



Second shot arterial phase to overcome degraded hepatic arterial phase in liver MR imaging

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Abstract

Objectives Second shot arterial phase (SSAP) imaging is an additional arterial phase image obtained by re-injecting a small amount of contrast medium after routine dynamic imaging in gadoxetic acid-enhanced liver MRI. We aimed to evaluate the feasibility and additional value of a SSAP image in gadoxetic acid-enhanced liver MRI.

Methods One hundred seventy-two patients who underwent SSAP imaging after re-injection of 4 mL of contrast material after routine dynamic imaging (original) in gadoxetic acid-enhanced liver MRIs were included. Motion artifacts on arterial phase (AP) images were rated using a 5-point scale and were compared between the original AP images and SSAP images. We evaluated visual detection rates of arterial hypervascularity on the original AP and SSAP images and their subtraction images in patients with hypervascular hepatocellular carcinoma (HCC).

Results The motion artifact of the SSAP images was significantly lower than that of the original AP images (mean score, 1.76 vs 2.06; $p < 0.001$). In particular, motion artifacts reduced significantly in the SSAP images of patients with substantial motion artifacts in their original AP images (2.28 vs 3.28; $p < 0.001$). Among the 30 HCC lesions showing hypervascularity on original AP images, only four (4/30, 13.3%) appeared hyperintense on SSAP images. However, subtraction images of SSAP clearly demonstrated arterial hypervascularity in all HCCs.

Conclusion SSAP images showed significantly fewer motion artifacts than the original AP images. Subtraction images of SSAP maintained the detectability of arterial hypervascularity, although SSAP images showed poor visual detection of arterial hypervascularity of HCC.

Key Points

- Arterial phase images obtained after a second injection of a small amount of contrast medium (second shot arterial phase [SSAP]) improved motion artifacts compared to the original AP images.
- The motion artifacts improved significantly in the SSAP images of patients with substantial motion artifacts in their original AP images.
- Subtraction images of SSAP demonstrated the arterial hypervascularity characteristic of HCC at a level comparable to that of the original AP image.

Keywords Artifacts · Contrast media · Liver · Liver neoplasms · Magnetic resonance imaging

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Abbreviations

AP	Arterial phase
CAIPIRINHA	Controlled aliasing in parallel imaging results in higher acceleration
HBP	Hepatobiliary phase
HCC	Hepatocellular carcinoma
LLC	Lesion-to-liver contrast
MRI	Magnetic resonance imaging
SI	Signal intensity

Table 1 Patients' characteristics

	Patient number
Total study population	172
M:F	108:64
Mean age (range)	63 years (36–84 years)
Reasons for MRI evaluation	
Suspected HCC or screening for HCC	46
Cholangiocarcinoma	11
Hemangioma	4
Hepatic abscess	2
Focal nodular hyperplasia	1
Body weight (mean 61.9 ± 11.4 kg)	
Less than 55 kg (group A)	52
55–65 kg (group B)	61
More than 65 kg (group C)	59
Estimated glomerular filtration rate (eGFR)	
Normal kidney function (eGFR > 90; stage 1)	145
Mildly reduced kidney function (eGFR 60–89; stage 2)	23
Moderately reduced renal function (eGFR 45–59; stage 3A)	4
Severely decreased renal function (eGFR < 30; stages 4 and 5)	0
Total number of HCCs analyzed in our study	30 HCCs in 24 patients
Mean tumor size (range)	1.6 ± 1.3 cm (0.5–7.8 cm)

The estimated glomerular filtration rate (eGFR) was calculated using serum creatinine levels within 1 month of the MRI examination. The diagnosis of 20 HCCs in 16 patients was confirmed using dense Lipiodol uptake on follow-up CT; five HCCs in four patients were confirmed using a combination of elevated tumor markers and characteristic imaging features, and five HCCs in four patients were confirmed by surgery

of the contrast medium at the aortic arch. A portal phase image, transitional phase image, and 20-min HBP image were acquired. The HBP image was obtained using a flip angle of 15° to increase lesion detectability. Thereafter, to obtain the SSAP image, 4 mL of contrast medium was injected using the same injection method and the same MRI parameters used in dynamic imaging were applied. For subtraction image of SSAP, another image was acquired immediately before re-injection of the contrast medium. The total amount of

gadoteric acid administered was 10 mL in all patients. The breath-hold time for each phase was approximately 13 s. Each subtraction image was generated automatically after acquisition of the original AP and SSAP using vendor-provided software.

