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Preoperative Assessment of Hepatocellular Carcinoma with Split-Bolus Combined Phase Contrast-Enhanced Computed Tomography

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Background: The aim of this study was to investigate the feasibility of a split-bolus combined phase contrast-enhanced computed tomography protocol in evaluation of liver vasculature in hepatocellular carcinoma (HCC) patients for the purpose of surgery guidance.

Material/Methods: Two groups of patients were recruited for the study: 24 consecutive cases of HCC who underwent multiphasic CT examination, and 22 consecutive cases who afterwards underwent split-bolus combined phase CT examination. The multiphasic protocol included an unenhanced scan and 3 image acquisitions after contrast injection. The injection of contrast medium was 440 mgI/kg in a single bolus. The split-bolus combined phase protocol included unenhanced scan and combined phase. The injection of contrast medium was 440 mgI/kg for the first bolus and 220 mgI/kg for the second bolus. The vascular delineation was evaluated with Likert scales. The CT values were measured, and the contrast-to-noise ratio (CNR) was calculated. We also compared the effective radiation dose (ED) of the 2 protocols.

Results: All mean CT values were significantly higher in the split-bolus protocol than in the multiphasic protocol (all $P<.05$), except for the hepatic vein ($P>.05$). The ED was significantly lower in the split-bolus protocol, corresponding to a dose reduction of 66% compared to the multiphasic protocol ($P<.05$). The scores of the branches of the hepatic vein in the split-bolus protocol were not lower than those in the multiphasic protocol.

Conclusions: For the preoperative HCC patients, the split-bolus combined phase CT examination meets the diagnostic requirement of surgical planning, with approximately 60% reduction in the radiation dose.

MeSH Keywords: Carcinoma, Hepatocellular • Radiation Dosage • Radiology

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Background

Hepatocellular carcinoma (HCC) is one of the most common neoplasms in the world. Surgery is regarded as a standard treatment for HCC patients [1–4]. Multidetector row computed tomography (MDCT) has been proven to be useful in displaying the relationship between the tumor and the hepatic blood vessels, which is greatly helps guiding surgery.

During the MDCT procedure, multiple phases of image acquisition are performed for the characterization of HCC and to provide anatomical information on the vasculature. With optimized image acquisition protocol, all the information might be displayed in a single phase, in which the hepatic artery, portal vein, hepatic vein, and the feeding artery of the tumor are clearly depicted simultaneously. Abbreviation of scanning phases leads to lower radiation exposure for the patient.

Split-bolus MDCT divides intravenous contrast medium into 2 or 3 parts and provides combined phase images in a single scan. Split-bolus MDCT has been tested in differentiation of focal liver lesions [5–8]. To our knowledge, the application of this technique in the preoperative assessment of HCC has not been reported. The aim of this study was to assess the feasibility of the split-bolus MDCT protocol in evaluation of HCC for the purpose of surgery guidance.

Material and Methods

Patient population

This prospective study was approved by the Institutional Review Board and written informed consent was obtained for each patient. From February 2015 to July 2015, 25 consecutive patients who were highly suspected of HCC (diagnosed as LI-RADS 5 with outside imaging) underwent a split-bolus contrast-enhanced MDCT examination before surgery or interventional treatment. Three (12%) of the 25 enrolled patients were excluded from the study because of: (a) patients with pathologically proven ICC (n=2) and (b) inadequate injection technique (n=1). We recruited 24 consecutive patients with pathologically proven HCC as a retrospective control cohort who underwent multiphasic contrast-enhanced MDCT examination between May and December 2014.

Protocols of CT Scanning and CT Image Acquisition

Split-bolus MDCT examination was performed with a dual-source 64-MDCT scanner (Somatom Definition, Siemens Healthcare). All patients underwent MDCT examinations with 100 kVp and 400 mAs. The parameters were: detector configuration 128×0.6-mm, gantry rotation time 0.5 s, pitch 0.6: 1, and display FOV=35 cm. The CT images were reconstructed with the sinogram-affirmed iterative reconstruction algorithm 3 (SAFIRE, soft-tissue kernel, I30s). For the control group, iodinated contrast medium (Ioversol, 320 mg I/mL, 440 mgI/kg) was injected into the antecubital vein with automatic power injector (Stellant, Medrad, USA). For the split-bolus group, iodinated contrast medium (Ioversol, 320 mg I/mL) was injected twice (440 mgI/kg and 220 mgI/kg) sequentially.

