Supplement

1. Standard of reference for lesion detection and lesion characterization

Lesion detection— The closest cross-sectional imaging (routine liver CT or contrast-enhanced liver MRI) and angiography for transarterial chemoembolization accompanied by lipiodol uptake within 3 months were used as the standard of reference for lesion detection in participants with LR-3, 4, 5, or -M. For those without focal lesions or with only benign lesions, remote cross-sectional imaging was used as the standard of reference when imaging within 3 months was not available.

Lesion characterization— For hepatocellular carcinoma (HCC), diagnosis was made using a composite algorithm. The pathologic diagnosis was used regardless of imaging features at spectral computed tomography. Lesions were diagnosed as HCCs on imaging basis in the following cases: a) Liver Imaging Reporting and Data System (LI-RADS) scores 4-5 (LR-4 or -5) with tumor staining on angiography for TACE, definite nodule on ultrasonography, or tumor progression or regression after chemotherapy (Sorafenib); b) LR-4 or LR-5 on following gadoxetic acid-enhanced liver MRI within 3 months; c) not visible on cross-sectional imaging but with tumor staining on angiography and compact lipiodol uptake after treatment with regression of tumor marker elevation; d) nodule-in-nodule appearance on imaging; or e) tumor in vein (TIV) with arterial phase hyperenhancement and portal washout. We considered LR-4 and -5 as HCCs as most participants had a history of HCC, and probable HCC (LR-4) often requires action for potential treatment.

Dysplastic nodules were defined as non-hypervascular hypoattenuating nodules at CT which remained stable on follow-up images. Nodules are also categorized as dysplastic nodules if they were non-hypervascular, hepatobiliary hypointense MRI without diffusion restriction or T2 hyperintense and were stable on follow-up images (1-3).

Regenerative nodules were defined as when nodules showed hyperintensity on the hepatobiliary phase which remained stable in size on follow-up images for more than six months (1-3).

Hemangiomas were clinically diagnosed based on its characteristic features including bright intensity on T2-weighted imaging and the peripheral nodular enhancement pattern on CECT or dynamic MRI (4), as well as no significant interval change during follow-up. Lesions treated via a method other than lipiodol were checked using their electronic medical record and prior imaging before treatment. Focal fat deposition was clinically diagnosed based on in-and opposed phases of MRI which showed a signal drop on the opposed phase.

2. Sample size determination

According to the study (5), the average lesion conspicuity score was 3.31 ± 0.46 on standard-dose FBP images and 3.86 ± 0.32 on double low-dose 50 keV images. Assuming a type I error of 0.05, type II error of 0.2, and 1:1 recruitment ratio of the two groups, each group required a minimum of eleven HCCs.

The positive predictive value of ultrasound-detected nodules ranged between 16.9 % to 69 % (6, 7), and the cumulative risk of HCC progression after locoregional therapy has been reported to range from 20 % to 50 % during the first 12 months (8, 9). Assuming that the prevalence of HCC would be 40 % in each group, the minimum number of patients was determined to be 28 in each group. The final sample size was determined to be 68 considering a 20 % dropout rate (34 in each group).

3. Focal liver lesions in the study participants

Focal liver lesions in each group— In the standard-dose group, there were 61 HCCs (mean size 14.9 ± 7.4 mm, range 6 – 49 mm), 32 dysplastic nodules (mean size 14.5 ± 5.7 mm, range 5 – 33 mm), two hemangiomas (8 mm, 10 mm), two treated lesions (n=10 mm, 12 mm), one regenerative nodule (29 mm), and one focal fat deposition (13 mm). In the double low-dose group, there were 46 HCCs (mean size 15.2 ± 12.7 mm, range 5 – 90 mm), 19 dysplastic nodules (mean size 14.5 ± 9 mm, range 6 – 40 mm), four hemangiomas (mean size 15.5 ± 3.7 mm, range 11 – 20 mm), one metastasis (60 mm), one

adenocarcinoma (24 mm), and one regenerative nodule (13 mm). No significant size difference was observed in all lesions (14.7 ± 6.8 mm in the standard-dose group, 15.8 ± 12.3 mm in the double low-dose group, P = 0.43) and HCCs (14.9 ± 7.4 mm in the standard-dose group, 15.2 ± 12.6 mm in the double low-dose group, P = 0.84) between the two groups.