Qualitative image analysis

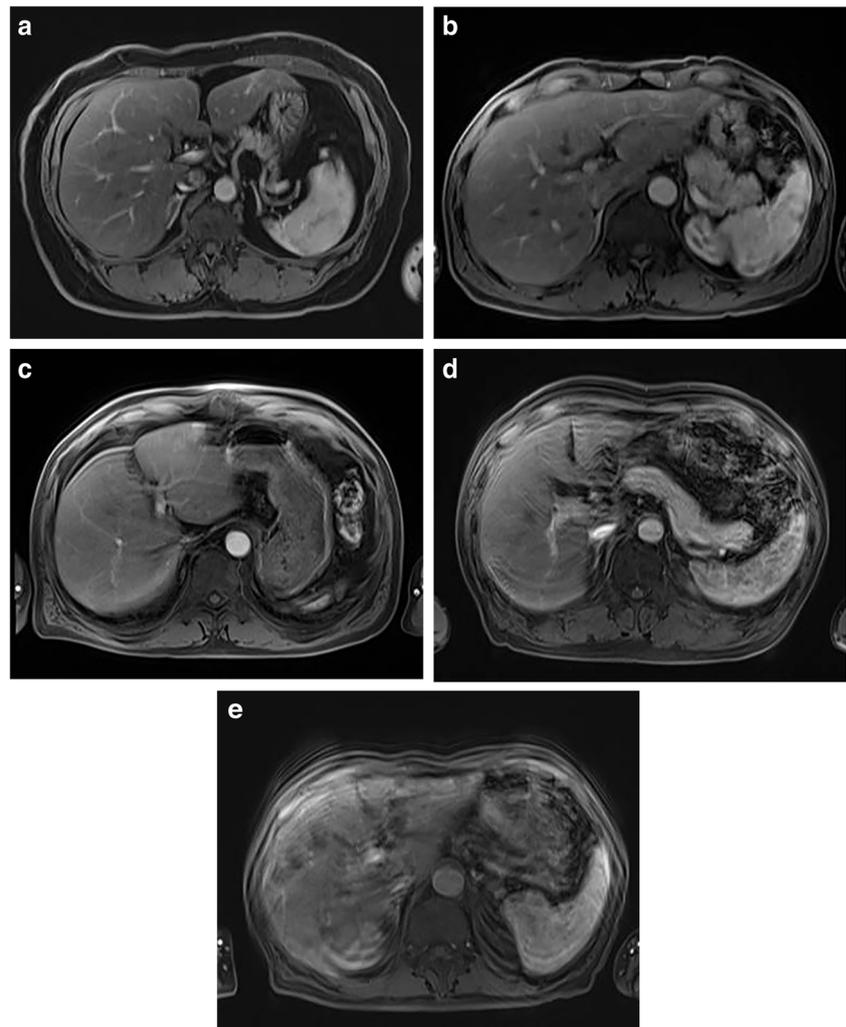
Two board-certified abdominal radiologists with 25 and 5 years of experience in abdominal imaging, respectively, reviewed the AP and subtraction images independently. At a 2-week interval after analyzing the original AP and subtraction image sets, they analyzed the SSAP and subtraction image sets to prevent recall bias. The motion artifact score was assigned for original AP and SSAP images using a 5-point scale: 1, no motion artifacts; 2, minimal motion artifact, no effect on diagnostic quality; 3, moderate motion artifact with mild effect on diagnostic quality; 4, severe motion artifact, images degraded but interpretable; and 5, extensive motion artifact, images of nondiagnostic quality (Fig. 2) [6, 7, 16, 17]. The subtraction image quality score was assigned on a scale of 1 (no artifact) to 5 (nondiagnostic) considering both misregistration artifacts and motion artifacts (Fig. 3). Scores were averaged across the two readers, and the average score

