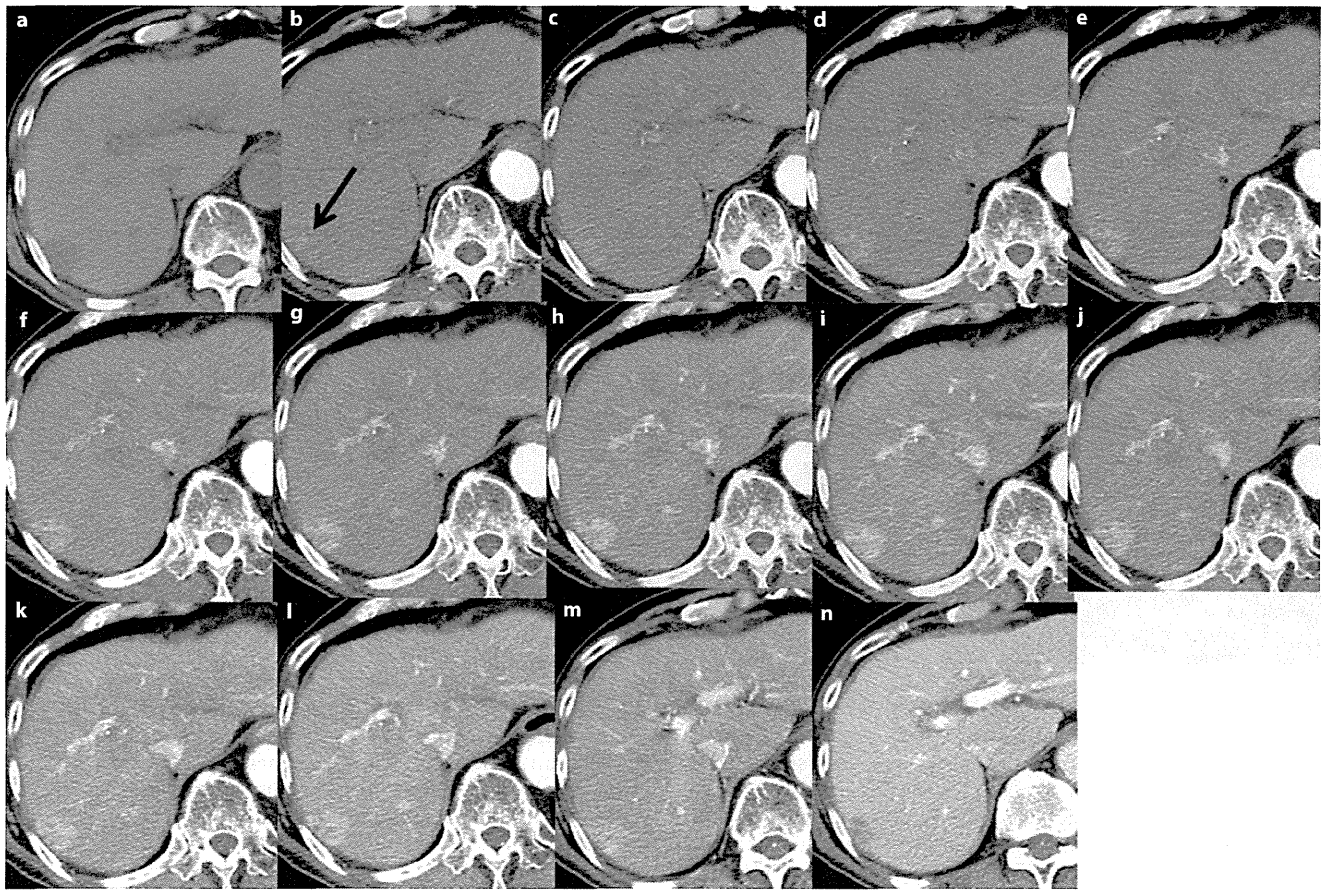


Fig. 11. Hemodynamics of HCC in the arterial phase evaluated by VHS scanning. Hypervascular HCC in liver segment 7: precontrast (**a**), the first arterial (**b**), second (**c**), third (**d**), fourth (**e**), fifth (**f**), sixth (**g**), seventh (**h**), eighth (**i**), ninth (**j**), tenth (**k**), eleventh (**l**), twelfth arterial phase (**m**), and PVP (**n**). Scan time of each phase is 2 s. HCC starts to be enhanced from the first phase (**b**; arrow), and the enhancement gradually increases in the late phases. Maximum tumor to liver contrast can be seen in the eighth phase.

ther workup of liver diseases. It can be injected intravenously as a bolus for imaging HCC [40]. SPIO acts as a negative contrast agent because SPIO particles are taken up by Kupffer cells in the reticuloendothelial system of the liver [41, 42], causing a local magnetic field inhomogeneity and resulting in considerable T2* shortening [42]. SPIO-enhanced MR is reported to be sensitive in detecting HCC [43–45]. SPIO-enhanced MR showed higher sensitivity especially in detecting small hypervascular HCC of less than 10 mm in diameter [4].

As mentioned before, arterial parenchymal enhancement due to AP shunt may become a false-positive lesion in the investigation of HCC on dynamic MDCT. In particular, certain HCCs, which do not show the washout of contrast medium in the portal or equilibrium phase, can be hard to diagnose. However, when SPIO is taken up by the region, it can be diagnosed as AP shunt.

It was reported that the combination of dynamic MDCT and SPIO-enhanced MRI could show the same diagnostic accuracy of hypervascular HCC as CTHA and CTAP, though the detection sensitivity of small HCC of less than 15 mm in diameter was higher in CTHA and CTAP [46, 47]. Moreover, the combination of dynamic MRI and SPIO-enhanced MRI was also reported to show the same diagnostic accuracy as CTHA and CTAP [48].

Gd-EOB-DTPA is another liver-specific contrast agent. Because Gd-EOB-DTPA acts as both an extracellular and hepatocyte-specific contrast agent, we can evaluate the hemodynamics of liver tumor [49] by dynamic