Quadruple-Phase MDCT of the Liver in Patients with Suspected Hepatocellular Carcinoma: Effect of Contrast Material Flow Rate

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OBJECTIVE. The purposes of this study were to evaluate the effect of contrast material flow rate (3 mL/sec vs 5 mL/sec) on the detection and visualization of hepatocellular carcinoma (HCC) with MDCT and the safety profile of iodixanol at different injection rates.

SUBJECTS AND METHODS. In a prospective, randomized multicenter trial, 97 patients (83 men and 14 women, with a mean age of 64 years) suspected of having HCC underwent quadruple-phase (double arterial, portal venous, delayed phase) 4- 16-MDCT. Patients were randomized to receive iodixanol, 320 mg I/mL (1.5 mL/kg body weight), at a flow rate of 3 mL/sec (48 patients) or 5 mL/sec (49 patients). Qualitative (lesion detection, image quality) and quantitative (liver and aortic enhancement, tumor–liver contrast) analyses and safety assessment were performed.

RESULTS. Overall, 145 HCCs were detected in the 5 mL/sec group and 100 HCCs in the 3 mL/sec group ($p < 0.05$). More lesions equal to or less than 1 cm were detected at 5 mL/sec (33 vs 16 lesions). The late arterial phase showed significantly more lesions than the early, arterial phase (133 vs 100 and 96 vs 67 lesions, respectively, $p < 0.0001$). Hyperattenuating HCCs were better visualized in the late arterial phase at 5 mL/sec (excellent visualization: 54% vs 27%). Using a flow of 5 mL/sec did not increase the rate of patient discomfort or contrast media–related adverse events. Most discomfort in both groups was of mild intensity and there was no severe discomfort.

CONCLUSION. For detection of HCC with MDCT, a higher flow rate of 5 mL/sec is recommended. Visualization of hyperattenuating HCC is improved with no greater discomfort or adverse events.

Contrast-enhanced CT plays a major role in the detection and characterization of hepatocellular carcinoma (HCC) in patients with chronic liver disease. HCC lesions are usually hypervascular tumors and are therefore best seen in the arterial phase CT scan in most patients [1–6]. Liver enhancement and detection of HCC during contrast-enhanced CT depend on several patient-dependent factors including cardiac output, body weight, and the vascularity of HCC [7, 8]. There are other technology-dependent factors, which can be controlled during CT, such as the scanning technique and the contrast injection protocol. The effects of contrast material dose, flow rate, iodine concentration of contrast material, and timing have been well studied in helical CT [2, 9, 10]. The development of MDCT has dramatically accelerated scan acquisition in liver CT [11]. With MDCT, high-speed volume coverage of the entire liver in 4–10 sec is possible, which allows the acquisition of two separate scans in the arterial phase, termed early arterial and late arterial phase scans [12–15]. There are, however, few reports about appropriate contrast material injection protocols for MDCT of the liver [16–18].

This study investigates the effect of contrast material flow rate on the detection and visualization of HCC with MDCT to determine the value of quadruple-phase CT studies, which include a double arterial phase scan, and to assess the safety profile of an isoosmolar contrast material at different injection rates.

Subjects and Methods

Patients

Between February and November 2003, 124 patients with suspected HCC, who were referred for an MDCT study of the liver, were included in this prospective, parallel group multicenter trial conducted in 11 centers in six European countries. Patients were randomly assigned to one of two MDCT proto-

cols in which iodixanol (320 mg I/mL) was administered at an injection rate of 3 mL/sec or 5 mL/sec.

Patients were considered eligible for the study if they were older than 18 years and were referred for a CT examination of the liver because of a high suspicion of HCC based on clinical criteria (e.g., chronic hepatitis B or C, liver cirrhosis, increased α-fetoprotein level [> 20 ng/mL]) and/or imaging findings (e.g., sonography, MRI, or CT). Criteria for exclusion were pregnancy, lactation, administration of an iodinated contrast medium within the previous 72 hr, history of allergy to iodixanol, manifest thyrotoxicosis, noncompensated cardiac insufficiency, or previous embolization or ablation procedure of a liver lesion. Approval of the ethical committee of each participating institution was obtained, and written informed consent was obtained from each patient before inclusion in the study. The study was conducted in full accordance with the current version of the Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice. The 124 patients enrolled in the study were dosed with the contrast agent, thus representing the safety population of the trial. The efficacy analysis included all patients with a radiologic diagnosis of HCC, confirmation of HCC, and absence of major protocol violations.

In three of 124 patients, no efficacy assessments were available. Eight patients showed no lesions at CT. In nine patients, lesions other than HCC were found at CT. In four patients, the radiologic diagnosis of HCC was not confirmed by the institutional diagnosis (metastasis from melanoma, adenoma, multifocal steatosis, or regenerative nodule). Major protocol violations (incomplete or missing scans) were observed in three patients. Thus, 97 patients (48 receiving 3 mL/sec and 49 receiving 5 mL/sec) were considered eligible for the per-protocol efficacy analysis. Both groups were comparable regarding demographic and baseline liver disease characteristics (Table 1).

Proof of Tumor Burden

Of the 97 positive patients, histopathologic proof of HCC was obtained in 46 patients by liver resection ($n = 7$) or percutaneous needle biopsy ($n = 39$). Patients with multiple lesions were presumed to have multifocal HCC when the other lesions had the same imaging appearance on multiphasic CT as the biopsy-proven lesion. In 51 patients for whom biopsy was not performed, diagnosis of HCC was established using either a combination of clinical and radiologic criteria according to the consensus of the European Association for the Study of the Liver (EASL) [19], including elevated α-fetoprotein (> 400 ng/mL) and confirmatory imaging studies by one or more additional techniques (gadolinium-enhanced or iron oxide–particle-enhanced MRI, digital subtraction angiography, and CT) within 1 month ($n = 33$), response to transcatheter arterial chemoembolization ($n = 6$), or interval growth at follow-up cross-section imaging (CT or MRI) for a minimum of 6 months ($n = 12$).