For the control group, multiphasic MDCT images were acquired of unenhanced phase, hepatic arterial phase (HAP) of upper abdomen, portal venous phase (PVP) of abdomen and pelvis, and delay phase of upper abdomen. For the split-bolus group, MDCT images of upper abdomen were acquired in 2 phases: unenhanced phase and combined contrast-enhanced phase. The scanning protocols are described in Figure 1.

The volume of CT dose index ($CTDI_{vol}$) and dose-length product (DLP) were recorded for all patients. The effective dose (ED) was estimated by multiplying the DLP by a conversion factor of 0.015 mSv mGy^{-1} cm^{-1} [9].

Image evaluation

CT values of the lesion, abdominal aorta, hepatic artery, main portal vein, trunk of hepatic vein, and right lobe of the liver by a region of interest (ROI) were measured on images of combined phase from split-bolus scans and on images of HAP (the lesion, abdominal aorta, proper hepatic artery, and right lobe of the liver) and PVP (main portal vein, trunk of hepatic vein, and right lobe of the liver) from multiphasic MDCT scans. Standard deviations (SDs) of the attenuation of subcutaneous fat of the anterior abdominal wall were recorded to represent the objective image noise. Contrast-to-noise ratio [CNR, ($ROI_{Tumor/Liver}$–$ROI_{parenchyma/Muscle}$)/noise] was calculated as the absolute attenuation difference between the hepatic parenchyma and the hepatic lesion or hepatic vessels [10].

The vascular anatomic display was evaluated for both trunk and branches of the hepatic arteries, portal veins, and hepatic veins using a 3-point scale (1-blurry border; 2-border can be defined, 3-sharp-defined border). According to a classification system created by Miches [11], the arterial anatomy was analyzed for the presence of anatomic variants, classified, and compared with surgery or DSA results.

Statistical analysis

Statistical analysis was performed with SPSS (version 12.0, SPSS) statistical software. All data are expressed as mean ± standard deviation unless otherwise indicated. The Mann-Whitney *U* test was used for comparison of the CT values, noise, CNR, and vasculature scoring in split-bolus MDCT examination

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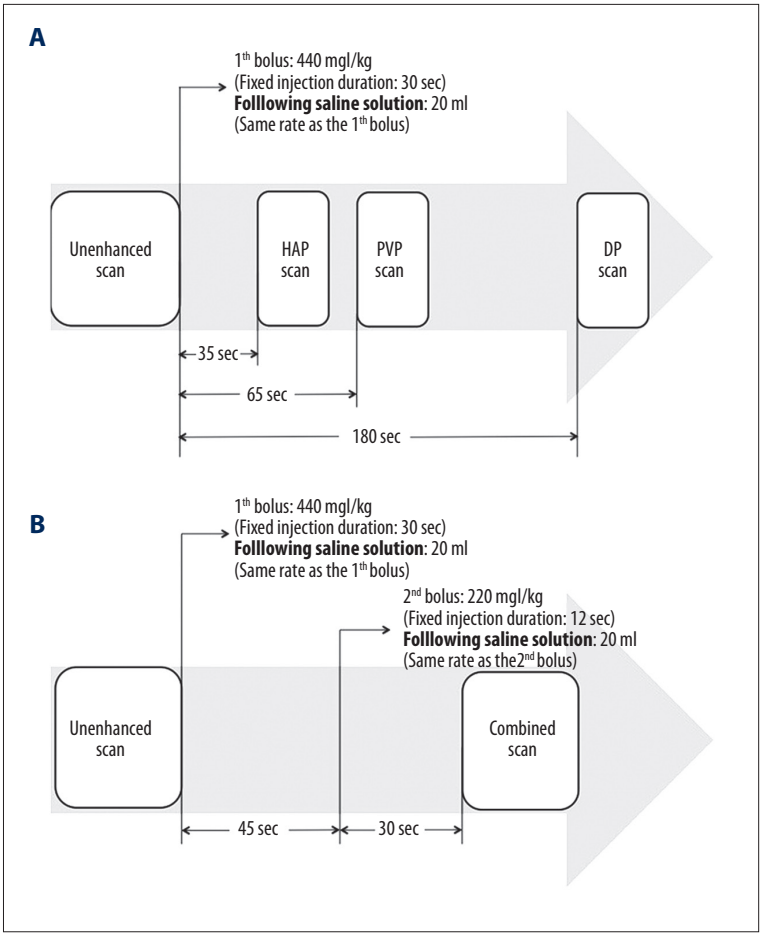