Table 2 Sequence parameters for dynamic MR study

Repetition time/echo time (ms)	3.97/1.29
Flip angle (°)	9
Slice thickness (mm)	3
Reconstruction interval (mm)	3
Field of view (mm)	308 × 309
Matrix	320 × 195
Number of frame	1
Fat suppression	Spectral saturation
Parallel acceleration factor	CAIPIRINHA 4
Acquisition time (s)	13
Sequence type	VIBE

CAIPIRINHA controlled aliasing in parallel imaging results in higher acceleration, VIBE volumetric interpolated breath-hold examination

Fig. 2 Representative images for motion artifact scoring used in this study. **a** Score 1 is no motion artifact. **b** Score 2 is minimal motion artifact with no effect on diagnostic quality. **c** Score 3 is moderate motion artifact with some but no severe effect on diagnostic quality. **d** Score 4 is severe motion artifact but image is still interpretable. **e** Score 5 is extensive motion artifact and image is nondiagnostic



was used in the analyses. A mean score of 3 or more was considered to indicate the presence of substantial artifacts.

HCC and quantitative analyses

Two board-certified abdominal radiologists with 18 and 5 years of experience who were not involved in the aforementioned image analysis performed qualitative and quantitative analyses of selected cases with HCCs. First, each HCC was evaluated based on the predominant signal intensity (SI) on the original AP, SSAP, and their subtraction images relative to the surrounding liver parenchyma as follows: 1, hyperintense; 2, isointense; and 3, hypointense. For qualitative evaluation, the discrepancies between the two readers were resolved by discussion to reach consensus. Second, region of interest measurements of the SIs were performed for the lesion-to-liver contrast (LLC) of the HCC on the AP and subtraction images, and signal-to-noise ratios (SNRs) were determined for the aorta and liver parenchyma on the AP and HBP images, respectively. The LLC of the HCC was calculated as the mean

SI difference between the tumor and liver parenchyma divided by the mean SI of the liver parenchyma. The SNRs of the AP aorta and the HBP liver parenchyma were calculated as the SI of the aorta or liver parenchyma divided by the background noise. Background noise was defined as the standard deviation of the SI measured in the liver parenchyma. Then, the average value was used in further analyses.