Injection Procedure and MDCT Examination

Each patient was randomly assigned to receive the isoosmolar, dimeric contrast medium iodixanol 320 mg I/mL (Visipaque, Amersham Health [trading as GE Healthcare]) at an injection rate of either 3 mL/sec or 5 mL/sec. Before administration, the contrast medium was preheated to 37°C. The volume of contrast medium delivered was 1.5 mL/kg body weight. Using double syringe power injectors (EnVision CT, Medrad, $n = 6$; Injektron CT2, Medtron, $n = 2$; Stellant Dual, Medrad, $n = 1$; CT 9000 ADV/OptiStat, Mallinckrodt, $n = 1$; Missouri, ulrich medical, $n = 1$), a saline flush of 40 mL followed the contrast medium injection, using the same injection rate as for the contrast agent.

In all participating centers, MDCT scanners were used. A four-row scanner was used in three centers (Somatom Volume Zoom, Siemens Medical Solutions; LightSpeed Plus, GE Healthcare), an eight-row scanner in one center (LightSpeed Ultra, GE Healthcare), and a 16-row scanner in seven centers (Sensation 16, Siemens Medical Solutions; LightSpeed 16, GE Healthcare). The CT scanner detector configuration was 4×2.5 mm, 8×1.25, 16×0.75, or 16×0.625 mm. The tube voltage applied throughout all CT studies was 120 kVp. The tube current was adjusted according to patient characteristics (mean, 235 mA; range, 102–440 mA). In all centers, axial images were reconstructed at an effective slice thickness of 2.5–3.0 mm, with a reconstruction interval of 1.5–2 mm.

Quadruple-phase CT consisted of early arterial, late arterial, portal venous, and delayed phase imaging. Scanning during each imaging phase was performed in the craniocaudal direction during a single breath-hold at deep inspiration. The injection-to-scan delay for early arterial phase imaging was determined by a test bolus injection in 29 patients and with automatic bolus tracking in 68 patients. Before the start of contrast material administration, a single scan was obtained at the level of the porta hepatis as a baseline reference for contrast enhancement measurements in the aorta, portal vein, and liver parenchyma. The mean injection-to-scan delay for early arterial phase imaging was 25.5 sec (range, 18–45 sec) for the 3 mL/sec group and 22.5 sec (range, 16–45 sec) for the 5 mL/sec group. In all centers, the timing of the contrast-enhanced CT scans was uniformly defined: Late arterial phase imaging started 16 sec after initiation of early arterial phase scanning. Portal venous phase imaging was initiated 50 sec after the start of the early arterial phase. Delayed phase images were obtained at a fixed delay of 300 sec after the start of contrast medium injection.

Qualitative Assessments

All studies were transferred to workstations where interpretation took place. All images were evaluated in soft-tissue window settings and liver window settings, and window width and level settings were set according to the routine of each individual center. However, within one center window width and level, settings were kept constant. The CT images were visually evaluated by two on-site radiologists. If consensus could not be reached between them, disagreement was resolved by majority opinion involving a third radiologist.

TABLE 1: Demographic and Baseline Characteristics in Both Study Groups

	3 mL/sec ($n = 48$)	5 mL/sec ($n = 49$)
Demographic data[a]		
Sex (men/women)	39/9	44/5
Age (years), mean ± SD	63.8 ± 10.7	64.8 ± 11.0
Weight (kg), mean ± SD	75.7 ± 14.8	76.8 ± 14.9
BMI (kg/m2), mean ± SD	26.7 ± 4.9	26.4 ± 3.9
Baseline liver disease characteristics[a]		
Liver cirrhosis (%)	71	71
Chronic hepatitis B (%)	10	14
Chronic hepatitis C (%)	40	47
Increased α-fetoprotein (%)	31	41
Iodixanol volume administered (ml)[a]	113.5 ± 22.2	115.4 ± 22.4

Note—BMI = body mass index.

[a]No significant difference was seen between the groups for any of the variables.

First, images from each phase were evaluated separately for the presence of lesions suspicious for HCC. The criteria for making the diagnosis of HCC were a nodular lesion with homogeneous or heterogeneous enhancement in the early or late arterial phase, with a decrease in attenuation in the venous and delayed phases; a nodule of low attenuation, which did not meet the criteria for a cyst or an area of confluent fibrosis; or a nodule with capsule enhancement in the delayed phase [20, 21].

Size, location (Couinaud classification for liver segments), and the typical contrast pattern of each suspicious HCC lesion compared with the adjacent hepatic parenchyma (i.e., hyperattenuation, hypoattenuation, mixed attenuation, or isoattenuation) were recorded. The maximum number of suspicious HCC lesions evaluated in each patient was limited to the six largest ones. In each imaging phase, visualization of lesions suspicious for HCC was assessed using a five-point scale: 5 = excellent, 4 = good, 3 = adequate, 2 = poor, and 1 = no visualization ("no visualization" was allocated retrospectively after review of all images). Second, images from the four contrast-enhanced phases were compared with each other, and lesions with a radiologic diagnosis of HCC were documented. For each of such designated lesions, the overall visualization was scored as follows: 4 = excellent, 3 = good, 2 = adequate, and 1 = poor. Detection sensitivity for HCC lesions in each imaging phase was defined as the percentage of HCC lesions visualized in the respective imaging phase.

The overall image quality of the contrast-enhanced CT examination was graded by the radiologists using the following criteria: 4 = excellent, 3 = good, 2 = sufficient, and 1 = insufficient.

Quantitative Assessments

Attenuation measurements were obtained in the aorta, portal vein, and hepatic parenchyma on a single unenhanced scan at the level of the hepatic hilum and on all contrast-enhanced imaging phases. Circular regions of interest (ROIs) were placed in the aorta at the level of the celiac trunk, in the mainstem of the portal vein, and in the liver at the level of the hilum. The ROI size was predefined to be at least 100 mm^2 for the portal vein and 150–200 mm^2 for the aorta and liver parenchyma. For each anatomic structure, ROIs identical in size and location were used throughout all contrast-enhanced imaging phases, so enhancement of the abdominal aorta, portal vein, and hepatic parenchyma could be calculated.