Figure 1. Schematic view of multiphase MDCT scanning (**A**) and split-bolus MDCT scanning (**B**) of the liver. For the multiphase MDCT protocol, patients received 440 mg I/kg of contrast medium with a fixed injection duration (30 seconds), followed by 20 ml of saline flush at the same flow rate. The late arterial, portal venous, and delay phase scanning started automatically 35 seconds, 65 seconds, and 180 seconds after the injection of contrast medium. For the split-bolus MDCT protocol, patients received 660 mg I/kg of contrast medium, which was split into 2 boluses. The first bolus of contrast medium (440 mgI/kg) with a fixed injection duration (30 seconds), followed by 20 ml of saline flush at same flow rate, was injected to obtain a desirable enhancement of hepatic parenchyma during the image acquisition phase. After a pause of 15 seconds, the second bolus of contrast medium (220 mgI/kg) was injected at a fixed injection duration of 12 seconds, followed by 20 ml of saline flush at the same flow rate to obtain hepatic arterial enhancement during the image acquisition phase. The combined phase scanning was performed 30 seconds after the start of the second bolus injection, resulting in a simultaneous contrast enhancement of the arterial and venous systems. HAP, hepatic arterial phase; PVP, portal venous phase; DP, delay phase.

and multiphasic MDCT examination. For detection of the arterial anatomy, we assessed the sensitivity, specificity, positive predictive value, and negative predictive value. *P*<.05 was considered statistically significant.

Results

Patient characteristics

Twenty-two patients (12 men and 10 women; mean age, 57 years; BMI, (24.13±2.90) Kg/m^2) underwent split-bolus MDCT and 24 patients (17 men and 7 women; mean age, 57 years; BMI, (26.20±1.79) Kg/m^2) underwent multiphasic MDCT. Between the 2 groups, there were no significant differences in age distribution or sex distribution; however, the difference in patient BMI was significant (*P*<.05).

Radiation dose and contrast dose

There were significant differences in $CTDI_{vol}$, DLP, and ED in all series between the 2 scanning protocols (*P*<.05). Compared with multiphasic MDCT protocol, the radiation dose in the split-bolus MDCT protocol demonstrated a reduction of 50% in $CTDI_{vol}$ and 66% in ED. The mean pre-examination contrast injection dose was 136.24±21.10 ml in the split-bolus protocol group and 103.61±11.69 in the multiphase protocol group (*P*<.001).

Image analysis

Mean CT value of lesion, abdominal aorta, proper hepatic artery, main portal vein, and hepatic parenchyma were significantly higher in the split-bolus protocol group than in the multiphase protocol group (all *P*<.05). The mean value of the hepatic vein at PVP of the multiphase protocol was not significantly different from that at combined phase of the split-bolus protocol (*P*>.05). Mean image noise did not differ significantly between PVP of the multiphase protocol and combined phase of split-bolus protocol (*P*>.05). There was no significant difference in the mean CNRs of tumor and liver between the multiphase protocol and the split-bolus protocol (*P*>.05) (Table 1).

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Table 1. Attenuation, image noise and contrast-to-noise with the split-bolus protocol and multiphase protocol.

Parameter	Split-bolus protocol	Multiphase protocol	*P* value
Attenuation (HU)			
Lesion	149.68±27.27	118.67±12.39	<.0001
Abdominal aorta	341.45±39.35	306.38±34.66	0.005
Hepatic artery	324.59±41.40	285.50±34.79	0.002
Portal vein	188.05±25.13	147.50±33.36	<.0001
Hepatic vein	168.50±24.05	163.08±21.55	0.441
Liver	111.82±8.72	107.21±9.68	0.041
Image noise	8.23±1.31	7.87±1.28	0.262
Mean CNR			
Lesion	4.70±3.22	5.45±1.31	0.052
Liver	6.71±1.44	6.77±1.44	0.613

Unless otherwise specified, data are means ± standard deviations. For the multiphasic protocol, the attenuation of lesion, abdominal aorta and hepatic artery were measured in the hepatic arterial phase, and the others' CT values were measured in the portal venous phase.

Table 2. Assessment for the hepatic vascular anatomy in the split-bolus protocol and multiphase protocol.