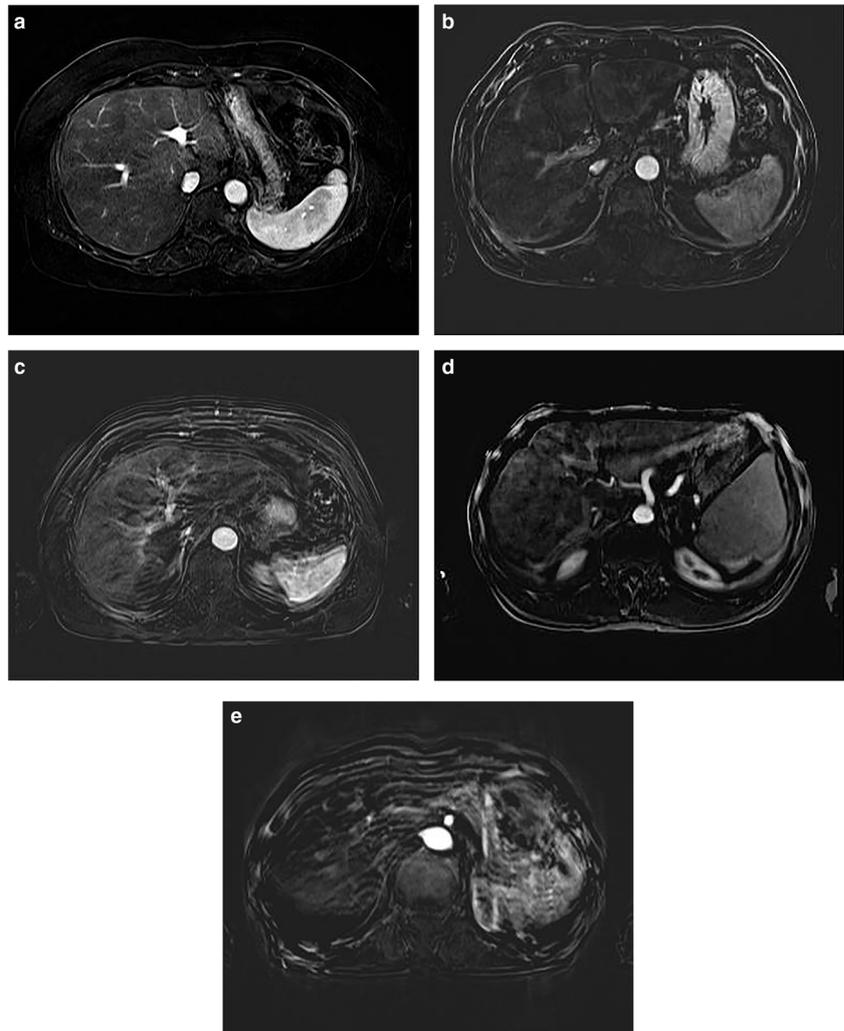
Statistical analyses

Interobserver agreements were analyzed using the intraclass correlation coefficient (ICC) and kappa statistics.

AP motion artifacts and subtraction image quality were compared between the original and second shot image sets using paired *t* tests. Patients were also subclassified according to the motion artifact score of the original AP image, and paired comparisons were made for motion artifacts and subtraction image quality in each subgroup.

In patients with hypervascular HCC, the visual detection rate of arterial hypervascularity was compared between the

Fig. 3 Representative images for subtraction image quality scoring used in this study. **(a)** Score 1 is no misregistration artifact. **(b)** Score 2 is minimal misregistration artifact with no effect on diagnostic quality. **(c)** Score 3 is moderate misregistration artifact with some but no severe effect on diagnostic quality. **(d)** Score 4 is severe misregistration artifact but image is still interpretable. **(e)** Score 5 is extensive misregistration artifact and image is nondiagnostic



original and SS image sets of AP and subtraction images using Fisher's exact test. The significance of differences in quantitative values between the original and SS image sets was evaluated using a paired *t* test.

To assess the adequacy of a fixed dose of 6 mL or 4 mL for AP, subtraction, and HBP images, we compared the enhancement degrees of the HCC, aorta, and liver parenchyma among the three body weight subgroups using analysis of variance with a post hoc test. A *p* value less than 0.05 was considered to indicate statistical significance. Statistical analyses were performed using commercial statistical software (version 19, IBM SPSS Inc.).

Results

Analysis of motion artifact and subtraction image quality

Reader agreement for the image quality score assignment was excellent (ICC, 0.851–0.905; Table 3). The original AP

images showed substantial motion artifacts (\geq score 3) in 41 patients (41/172, 23.8%), including severe motion artifacts (score 4) in 10 patients (10/172, 5.8%), whereas the SSAP image showed substantial motion artifacts in 19 patients (19/172, 11.0%), including severe motion artifacts in four patients (4/172, 2.3%). No original AP images or SSAP images were nondiagnostic (score 5). However, a score of 5 was assigned to one SS subtraction image because significant misregistration occurred due to a striking difference in breath-holding degree, not because of motion artifacts.

For the whole study population, the motion artifact score of the original AP images was significantly higher than that of the SSAP images (2.06 and 1.76; $p < 0.001$) (Table 3). The image quality did not differ significantly between the original and SS subtraction images (2.06 and 2.07; $p = 0.932$). In patients without substantial motion artifacts in the original AP images, motion artifacts were not significantly different between the original AP image and SSAP image, whereas the original subtraction image was better than the SS subtraction image ($p = 0.098$ and 0.002, respectively). However, in

Table 3 Qualitative analysis of image quality according to motion artifacts in the original AP images