For quantitative determination of tumor–liver contrast, HCC lesions greater than 10 mm in diameter that were hyperattenuated during late arterial phase imaging were selected. Only the three largest nodules within a patient were used for the attenuation measurements. Circular ROIs were placed in the HCC lesion and the adjacent hepatic parenchyma. The tumor ROI was to be chosen as large as possible while still avoiding regions of rim enhancement, tumor capsule, necrosis, calcifications, and shunt vessels. Tumor–liver contrast was calculated with the formula [9–24]:

[tumor–liver contrast] = [attenuation of HCC] – [attenuation of adjacent liver parenchyma]

Safety Assessments

All patients were monitored for side effects and adverse events during the CT examination and over a period of 1 hr after the CT examination. All patients were checked again at 72 hr after contrast agent administration. Because the contrast agent has been on the market since 1993, no blood samples for clinical chemistry and hematology evaluations were drawn.

During contrast material administration, the presence or absence of contrast material extravasation was monitored clinically. Tolerance was evaluated by assessing the frequency and intensity of injection-associated discomfort and adverse events. Discomfort was defined as a transient and self-limiting sensation of pain, warmth/heat, cold, or pressure associated with the injection of the contrast medium. Intensity of discomfort and adverse events were graded as mild, moderate, or severe. All adverse events were recorded, regardless of whther they were considered probably drug-related or not by the investigators.

Statistical Methods

The sample size calculation for the primary end point, the overall visualization of HCC lesions, was based on a score difference of 0.4, assuming mean scores of 2.8 and 2.4 for the 5 mL/sec and 3 mL/sec groups, respectively. To ensure independence between the observations, the mean score for overall visualization per patient was applied in the testing. Presuming a mean of two HCC lesions per patient and taking into consideration a weak correlation of 0.2 between the visualization scores of HCC lesions within a patient, a distribution of visualization to seven categories was calculated. With a two-sided significance level of 5% and a power of 80%, at least 36 patients in each group were needed to reject the null hypothesis of no difference in the visualization score, using the Wilcoxon's rank sum test.

Comparisons of categoric variables between groups were performed using the Wilcoxon's rank sum test, the Fisher's exact test, or a chi-square test, whereas the McNemar test was applied to analysis of categoric variables within groups. Continuous variables were tested using the Student's *t* test. All statistical analyses were conducted at a significance level of 5% using SAS statistical software (SAS V 8.2, SAS Institute). Confidence intervals were calculated at a confidence level of 95%.

Results

Efficacy

A total of 145 HCC lesions were detected in the 5 mL/sec group (mean number of HCC, 2.1; range, 1–6), and 100 HCC lesions were reported in the 3 mL/sec group (mean number of HCC, 3.0; range, 1–6). The difference was statistically significant ($p < 0.05$). The mean size of lesions was 4.1 cm (range, 0.6–20 cm) in the 3 mL/sec group and 2.8 cm (range, 0.5–19 cm) in the 5 mL/sec group. More lesions with a diameter equal to or greater than 1 cm were seen with a flow rate of 5 mL/sec (33 vs 16), although the difference was not significant ($p = 0.067$). The frequencies of HCC lesions according to lesion size are depicted in Table 2.

TABLE 2: Distribution of HCC Lesions Grouped by Lesion Diameter

	3 mL/sec (*n* = 48)	5 mL/sec (*n* = 49)
Total number of HCC	100[a]	145[a]
HCC (%) grouped by diameter		
1 cm	16 (16)[b]	33 (23)[b]
1.1–2.0 cm	31 (31)	48 (33)
2.1–3.0 cm	14 (14)	25 (17)
3.1–6.0 cm	21 (21)	27 (19)
6.1–10.0 cm	9 (9)	6 (4)
> 10 cm	9 (9)	6 (4)

Note—HCC = hepatocellular carcinoma.

[a]Significantly more HCCs found per patient at a flow rate of 5 mL/sec ($p < 0.05$).

[b]Tendency toward more HCCs ≤ 1 cm found per patient at a flow rate of 5 mL/sec ($p = 0.067$).

Most HCC lesions were identified during the late arterial phase. Detection sensitivities were 96% and 92% for the 3 mL/sec group and 5 mL/sec group, respectively. Typically, lesions revealed a hyperattenuating enhancement pattern (53% at 3 mL/sec and 64% at 5 mL/sec). Mixed (38% at 3 mL/sec and 20% at 5 mL/sec) and hypoattenuating (9% at 3 mL/sec and 16% at 5 mL/sec) lesions were less frequently seen. Significantly more hyperattenuating lesions with excellent visualization were observed on late arterial phase images using the higher flow rate (54% vs 27%, $p < 0.01$) (Figs. 1 and 2). Similar values were found in both groups for detection sensitivities of early arterial and portal venous phase imaging. Detection rates for the early arterial phase