Parameter	Split-bolus protocol	Multiphase protocol	*P* value
Hepatic arteries	3.0±0.0	3.0±0.0	1.000
Branch of hepatic arteries	3.0±0.0	3.0±0.0	1.000
Portal veins	2.91±0.29	2.75±0.44	0.160
Branch of portal veins	2.64±0.58	2.50±0.72	0.582
Hepatic veins	2.55±0.67	2.13±0.90	0.108
Branch of hepatic veins	2.68±0.57	2.21±0.72	0.016

Unless otherwise specified, data are means ± standard deviations. For the multiphasic protocol, the trunk and branch of hepatic arteries were assessed in the hepatic arterial phase, and the other vessels were assessed in the portal venous phase.

Table 3. Assessment for the hepatic arterial anatomic variation in the split-bolus protocol and multiphase protocol.

Hepatic arterial anatomic variation (Michels)	Number	
	Split-bolus protocol	Multiphase protocol
Type I	14	15
Type II	2	3
Type III	1	1
Type V	1	1
Type VI	2	0
Type VIII	2	3
Type IX	0	1

The scores of both trunk and branches of hepatic artery, portal vein, and the trunk of the hepatic vein of the split-bolus protocol were similar to those of the multiphase protocol (all P values >.05) (Table 2). The score of the branches of the hepatic vein in the split-bolus protocol was significantly higher than in the multiphase protocol (*P*<.05). In addition, the scores of the trunk and branches of the hepatic artery were 3 and excellent, respectively, in both protocols. The split-bolus protocol and the multiphase protocol confirmed the arterial anatomy identified by surgery or DSA results with a sensitivity, specificity, positive predictive value, and negative predictive value of 100% (Table 3).

Representative cases by split-bolus MDCT protocol are shown in Figures 2–4, which display all tumor-associated blood vessels in the combined phase.

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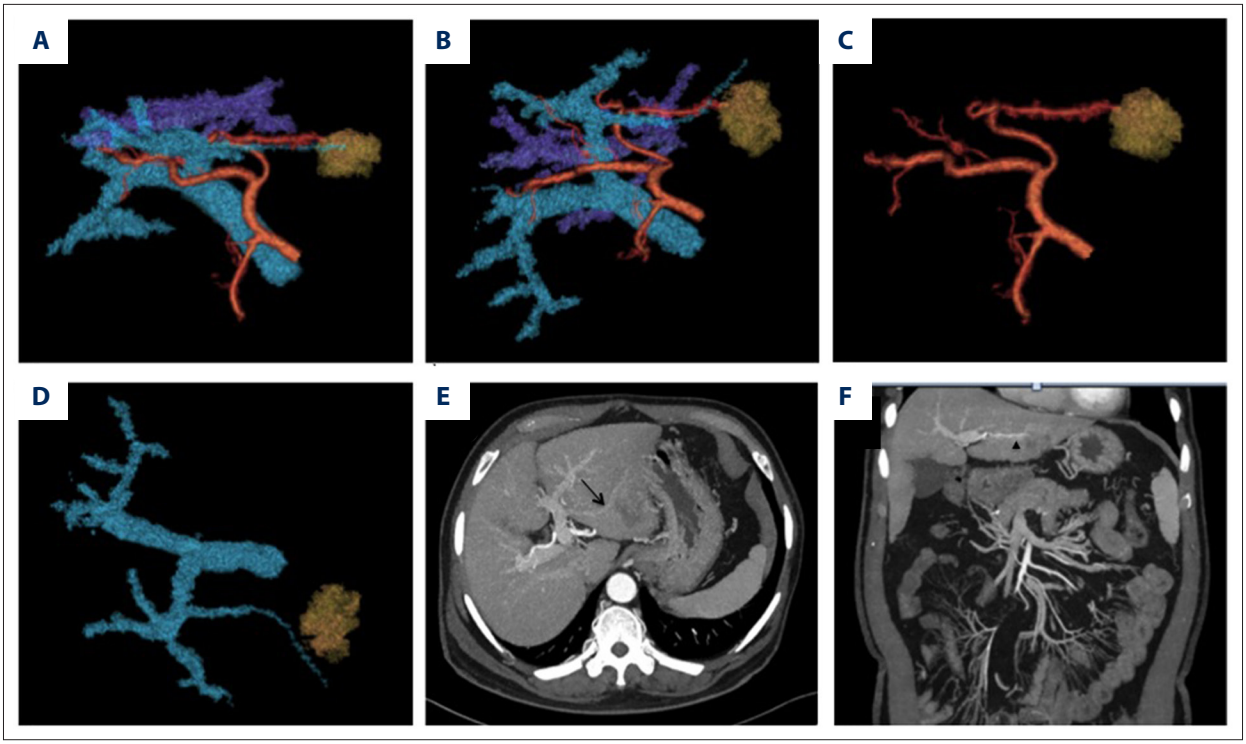