		Original AP image	SSAP image	<i>p</i> value	Original subtraction image	SS subtraction image	<i>p</i> value
Interobserver agreement		0.905	0.851		0.891	0.874	
Study population (<i>n</i> = 172)	Reader 1	2.02 ± 0.91	1.74 ± 0.79	< 0.001	2.10 ± 0.93	2.12 ± 0.89	0.757
	Reader 2	2.10 ± 0.84	1.78 ± 0.76	< 0.001	2.04 ± 0.85	2.03 ± 0.80	0.864
	Average	2.06 ± 0.83	1.76 ± 0.72	< 0.001	2.06 ± 0.84	2.08 ± 0.79	0.932
In patients without substantial motion artifacts on original AP image (< 3) (<i>n</i> = 131)	Reader 1	1.53 ± 0.50	1.56 ± 0.69	0.539	1.69 ± 0.67	2.01 ± 0.87	< 0.001
	Reader 2	1.67 ± 0.47	1.56 ± 0.67	0.052	1.67 ± 0.55	1.85 ± 0.74	0.010
	Average	1.68 ± 0.50	1.60 ± 0.62	0.098	1.74 ± 0.58	1.96 ± 0.76	0.002
In patients with substantial motion artifacts on original AP image (≥ 3) (<i>n</i> = 41)	Reader 1	3.25 ± 0.43	2.18 ± 0.86	< 0.001	3.12 ± 0.70	2.41 ± 0.86	< 0.001
	Reader 2	3.23 ± 0.42	2.35 ± 0.70	< 0.001	3.00 ± 0.71	2.48 ± 0.77	0.001
	Average	3.28 ± 0.43	2.28 ± 0.78	< 0.001	3.12 ± 0.69	2.44 ± 0.81	< 0.001
In patients with severe motion artifacts on original AP image (≥ 4) (<i>n</i> = 10)	Reader 1	4.00 ± 0.00	2.88 ± 0.99	0.015	4.13 ± 0.35	3.25 ± 0.71	0.006
	Reader 2	4.00 ± 0.00	3.00 ± 0.76	0.007	3.88 ± 0.35	3.13 ± 0.64	0.019
	Average	4.00 ± 0.00	2.9 ± 0.84	0.003	4.00 ± 0.24	3.10 ± 0.70	0.003

All values are means ± standard deviations. *P* values were calculated by paired *t* test

AP arterial phase, SS second shot

patients with either substantial motion artifacts or severe motion artifacts in the original AP images, the motion artifacts were reduced significantly in the SSAP images ($p < 0.001$ and 0.003 , respectively). Moreover, their subtraction image quality also improved on the SS subtraction images ($p < 0.001$ and 0.003 , respectively).

Analysis of arterial hypervascularity of HCC

Visual assessment of the arterial hypervascularity of HCC showed excellent interreader agreement (k , 0.79–0.94). All HCCs were hyperintense on both the original and SS subtraction images. However, only four HCCs (4/30, 13.3%) were hyperintense in the SSAP images ($p = 0.021$), whereas 19 HCCs (19/30, 63.3%) were isointense and seven HCCs (7/30, 23.3%) were hypointense compared with the adjacent liver parenchyma (Fig. 4).

For quantitative analysis, reader agreement was also excellent (ICC, 0.87–0.92). The SNR of the aorta and the LLC of the HCC were significantly higher in the original AP images than in the SSAP images ($p = 0.005$ and < 0.001 , respectively). When subtraction images were compared, the LLC of the HCC showed higher tendency on the original subtraction images than on the SS subtraction images (9.81 and 9.14; $p = 0.305$).