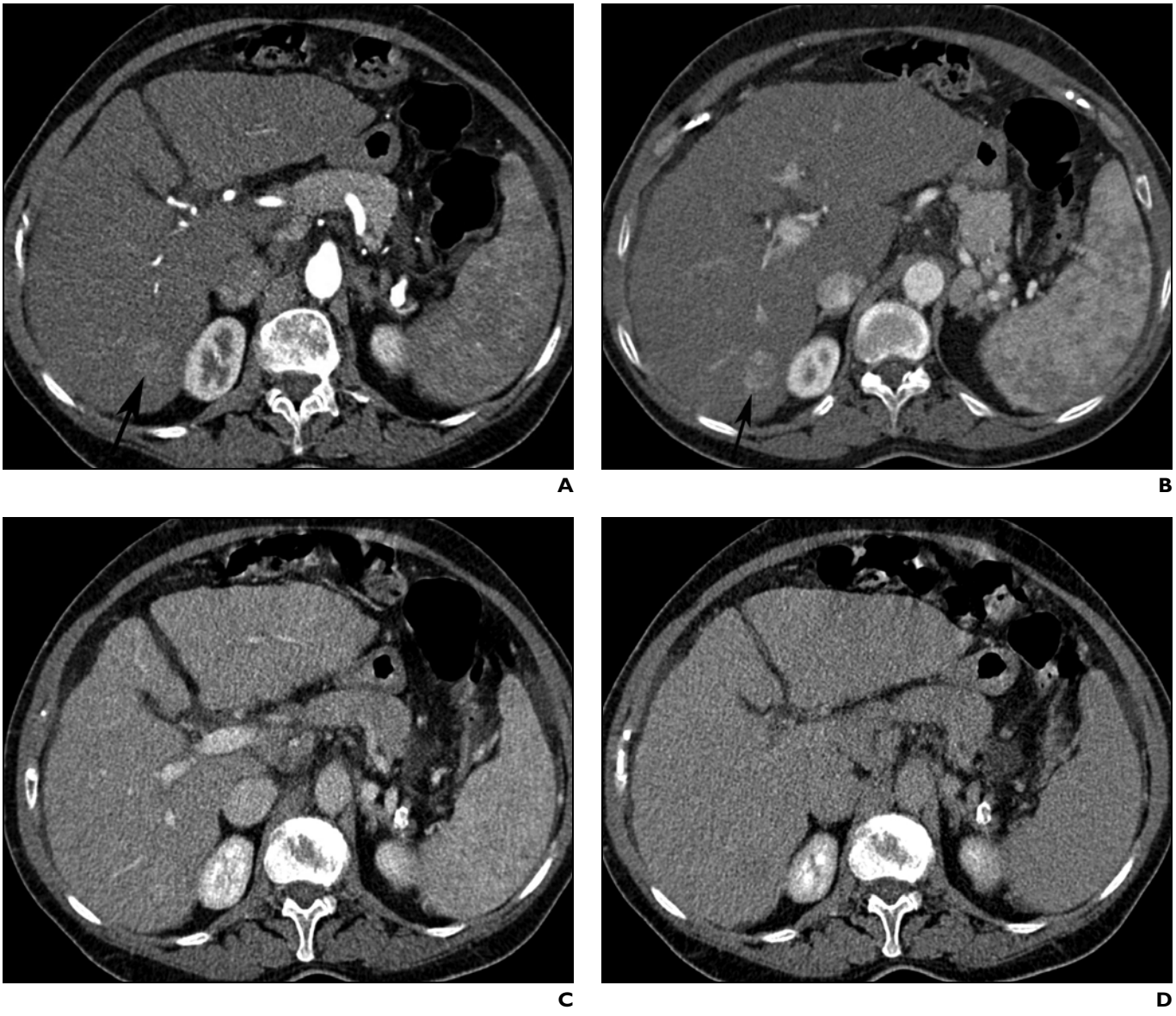

Fig. 1—60-year-old woman with multicentric hepatocellular carcinoma (HCC).
A, Early arterial phase MDCT (performed at flow rate of 5 mL/sec) image shows minimally hyperattenuating HCC in the right lobe in segment 6 (*arrow*). Qualitatively, lesion visualization was classified as adequate.
B, Late arterial phase image reveals the lesion with much better tumor–liver contrast (*arrow*). Lesion visualization was classified as excellent.
C, Rapid washout of contrast material renders lesion invisible on portal venous phase image.
D, Lesion is not seen on delayed phase image.
(Fig. 1 continues on next page)

were 67% at 3 mL/sec and 69% at 5 mL/sec ($p = 0.78$); the results for the portal venous phase were 76% at 3 mL/sec and 70% at 5 mL/sec ($p = 0.38$). Comparison of both arterial phases showed superior detection sensitivity for late arterial phase imaging at both injection rates ($p < 0.0001$ each). Delayed phase imaging revealed a higher sensitivity for HCC lesions with the lower flow rate (77% vs 64%, $p < 0.05$). The results are summarized in Table 3. False-positive diagnoses of HCC were made in four patients, which were subsequently proved to be metastatic melanoma, adenoma, tumor-simulating steatosis, and regenerative nodule, respectively.

Of the total 245 HCC lesions, 34 (14%) lesions in 17 patients were seen only in one contrast-enhanced imaging phase, including 10 lesions at 3 mL/sec and 24 at 5 mL/sec. Most of these lesions were identified only in the late arterial phase (nine at 3 mL/sec, 16 at 5 mL/sec). HCC lesions seen only on early arterial phase images included one lesion at 3 mL/sec and two at 5 mL/sec. Using the higher flow rate, three lesions were detected only on portal venous images and three different lesions only on delayed phase images. In two patients, one at each injection rate, all HCC lesions were exclusively identified in only one imaging phase: one lesion (7 mm in size)