Figure 2. A 67-year-old man (BMI 31.0 kg/m^2) with hepatitis B cirrhosis and biopsy-proven hepatocellular carcinoma. The split-bolus contrast-enhanced MDCT was performed at 100 kV (ED 8.52 mSv), (**A–D**) 3D volume-rendering of reconstruction images, with arteries in red, portal vein in blue, and hepatic vein in purple (**E**), axial MIP image, and (**F**) coronal MIP image in combined phase. A tumor appears as a space-occupying lesion in the left lobe of the liver, with feeding artery (black arrowhead) and surrounding portal venous (black arrow). 3D volume-rendering reconstruction images show the relationship between the blood vessels and the tumor. MIP, maximum intensity projection.

Discussion

Cross-sectional imaging and image-guided procedures can greatly assist in the surgical management of HCC. Imaging techniques should be optimized and tailored to address the issues of patient management and surgery guidance. Appropriately timed, contrast-enhanced imaging is critical to identify the scope of the tumor, the tumor-related vasculature, and the residual liver parenchyma [12]. One of the major concerns for preoperative assessment of HCC is to evaluate the tumor-associated blood vessels [13,14]. The split-bolus technique used in the present study combines different contrast phases into one acquisition. Our results showed that this split-bolus combined phase protocol was feasible in a clinical setting, and enabled better vascular and hepatic parenchymal imaging.

To meet the demand of image evaluation for liver vasculature with combined phase, the injection of contrast medium was separated in 2 boluses: the first bolus was injected approximately 75 seconds before scanning to guarantee the enhancement of hepatic and portal veins, and the second bolus was injected approximately 30 seconds before scanning to fulfill arterial enhancement (Figure 5). According to the liver circulation pattern, during the scanning window, the first injected contrast medium was distributed in the portal vein, hepatic parenchyma, and hepatic vein and the second bolus was mainly distributed in the aorta, hepatic artery, hepatic sinusoids, and the branches of the hepatic vein [15]. Due to injecting contrast material twice, the CT values of the aorta, liver parenchyma, and portal vein in the split-bolus protocol were significantly greater than in the multiphase MDCT protocol. By the time of image acquisition, the second bolus did not flow into the trunk of the hepatic venous, resulting in no significant difference in mean enhancement values in the main hepatic veins between the 2 protocols. Though the CT value of the vessels differed significantly between the multiphase protocol and split-bolus combined phase protocol, all the assessment scores of the hepatic vessels were compatible with those of the 2 protocols except for branches of the hepatic veins.

Besides being convenient to use for evaluation of the liver vessels with single-phase imaging, there was another obvious advantage of the split-bolus combined phase protocol, which was to reduce radiation dose. Many studies have tried to the reduce radiation dose in contrast-enhanced CT of the liver; some of them by reducing the kVp and mA, which