Adequacy of dosage of contrast material for imaging

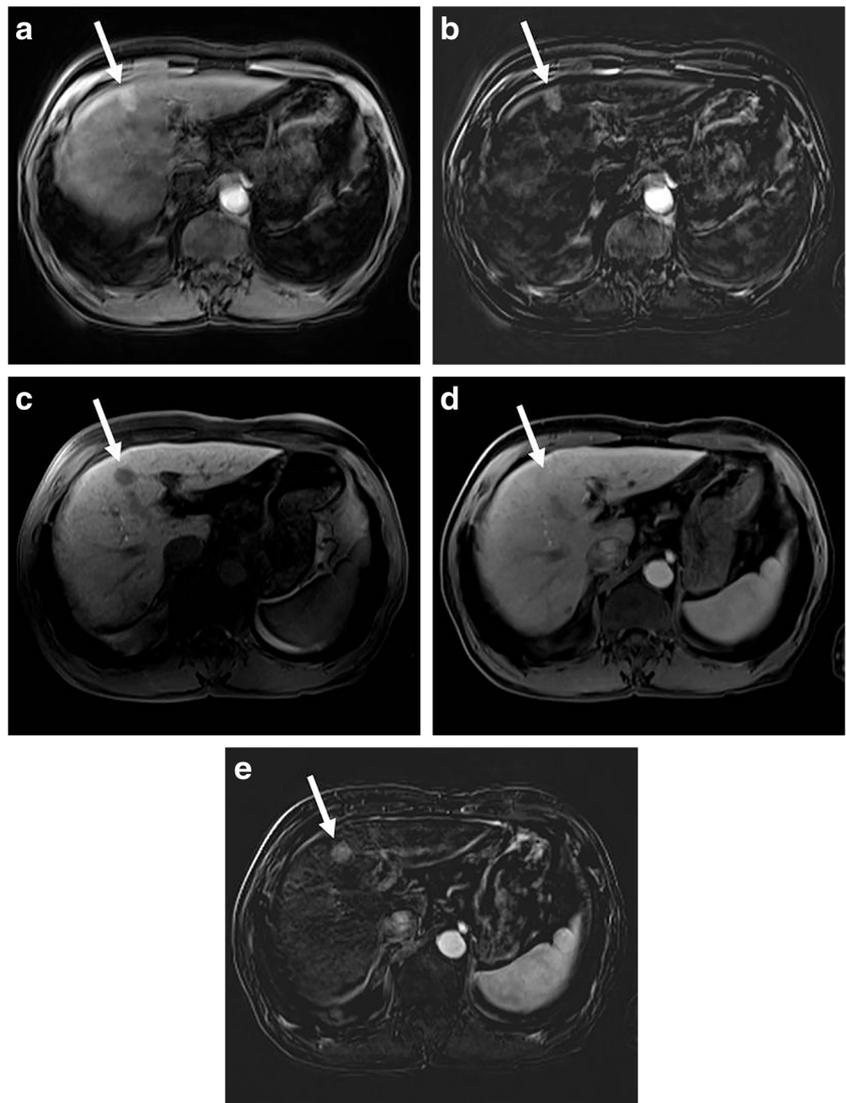
To assess whether the first injected contrast volume of 6 mL was appropriate (Table 4), SNRs of the aorta on the original AP images and liver parenchyma on the HBP image were significantly higher in group A (less than 55 kg) than in group C (more than 65 kg) ($p = 0.006$ and 0.003 , respectively). The

LLCs of HCC on the original AP and HBP images did not differ significantly among the three body weight groups ($p = 0.577$ and 0.554 , respectively). To assess whether the second injected contrast volume of 4 mL was appropriate, the SNR of the aorta and LLC of HCC on the SSAP images were not statistically significant ($p = 0.444$ and 0.427 , respectively).

Discussion

We investigated whether a second injection of a small amount of contrast medium could effectively correct low-quality AP images in gadoteric acid-enhanced liver MRI. Our results demonstrated that SSAP images, obtained after a second injection of 4 mL of gadoteric acid, had significantly fewer motion artifacts than the original AP images, especially in patients with substantial or severe motion artifacts on their original AP images. Therefore, SSAP images can be considered as an alternative to damaged arterial phase images with severe motion artifacts in patients in whom an arterial phase image is essential for diagnosis of HCC. However, on the SSAP images, visual assessment of the arterial hypervascularity characteristic of HCC was limited by increased parenchymal enhancement from the previously injected contrast agent and decreased arterial enhancement of the HCC because of the small amount of additional contrast agent injected. Fortunately, subtraction images maintained the lesion conspicuity of hypervascular HCCs, compensating for the potential disadvantage of suboptimal enhancement in SSAP images. Nonetheless, the improvement in motion artifacts did not lead to statistical improvements in detection of arterial hypervascularity, presumably because no case with an arterial phase image of nondiagnostic quality was included in our study.

Fig. 4 A 73-year-old man with a hypervascular hepatocellular carcinoma (HCC). The original AP image (a) and its subtraction image (b) show severe motion artifacts and poor subtraction image quality. HCC (arrow) also suffered from the motion artifact on the original AP (a) and its subtraction (b) images, comparing with clear demonstration on the HBP image (c). The SSAP image (d) shows less motion artifact, and its subtraction image (e) shows improved subtraction image quality. Although it is difficult to distinguish HCC (arrow) from the adjacent liver parenchyma on the SSAP image (d), the SS subtraction image (e) clearly revealed arterial hypervascularity of the HCC on the exact location



Bashir et al reported that patients with prior episodes of transient severe motion are at risk for recurrence of severe motion artifacts in subsequent MR imaging with gadoteric acid [16]. However, we found significantly reduced motion artifacts on