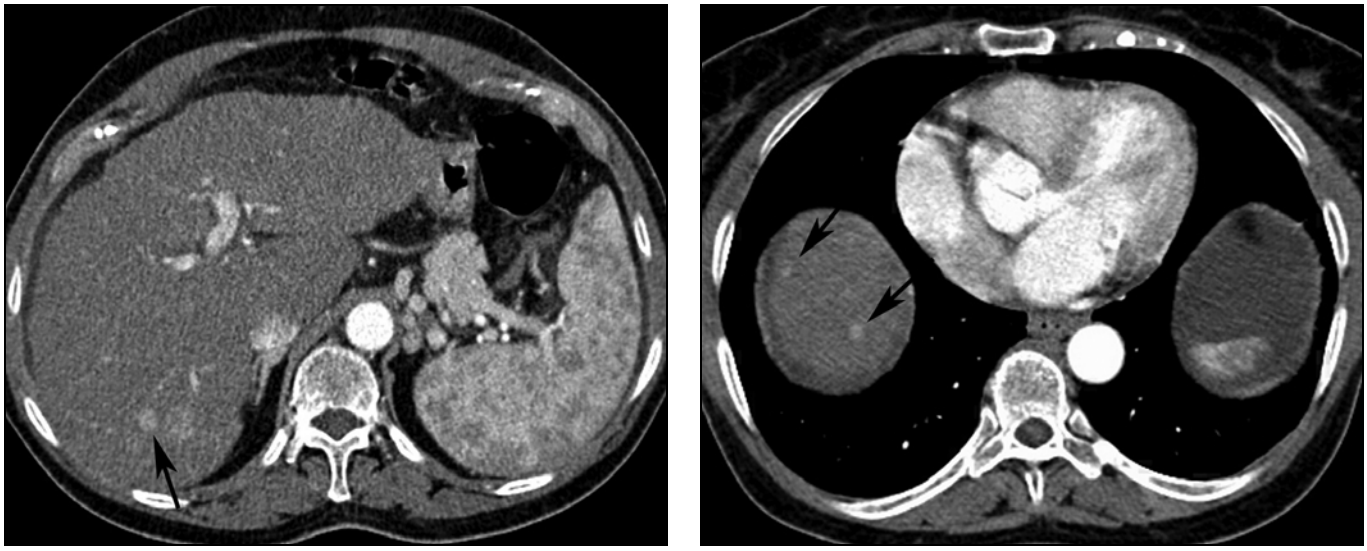

Fig. 1 (continued)—60-year-old woman with multicentric hepatocellular carcinoma (HCC).
E, Late arterial phase MDCT reveals small satellite HCC (*arrow*), which was not seen in other phases.
F, Late arterial phase MDCT reveals two more small lesions (*arrows*) in dome of liver (segment 8) that were not visible during other scans. Both lesions showed interval growth at 6-month follow-up indicative of HCC (not shown).

on late arterial phase images at 3 mL/sec and four lesions (10–20 mm in size) on late arterial phase images at 5 mL/sec.

No difference was found in the overall visualization of HCC lesions ($p = 0.39$). The mean scores for the 3 mL/sec group and the 5 mL/sec group were 3.11 ± 0.89 and 3.24 ± 0.84, respectively. The distribution of assessment scores, however, varied between both groups. More lesions with excellent (50% vs 34%) or adequate (21% vs 12%) visualization were seen using the higher flow rate, whereas the proportion of HCC lesions with good (42% vs 23%) or poor (12% vs 6%) visualization was higher at 3 mL/sec (Table 4).

Overall image quality was comparable in both treatment groups. Respective scores were 3.65 each ($p = 0.94$). Good to excellent image quality was noted in 92% of the patients in the 3 mL/sec group and in 94% of the patients in the 5 mL/sec group.

Mean aortic enhancement was significantly higher during the early arterial phase with 5 mL/sec (292 ± 78 H vs 188 ± 42 H, $p < 0.0001$), but not during the late arterial phase (208 ± 61 H at 3 mL/sec vs 204 ± 93 H at 5 mL/sec, $p = 0.77$). Subsequently, the aortic time–enhancement curves similarly declined in both groups (102 ± 23 H and 55 ± 11 H at 3 mL/sec vs 100 ± 22 H and 54 ± 13 H at 5 mL/sec). During the late arterial phase, mean enhancement of the portal vein was superior at the higher flow rate (124 ± 63 H vs 88 ± 43 H, $p < 0.01$). No significant difference was seen between the two groups in the other phases (early arterial, 24 ± 25 H vs 31 ± 45 H; portal venous, 113 ± 32 H vs 119 ± 37 H; delayed phase, 54 ± 15 H vs 60 ± 24 H, respectively). A trend toward higher enhancement of the hepatic parenchyma was noted during the late arterial phase with 5 mL/sec (30 ± 17 H vs 24 ± 12 H, $p = 0.053$). No differences between the 5 mL/sec and 3 mL/sec groups were observed for hepatic enhancement during the other phases (early arterial, 9 ± 10 H vs 8 ± 9 H; portal venous, 51 ± 14 H vs 46 ± 12 H; delayed phase, 34 ± 10 H vs 33 ± 9 H).

Tumor–liver contrast was evaluated in a total of 103 hyperattenuating HCC lesions, consisting of 41 lesions in 26 patients at 3 mL/sec and 62 lesions in 36 patients at 5 mL/sec (Fig. 3). Tumor–liver contrast was most pronounced in both groups on late arterial phase images (35 ± 19 H at 3 mL/sec vs 35 ± 14 H at 5 mL/sec), followed by the early arterial phase (17 ± 19 H at 3 mL/sec vs 15 ± 18 H at 5 mL/sec), the delayed phase (−8 ± 15 H at 3 mL/sec vs −5 ± 12 H at 5 mL/sec), and the portal venous phase (6 ± 20 H at 3 mL/sec vs −4 ± 13 H at 5 mL/sec). No significant differences between the groups were seen at early and late arterial phase imaging. Comparison of both arterial phases showed superior tumor–liver contrast during late arterial phase imaging at both flow rates ($p < 0.0001$ each).

Safety

The safety analysis comprised all 124 patients who received iodixanol at one of two flow rates (3 mL/sec, $n = 63$; 5 mL/sec, $n = 61$). No significant differences between the groups were observed for incidence ($p = 0.80$) and intensity ($p = 0.53$) of injection-associated discomfort or the incidence of adverse events ($p = 0.44$). Eight (13%) and nine (15%) patients at 3 mL/sec and 5 mL/sec, respectively, reported sensations of warmth/heat or cold (cold in one patient from each group). Discomfort was of mild intensity in seven patients from each group and of moderate intensity in one and two patients in the 3 mL/sec and 5 mL/sec groups, respectively. Contrast media–related adverse events were observed in three patients (5%) at 3 mL/sec and one patient (2%) at 5 mL/sec. All were of mild intensity. The results of the safety assessment are presented in Table 5.