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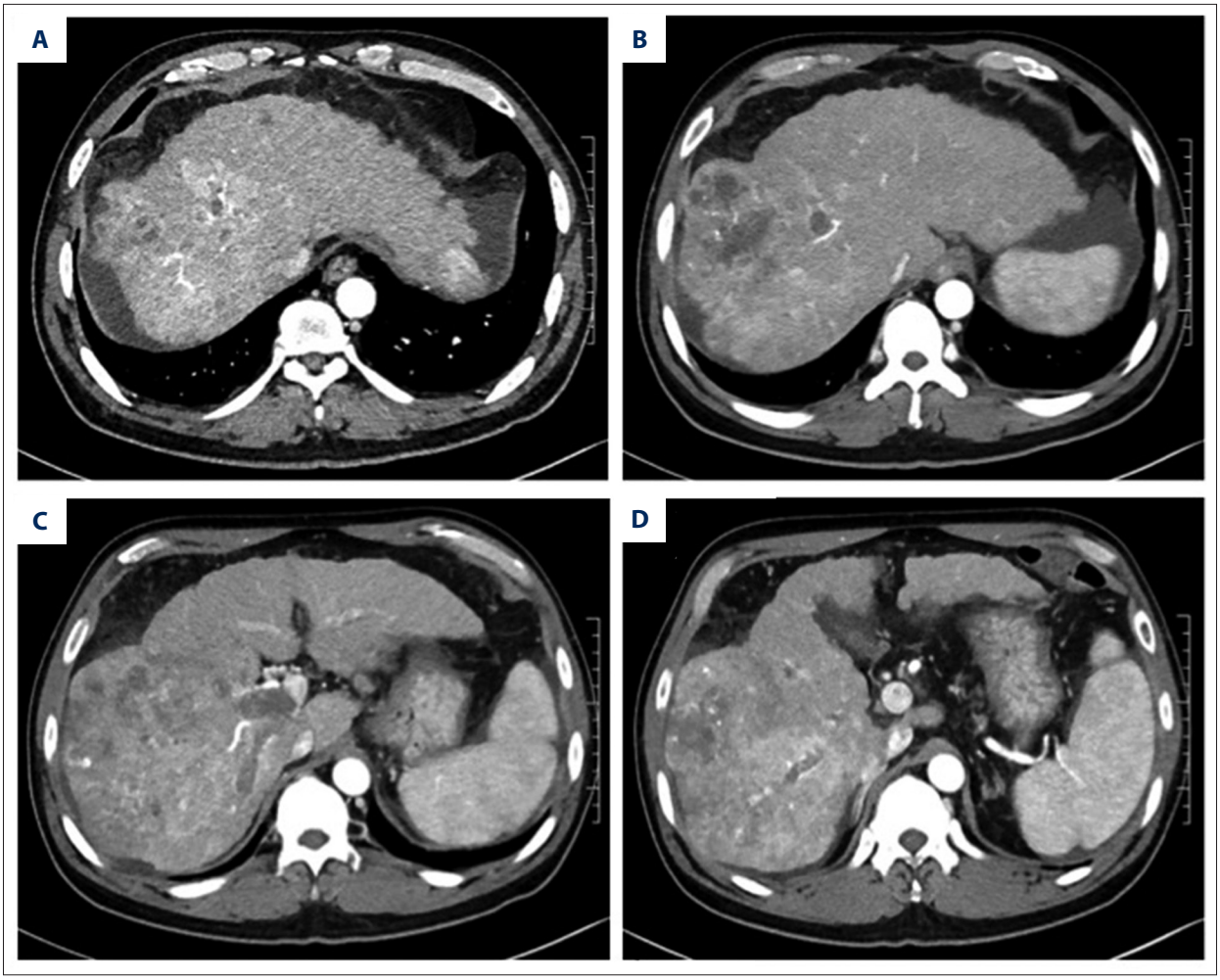

Figure 3. A 52-year-old man (BMI, 23.9 kg/m^2) with hepatitis B cirrhosis and biopsy-proven hepatocellular carcinoma. The split-bolus contrast-enhanced MDCT was performed at 100 kV (ED 7.83 mSv), (**A–D**) Axial combined phase images. A large tumor with heterogeneous enhancement appears as a space-occupying lesion in the right lobe of the liver, with portal vein thrombus.

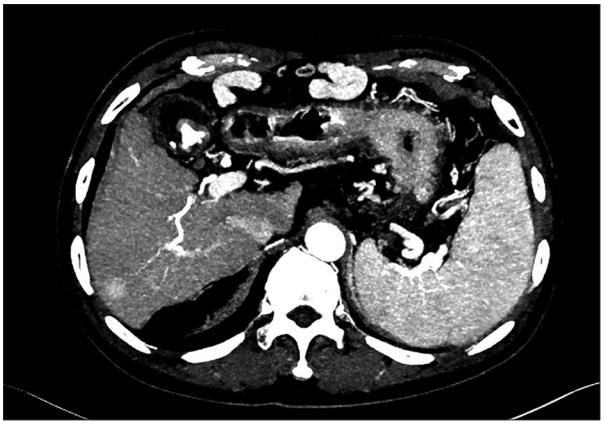

Figure 4. A 75-year-old man (BMI, 26.1 kg/m^2) with hepatitis B cirrhosis and biopsy-proven hepatocellular carcinoma. The split-bolus contrast-enhanced MDCT was performed at 100 kV (ED 7.97 mSv) in axial combined phase image. A hypervascular tumor appears as a space-occupying lesion in the right lobe of the liver, with clearly manifested feeding artery.