Lesion characterization— Metastasis from a brain tumor (n = 1) and adenocarcinoma (n = 1) were diagnosed pathologically. One hundred and seven HCCs were diagnosed pathologically (n = 8) or clinically (n = 99): LR-4 or -5 at follow-up MRI within 3 months (n = 27), LR-4 or LR-5 at CT with either tumor staining on follow-up TACE (mean interval, 20.7 ± 11.8 days after CT) (n = 63), tumor staining on angiography with compact lipiodol uptake and tumor marker decrease (n = 1), and progression on follow-up images during chemotherapy (n = 8). There were 62 benign lesions including hemangiomas (n = 6), regenerative nodules (n = 2), dysplastic nodules (n = 51), focal fat deposition (n = 1), and treated lesions (n = 2). For the diagnosis of benign lesions, the aforementioned imaging features and stability in size and imaging features during follow-up were used. The average follow-up interval was 8.8 ± 3.3 months (range, 5.2 – 17.9 months) in those lesions.

Lesion detection— The reference standard for lesion detection was contrast-enhanced CT using 120 kVp (n = 46) followed by MRI using gadoxetic acid (n = 19) or extracellular contrast media (n = 2). There was no significant difference of follow-up modality between the two groups: CT (n = 27) and MRI (n = 8) in double low-dose group and CT (n = 19) and MRI (n = 13) in standard-dose group (P = 0.19). The median interval between spectral CT and the reference standard examination was 46 days (6 – 128 days) in participants with LR-3, -4, -5 or -M. For the 12 participants with definite or probable benign lesions only (n = 6) or no detectable lesions (n = 6), the median interval was 109.5 days (range: 21 – 500 days).

4. Readers' agreement for qualitative image analysis

Intraclass coefficients (ICCs) of image noise were 0.60 (95 % CI: 0.42 – 0.74) and 0.60 (95 % CI: 0.41 – 0.73) on arterial and portal venous phases, respectively. As for image contrast, ICCs were 0.87 (95 % CI: 0.82 – 0.92) and 0.87 (95 % CI: 0.81 – 0.91) on arterial and portal venous phases, respectively. ICCs of image quality were 0.80 (95 % CI: 0.71 – 0.87) on the arterial phase and 0.73 (95 % CI: 0.61 – 0.82) on the portal venous phase. ICCs were obtained based on an average-rating (k = 4), consistency, two-way model.

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Table S1. Scoring scale for qualitative image analyses

Items	Score	Scoring system
Image noise	1-5	Score 1, undiagnostic; Score 2, significant image noise affecting diagnostic confidence; Score 3, diagnostically acceptable but noticeable image quality decrease; Score 4, mild image noise and no or mild image quality decrease Score 5, no definite image noise, similar to model-based iterative reconstruction
Image contrast	1-5	Score 1, substantial lack of contrast similar to non-contrast CT or nephrogenic phase Score 2, poor contrast Score 3, average contrast Score 4, good contrast Score 5, very strong contrast of the images
Overall image quality	1-5	Score 1, undiagnostic Score 2, poorer than average but does not require re-examination Score 3, average Score 4, better than average Score 5, excellent

Table S2. Qualitative image analysis between iDose and 50 keV in all participants