Discussion

CT in the arterial dominant phase after IV administration of contrast material is crucial in the detection of hypervascular liver tumors, such as HCC. Small HCC lesions, in particular, tend to be well differentiated and, thus, hypervascular [24]. This renders rapid bolus injection of contrast material and optimal timing of CT in the arterial dominant phase during maximum enhancement of tumor essential. The capability of helical CT to obtain separate scans in the ar-

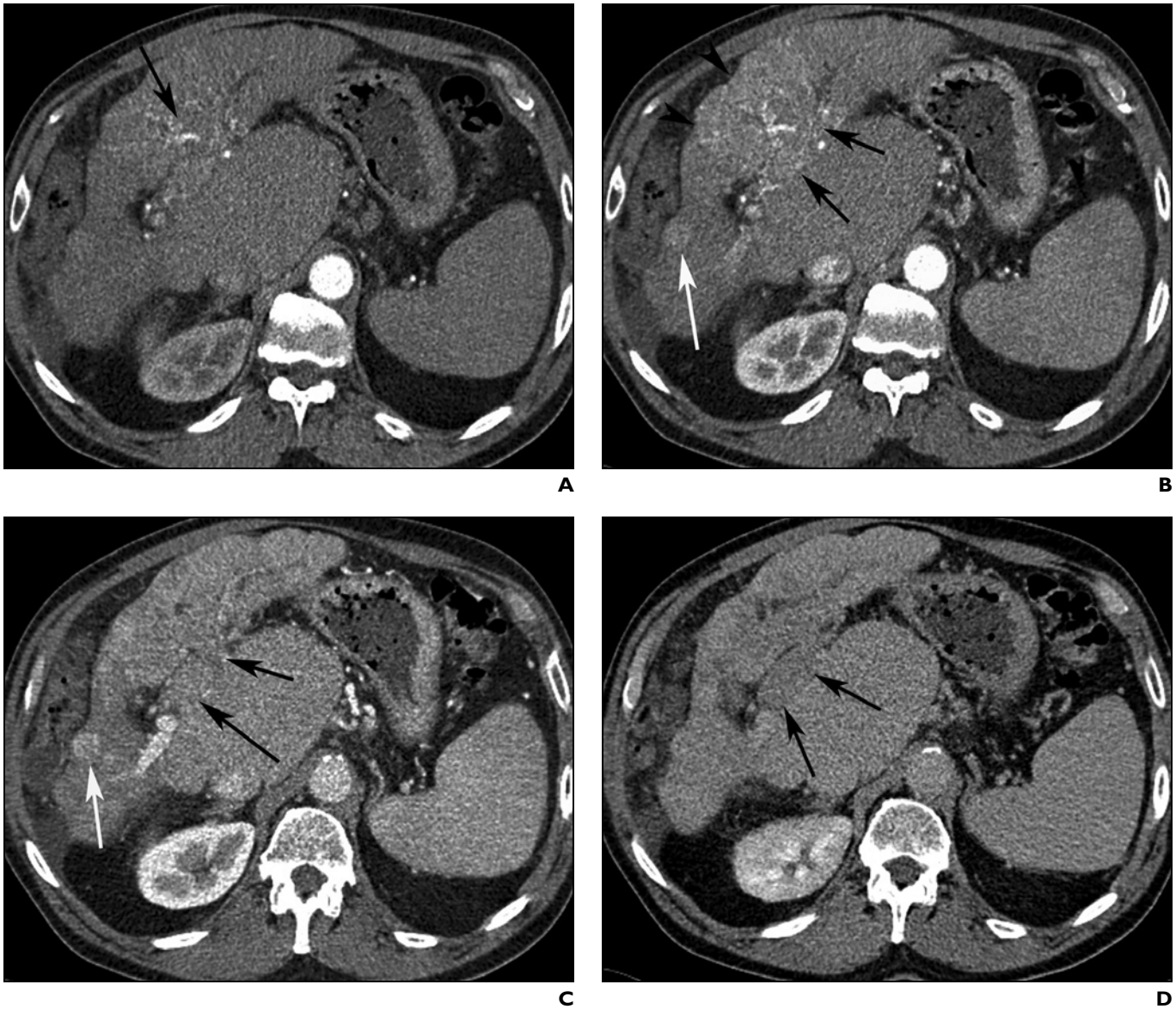

Fig. 2—57-year-old man with infiltrative hepatocellular carcinoma (HCC) with tumor thrombus in portal vein.
A, Early arterial MDCT scan (performed with flow rate of 3 mL/sec) shows tumor vessels in portal vein (*arrow*). Infiltrative HCC in adjacent part of segment 4 is not well depicted (subjective assessment, adequate).
B, Late arterial phase scan shows tumor thrombus (*black arrows*). There is only moderate enhancement of HCC (*arrowheads*) with low contrast material flow rate. Another lesion in right lobe (segment 8/5) is depicted (*white arrow*). Visualization of both lesions was classified as good.
C, Portal venous phase shows tumor thrombus (*black arrows*), but not infiltrative HCC, which grows into portal vein (subjective assessment, poor visualization). HCC in right lobe (*white arrow*) is well depicted (subjective assessment, good visualization).
D, Delayed phase scan reveals only thrombosis of portal vein (*arrows*).

terial dominant and portal venous phases has dramatically improved the sensitivity of CT for detection of HCC [1–4]. In a study by Hollett et al. [3], 38% of malignant lesions 1.5 cm or smaller in diameter were only visible or more conspicuous in the arterial phase scan. Baron et al. [1] found the advantage of arterial phase scanning to extend beyond 1.5-cm tumors. In their study, tumors of up to 4 cm were found only during arterial phase scanning. Studies on contrast injection protocols for helical CT show that arterial phase CT using iopamidol 300 mg/mL at 2 mL/kg body weight with a contrast material flow rate of 4 mL/sec is superior to a flow rate of 2 mL/sec for detection of hypervascular HCC [2]. A higher flow rate of contrast material was found to improve peak aortic enhancement and tumor–liver contrast in the arterial phase [2]. Kim et al. [9] studied the effect of changing contrast material injection rates of 2, 3, 4, and 5 mL/sec during helical CT. Higher injection rates provided better enhancement of the liver in the arterial phase without decreasing the length of the arterial phase itself. However, in both studies, the effect of contrast material flow rate on lesion detection in the arterial phase was not studied. The effect of contrast

TABLE 3: Detection of HCC Lesions in Each Imaging Phase

Phase	Number of Detected Lesions (Sensitivity %)		*p*
	3 mL/sec flow rate (*n* = 100 lesions)	5 mL/sec flow rate (*n* = 145 lesions)	
Early arterial	67 (67)	100 (69)	.78
Late arterial	96 (96)	133 (91.7)	.29
Venous	76 (76)	102 (70.3)	.38
Delayed	77 (77)	93 (64.1)	< .05

Note—HCC = hepatocellular carcinoma.