reduced the radiation dose by 37–57% [16,17], and some of them by reducing the number of scans [18,19]. With split-bolus combined phase protocol, the 2 methods are integrated together into a single CT scan with 100 kVp. Lowering the kVp could improve the visualization of contrast material-enhanced structures like hypervascular lesion and vessels. A split-bolus technique combines different contrast phases into one acquisition, thereby diminishing radiation exposure with only limited increase in the amount of contrast medium. Many studies showed that intravenous administration of contrast media was not as harmful as using the intra-arterial route [20–22]. Although the dose of the contrast medium was increased in the split-bolus MDCT protocol compared with the multiphase MDCT protocol, the radiation dose also clearly reduced. It is

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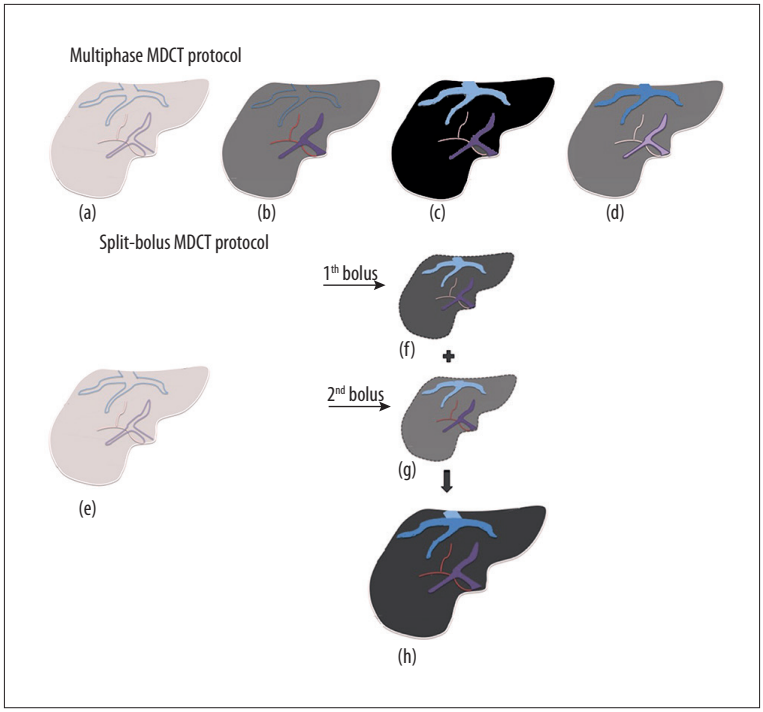

Figure 5. Schematic view of the enhancement method of the blood vessels and liver parenchyma in multiphase MDCT scanning protocol and split-bolus MDCT scanning protocol. For multiphase MDCT scanning protocol, unenhanced phase (a), late arterial phase (b) was acquired to have the hepatic artery fully enhanced with portal vein early enhanced; portal venous phase (c) was acquired to have the liver parenchyma and portal vein fully enhanced, with hepatic veins enhanced by antegrade flow; delay phase (d) was acquired to have the portal vein fully enhanced. For the split-bolus MDCT scanning protocol, unenhanced phase (e), the first injected contrast medium was distributed in the portal vein, hepatic parenchyma, and hepatic vein (f). The second bolus was mainly distributed in the aorta, hepatic artery, hepatic sinusoids, and the branches of the hepatic vein (g). The combined contrast-enhanced phase showed higher CT values of the aorta, liver parenchyma, and portal vein compared with the multiphase MDCT protocol (h).

reasonable to consider that this technique does more good than harm for preoperative patients with HCC.

This study has a number of limitations. First, the intended population of the split-bolus combined phase protocol was limited to assess the liver vasculature, for the purpose of preoperational evaluation. More patients should be included to expand the sample size in further studies to analyze the enhancement pattern of HCC in the split-bolus protocol. Second, the comparison between the 2 techniques was not performed in the same patients; therefore, it could be biased by different patient selection. However, except for BMI, the overall clinical characteristics of the 2 groups were similar. Further studies with larger groups of patients will be helpful to confirm our findings.

Conclusions

For preoperative HCC patients, the split-bolus combined phase CT examination can meet the diagnostic requirement of surgical planning, with a 60% reduction in radiation dose.

Acknowledgments

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Conflicts of interests

None.

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