	Arterial phase			Portal venous phase		
	iDose	**50 keV**	***P*-value**	**iDose**	**50 keV**	***P*-value**
All (n = 67)						
Image noise	3.3 ± 0.4 (2.3 – 4.3)	4.3 ± 0.5 (3.3 – 5.0)	<0.001	3.4 ± 0.4 (2.3 – 4.3)	4.3 ± 0.4 (3.3 – 5.0)	<0.001
Contrast	2.9 ± 0.5 (2.0 – 4.0)	4.5 ± 0.6 (2.5 – 5.0)	<0.001	3.2 ± 0.5 (2.0 – 4.3)	4.8 ± 0.3 (3.8 – 5.0)	<0.001
Image quality	3.0 ± 0.5 (2.0 – 4.0)	4.2 ± 0.5 (3.0 – 5.0)	<0.001	3.1 ± 0.5 (2.0 – 4.3)	4.4 ± 0.4 (3.3 – 5.0)	<0.001
Participants with BMI (< 25, n = 43)						
Image noise	3.3 ± 0.4 (2.3 – 3.8)	4.3 ± 0.5 (3.3 – 5.0)	<0.001	3.4 ± 0.4 (2.5 – 4.3)	4.5 ± 0.6 (3.3 – 5.0)	<0.001
Contrast	3.0 ± 0.5 (2.0 – 4.0)	4.5 ± 0.6 (2.5 – 5.0)	<0.001	3.3 ± 0.5 (2.3 – 4.3)	4.8 ± 0.3 (3.8 – 5.0)	<0.001
Image quality	3.0 ± 0.5 (2.0 – 4.0)	4.3 ± 0.5 (3.0 – 5.0)	<0.001	3.2 ± 0.5 (2.3 – 4.3)	4.4 ± 0.4 (3.5 – 5.0)	<0.001
Participants with BMI (≥ 25, n = 24)						
Image noise	3.3 ± 0.3 (2.3 – 4.0)	4.2 ± 0.5 (3.3 – 5.0)	<0.001	3.4 ± 0.3 (2.3 – 4.0)	4.3 ± 0.4 (3.3 – 5.0)	<0.001

Contrast	2.8 ± 0.5 (2.0 – 3.8)	4.3 ± 0.6 (3.0 – 5.0)	<0.001	3.1 ± 0.4 (2.0 – 3.8)	4.8 ± 0.3 (3.0 – 5.0)	<0.001
Image quality	2.9 ± 0.5 (2.0 – 3.8)	4.1 ± 0.5 (3.3 – 5.0)	<0.001	3.1 ± 0.5 (2.0 – 4.0)	4.4 ± 0.4 (3.3 – 5.0)	<0.001
Standard-dose group (n = 32)						
Image noise	3.6 ± 0.3 (2.8 – 4.1)	4.6 ± 0.3 (3.8 – 5.0)	<0.001	3.7 ± 0.3 (3.0 – 4.3)	4.7 ± 0.3 (3.8 – 5.0)	<0.001
Contrast	3.2 ± 0.5 (2.3 – 4.0)	4.6 ± 0.5 (3.3 – 5.0)	<0.001	3.6 ± 0.3 (3.0 – 4.3)	4.9 ± 0.1 (4.5 – 5.0)	<0.001
Image quality	3.3 ± 0.5 (2.5 – 4.0)	4.5 ± 0.4 (2.5 – 4.3)	<0.001	3.5 ± 0.4 (3.0 – 4.3)	4.6 ± 0.3 (4.0 – 5.0)	<0.001
Double low-dose group (n = 35)						
Image noise	3.1 ± 0.3 (2.3 – 3.8)	4.0 ± 0.3 (3.3 – 4.8)	<0.001	3.1 ± 0.3 (2.3 – 3.8)	4.1 ± 0.3 (3.3 – 4.8)	<0.001
Contrast	2.7 ± 0.5 (2.0 – 3.8)	4.3 ± 0.7 (2.5 – 5.0)	<0.001	2.9 ± 0.5 (2.0 – 3.8)	4.7 ± 0.3 (3.8 – 5.0)	<0.001
Image quality	2.7 ± 0.4 (2.0 – 3.5)	4.0 ± 0.5 (3.0 – 4.8)	<0.001	2.8 ± 0.4 (2.0 – 3.8)	4.2 ± 0.4 (3.3 – 4.8)	<0.001

Note—. Values are mean ± standard deviation (range). BMI = body mass index. A *P*-value < 0.05 indicates a significant difference between iDose and 50 keV images.

Table S3. Comparison of lesion conspicuity between iDose and 50 keV in all participants