TABLE 4: Overall Visualization of HCC Lesions[a]

	3 mL/sec (*n* = 48)	5 mL/sec (*n* = 49)
Score of overall visualization of HCC (mean ± SD)	3.11 ± 0.89[b]	3.24 ± 0.84[b]
Individual assessment of HCC		
Total no. HCC lesions	100	145
Excellent visualization	34 (34%)	72 (50%)
Good visualization	42 (42%)	34 (23%)
Adequate visualization	12 (12%	31 (21%)
Poor visualization	12 (12%)	8 (6%)

Note—HCC = hepatocellular carcinoma.

[a]For each HCC lesion, the visualization was scored as follows: 1 = poor, 2 = adequate, 3 = good, 4 = excellent.
[b]No significant difference was seen (*p* = 0.39).

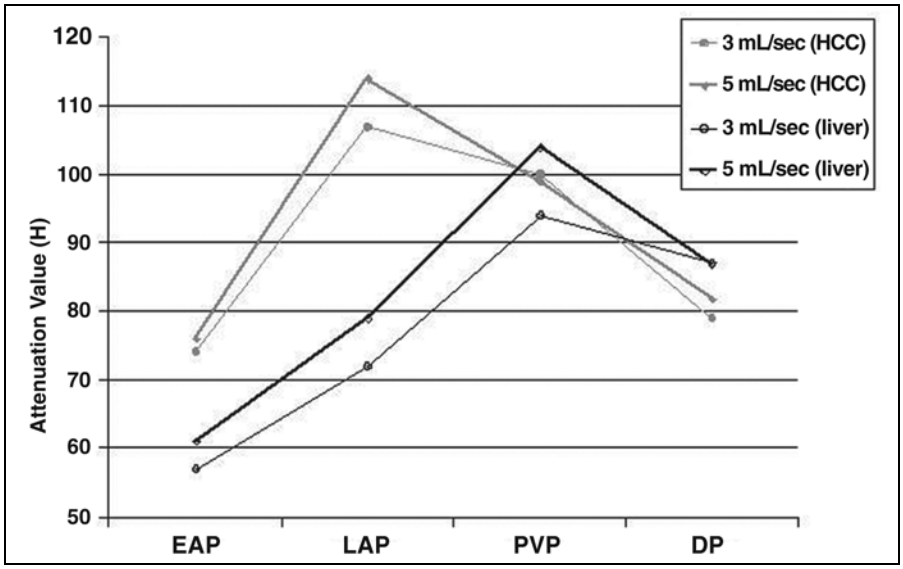

Fig. 3—Mean time–attenuation curves of HCC lesion and hepatic parenchyma during early arterial, late arterial, portal venous, and delayed phase imaging. HCC = hepatocellular carcinoma, EAP = early arterial phase, LAP = late arterial phase, PVP = portal venous phase, DP = delayed phase.

material injection protocols in MDCT scanning of patients with suspected HCC has rarely been studied [16–18, 25]. Furuta et al. [25] and Yagyu et al. [17] have evaluated the effect of contrast material concentration. According to their results, using a higher concentration (370 mg I/mL vs 300 mg I/mL) improves contrast enhancement and detection of HCC. These results are not surprising because the use of the same amount of a more concentrated contrast material results in a 23% increase of iodine load per patient. In contrast, Awai et al. [18] found that a higher concentration of contrast material (350 mg I/mL) does not offer better enhancement than that achieved with a contrast agent of 300 mg I/mL if the total iodine dose and the injection duration are kept constant. Our study focused on the effect of contrast material flow rate with the iodine dose kept constant.

In our study, significantly more HCC lesions were detected in the group with the 5 mL/sec flow rate than in the 3 mL/sec group (145 vs 100 lesions). For lesions 1 cm and smaller, the effect of the higher flow rate was even more pronounced, with 33 lesions detected in the 5 mL/sec flow group versus 16 lesions in the 3 mL/sec flow group. However, the difference did not reach statistical significance because of the small sample size of patients with HCC lesions 1 cm and smaller. Analysis of both patient groups showed no difference in demographics with regard to age, weight, severity of liver disease, and so forth (Table 1), which makes an inclusion bias as a cause of this difference unlikely. The on-site interpreters rated tumor conspicuity of HCC in the late arterial phase superior in the 5 mL/sec flow rate group. There was a trend toward better arterial phase enhancement of the liver parenchyma and hypervascular HCC in the 5 mL/sec group, but the tumor–liver contrast was not significantly better. In the helical CT study of Mitsuzaki et al. [2], tumor-to-liver contrast was quantitatively significantly better in the 4 mL/sec flow rate group than in the 2 mL/sec group (25.5 H vs 14.4 H). The discrepancy between the two studies may be explained by the higher dose of contrast material given in the Mitsuzaki et al. study (2 mL/kg of 300 mg/mL iodine, equivalent to 48 g of iodine in a patient of 80 kg body weight). In our study, 1.5 mL/kg of 320 mg/mL iodine were administered, which amounts to 38.4 g iodine in a patient weighing 80 kg. The mean dose of iodine was 36.3 g in the 3 mL/sec group and 36.9 g in the 5 mL/sec group. However, the dose-finding study of Brink et al. [26] showed that in helical CT a dose of at least 38 g of iodine provides adequate enhancement of the liver (> 50 H in > 70% of patients) without unnecessarily increasing the cost. In a study by Heiken et al. [7], a maximum hepatic enhancement of at least 50 H was necessary for high quality helical CT. These results are in keeping with our study, in which the mean hepatic enhancement was 46–51 H in the portal venous phase. By using a saline flush after a

TABLE 5: Injection-Associated Discomfort and Adverse Events

	3 mL/sec (n = 63)	5 mL/sec (n = 61)
Drug-related adverse events	12 (3%)	1 (2%)
Mild intensity	7	7
Moderate intensity	1	2
Severe intensity	0	0
AEs, overall	8 (13%)[a]	9 (15%)[a]
Discomfort, overall	5 (8%)[a]	1 (2%)[a]
Mouth dryness	1	0
Facial rash	1	0
Throat tightness	1	0
Abnormal taste	0	1
AEs not related to contrast agent	3 (5%)[a]	2 (3%)[a]
Extravasation	1	1
Chest pain	1	0

Note—AEs = adverse events.
[a]No significant difference was seen between the groups for any of the variables.

contrast material bolus of 120 mL of iopromide at 300 mg/mL, the dose of contrast material could be reduced even further by 6 g of iodine compared with a standard injection protocol without a saline flush [27].