	iDose	**50 keV**	**Diff (95 % CI)**	***P*-value**
	Estimate (95 % CI)	Estimate (95 % CI)		
Arterial phase				
All lesions	1.93 (1.74 – 2.11)	2.52 (2.23 – 2.82)	0.60 (0.43 – 0.76)	<0.001
Lesion size				
< 20 mm (n = 142)	1.74 (1.57 – 1.91)	2.32 (2.03 – 2.60)	0.58 (0.40 – 0.76)	<0.001
≥ 20 mm (n = 29)	2.84 (2.33 – 3.36)	3.52 (2.93 – 4.10)	0.67 (0.37 – 0.98)	<0.001
BMI*				
< 25 (n = 38, 100 lesions)	1.98 (1.71 – 2.25)	2.55 (2.12 – 2.97)	0.57 (0.35 – 0.78)	<0.001
≥ 25 (n = 22, 71 lesions)	1.85 (1.57 – 2.12)	2.49 (2.10 – 2.88)	0.64 (0.37 – 0.91)	<0.001
Protocol†				
Standard-dose (n = 29, 99 lesions)	2.02 (1.73 – 2.30)	2.45 (2.00 – 2.89)	0.43 (0.24 – 0.62)	<0.001
Double low-dose (n = 31, 72 lesions)	1.80 (1.58 – 2.02)	2.62 (2.31 – 2.93)	0.82 (0.59 – 1.05)	<0.001
Portal venous phase				
All lesions	1.83 (1.67 – 1.99)	2.35 (2.16 – 2.55)	0.52 (0.42 – 0.63)	<0.001
Lesion size				
< 20 mm (n = 142)	1.65 (1.52 – 1.78)	2.12 (1.94 – 2.30)	0.47 (0.35 – 0.60)	<0.001
≥ 20 mm (n = 29)	2.72 (2.26 – 3.17)	3.48 (3.13 – 3.84)	0.77 (0.50 – 1.04)	<0.001
BMI*				

< 25 (n = 38, 100 lesions)	1.93 (1.69 – 2.17)	2.46 (2.20 – 2.72)	0.53 (0.39 – 0.67)	<0.001
≥ 25 (n = 22, 71 lesions)	1.69 (1.45 – 1.93)	2.20 (1.89 – 2.52)	0.51 (0.35 – 0.67)	<0.001
Protocol†				
Standard-dose (n = 29, 99 lesions)	1.88 (1.67 – 2.10)	2.32 (2.06 – 2.59)	0.44 (0.33 – 0.56)	<0.001
Double low-dose (n = 31, 72 lesions)	1.76 (1.50 – .02)	2.39 (2.11 – 2.67)	0.63 (0.44 – 0.82)	<0.001

Note—. BMI = body mass index. *: Seven participants (five with BMIs ≤ 25 and two with BMIs > 25) without focal lesions were excluded from lesion conspicuity analysis. †: Seven participants (three in standard-dose group and four in double low-dose group) without focal lesions were excluded from lesion conspicuity analysis. A *P*-value < 0.05 indicates a significant difference between iDose and 50 keV images.

Table S4. Comparison of focal liver lesion detection rates between iDose and 50 keV in all participants

	Figure of merit (95 % CI)		Diff (95 % CI)	*P*-value
	iDose	50 keV		
All lesions	0.74 (0.67 – 0.81)	0.81 (0.71 – 0.90)	0.07 (0.03 – 0.1)	0.001
Lesion size				
< 20 mm (n = 142)	0.64 (0.58 – 0.69)	0.68 (0.59 – 0.77)	0.04 (-0.01 – 0.09)	0.07
≥ 20 mm (n = 29)	0.60 (0.55 – 0.65)	0.62 (0.57 – 0.66)	0.02 (-0.01 – 0.04)	0.1
BMI*				
< 25 (n = 38, 100 lesions)	0.69 (0.62 – 0.76)	0.71 (0.64 – 0.78)	0.02 (-0.01 – 0.05)	0.16
≥ 25 (n = 22, 71 lesions)	0.55 (0.51 – 0.58)	0.59 (0.55 – 0.63)	0.04 (0.02 – 0.07)	0.003
Protocol†				
Standard-dose (n = 29, 99 lesions)	0.63 (0.57 – 0.68)	0.64 (0.59 – 0.70)	0.02 (-0.01 – 0.04)	0.1
Double low-dose (n = 31, 72 lesions)	0.61 (0.56 – 0.66)	0.65 (0.60 – 0.70)	0.04 (0.01 – 0.07)	0.007

Note—. *: Seven participants (five with a BMI < 25 and two with a BMI ≥ 25) without focal lesions were excluded from lesion conspicuity analysis. †Seven participants (three in the standard-dose group and four in the double low-dose group) without focal lesions were excluded. A *P*-value < 0.05 indicates a statistically significant difference between iDose and 50 keV images.