MDCT scanners allow a faster z-axis speed, thus enabling volume coverage of the liver in 4–10 sec and the capability of more imaging passes of the liver than with single-slice helical scanners [11]. In the MDCT study by Foley et al. [11], the so-called arterial dominant phase of helical CT could be split in two phases, the early arterial phase and the portal venous inflow (or late arterial) phase. As a result of the bolus tracking technique, a wide variation of scan delays for start of the early arterial phase scan was observed, ranging from 16–45 sec. These results are in keeping with the study of Murakami et al. [12], in which a scan delay of 14–36 sec was observed. It is therefore doubtful whether a fixed scan delay would result in optimal timing arterial phase MDCT scanning. The early arterial phase provides a data set for CT angiography, but the most valuable phase for detection of hypervascular tumors is the late arterial phase. Murakami et al. evaluated double arterial phase MDCT scanning during one breath-hold. In their study, late arterial phase imaging proved superior to early arterial phase with a sensitivity of 78% versus 54% for detection of HCC, but the double arterial phase showed significantly more HCC lesions and fewer false-positive lesions than any one phase alone. In the present study, the late arterial phase was significantly superior to early arterial phase imaging for both of the study's flow rates (96 vs 67 lesions for 3 mL/sec, and 133 vs 100 lesions for 5 mL/sec). The addition of early arterial phase imaging contributed to the visualization of the vasculature, but added little to the detection of HCC. There were only three lesions not seen in the late arterial phase that were identified during the early arterial phase. This confirms the findings of studies by Kim et al. [20] and Laghi et al. [28], which did not show a benefit of early arterial phase CT for detection of HCC. Assessment of hepatic vessels was not within the scope of our study, but early arterial phase CT provided excellent image quality for visualization of normal variants of hepatic arteries.

In our study, there were two patients with one and four lesions respectively (overall, five HCC lesions) in whom all the lesions were detected only during a single phase of quadruple-phase scanning. In both patients, late arterial phase imaging showed these lesions, which were completely missed by the other phases. Our study confirms the results of Kim et al. [20] and Ichikawa et al. [13]. Kim et al. showed that four-phase MDCT (including an early arterial phase) is not more sensitive than three-phase MDCT for detection of HCC. In the study of Ichikawa et al., late arterial phase imaging was as good as combined interpreting of early and late arterial phase for detection of hypervascular HCC (sensitivity, 88% vs 90%). Thus, acquisition of an early arterial phase at MDCT does not seem to be necessary for detection of hypervascular HCC. In the present study, delayed phase scans at 5 min added only little information. The sensitivity of delayed phase scans was not higher than in the portal venous phase. Only three of 245 lesions (1%) were only seen in the delayed phase, but none of these lesions was solitary. However, in the study of Iannaccone et al. [21], which included 250 HCCs, delayed phase imaging revealed nine additional HCCs and showed the typical capsule in 10% of HCCs, which increased interpreter confidence to make the correct diagnosis.

One may argue that higher flow rates of contrast material may increase the risk of patient discomfort during injection and the risk of adverse events caused by extravasation. However, in the flow range studied, no increased risk of adverse events was observed [29, 30]. These findings agree with the literature on CT angiography and MR angiography studies, which show that high flow administration (at 8–9 mL/sec) of contrast material can be safely performed [31, 32].

There are some limitations to the study. First, it was a parallel group study. The different results between the two groups may, in part, be attributable to a patient inclusion bias. Ideally, both contrast material flow rates should have been tested in the same patient. However, the demographics of both groups were similar with regard to all the parameters tested, which renders this possibility unlikely. Second, our study population was not a screening population. All patients referred for CT had a high clinical suspicion for HCC or even a lesion already identified at sonography or CT, which induces a bias. Third, the high sensitivity in our study does not reflect absolute sensitivity because we do not have absolute proof of tumor burden. We may have missed some HCC nodules because we do not have pathologic proof of all lesions and because of the absence of lesions, which is only feasible, if all patients undergo liver transplantation. Thus, absolute sensitivity and specificity cannot be calculated. However, the presence of hypervascular lesions 2 cm or greater combined with α-fetoprotein levels greater than 400 ng/mL is accepted as diagnostic for HCC by the European Association for Study on the Liver Consensus Report [19]. Fourth, for subcentimeter nodules, the presence of hypervascularity is not a precise indicator of the presence of HCC because high-grade dysplastic nodules may exhibit hypervascularity at contrast-enhanced CT as well [33]. Thus, we cannot completely exclude the possibility of a false-positive diagnosis of HCC in patients in whom histologic confirmation was not ob-

tained for all lesions. However, a combination of biopsy, surgery, response to embolization, and interval growth at follow-up was used to confirm the diagnosis of HCC, and lesions with the same appearance as those lesions with histologic proof was sufficient for a presumptive diagnosis of HCC. Although some of the latter criteria are not a gold standard, we think they constitute very good evidence of HCC. A small arterioportal venous shunt can be reliably differentiated from HCC with multiphasic CT [22, 23, 28].

In conclusion, a faster contrast material injection rate of 5 mL/sec during MDCT appears to improve the detection of hypervascular HCC with MDCT, mainly at the later arterial phase. Early arterial phase imaging does not add significant information for detection of HCC and can be omitted. By using a higher flow rate, the visualization of small HCC lesions is improved without increasing the rate of discomfort or the risk of adverse events.

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