SSAP images obtained following a second injection of 4 mL of contrast given immediately after acquiring a 20-min HBP image, especially in patients with substantial or severe motion artifacts on their original AP images. Severe motion artifacts are more

Table 4 Quantitative analysis of AP and HBP images in patients with HCC

	Original AP		HBP		SSAP	
	SNR of aorta	LLC	SNR of liver parenchyma	LLC	SNR of aorta	LLC
All HCCs (n = 30)	323.75 ± 196.44	0.47 ± 0.31	372.43 ± 320.68	-0.40 ± 0.24	229.62 ± 136.96	-0.06 ± 0.23
Group A (n = 6)	495.82 ± 190.05	0.44 ± 0.19	671.05 ± 477.12	-0.38 ± 0.14	279.9 ± 62.20	1.09 ± 0.13
Group B (n = 8)	385.82 ± 151.79	0.38 ± 0.17	480.32 ± 251.17	-0.48 ± 0.11	249.73 ± 148.18	-0.14 ± 0.08
Group C (n = 16)	228.18 ± 190.05	0.52 ± 0.39	206.51 ± 149.18	-0.37 ± 0.31	200.70 ± 150.37	-0.01 ± 0.29

Group A refers to patients with body weight of less than 55 kg. Group B refers to patients with body weight of 55–65 kg. Group C refers to patients with body weight of more than 65 kg

AP arterial phase, SSAP second shot arterial phase, HBP hepatobiliary phase, SNR signal-to-noise ratio, LLC lesion-to-liver contrast

likely to occur in the context of the off-label dosage of 20 mL [17], whereas we injected subjects the second time with a much smaller volume of contrast medium (4 mL), which might explain the different results between studies.

In addition to motion-related artifacts, a steep change in gadolinium concentration during sampling at or near the center of the k-space, called a ringing artifact, is also known to degrade the image quality of AP images [6, 18]. In our study, the SSAP image quality was better than that of the original AP images. Given that all the other conditions of the MR scans were the same for the original AP and SSAP images, we hypothesize that the overall increase in SI of background liver parenchyma caused by the previously injected contrast medium could account for the less rapid change in gadolinium concentration after injecting the second dose of contrast medium, resulting in fewer artifacts. Although we did not explicitly assess ringing artifacts on the AP images, it is easy to distinguish between significant ringing artifacts and motion artifacts, but minor ringing artifacts can be misrecognized as mild motion artifacts.

In terms of injected contrast volume, the fixed dose of 6 mL in the first injection was an overdose for patients in group A (less than 55 kg) and an insufficient dose for patients in group C (more than 65 kg). A fixed dose of 4 mL in the second injection was an insufficient dose for most patients in the study population. Because the degree of arterial enhancement of hypervascular HCC is dose-dependent [19], it is obvious that a fixed dose of either 6 mL or 4 mL would result in inadequate enhancement in AP images, especially in heavier patients (group C). Enhancement of the aorta and HCC on AP images tended to decrease from group A to group C. However, the LLCs of HCC on AP and HBP images, which are more important for the diagnosis of HCC, showed no significant differences. Therefore, its application should be considered carefully in overweight patients because of decreased enhancement.

Subtraction images have recently become an essential part of liver MRI in many hospitals, and subtraction image quality has improved due to technical advances in image registration [5, 20, 21]. Subtraction images can address weak arterial enhancement caused by a smaller injected volume and gadolinium content in gadoxetic acid-enhanced MRI [5]. In agreement with previous studies, we found that subtraction images helped compensate for suboptimal arterial enhancement of HCC caused by the suboptimal dosage of 4 mL in the second injection. Thus, analyzing subtraction images is essential and the subtraction process is critical for the proposed SSAP method. Any misregistration can lead to failure of the SSAP method, and peripheral lesions at the liver dome may be at particular risk for misregistration artifact. Unfortunately, in our study, there was one case with nondiagnostic quality of the SS subtraction image due to misregistration artifact, in which arterial hypervascularity of HCC failed to be detected. Therefore, when applying the SSAP method, careful attention should be paid to examine this additional step.

In our study, we used a total of 10 mL of gadoxetic acid in each subject. Off-label dosing of gadoxetic acid has been discontinued in some institutions because a high dosage of gadolinium-based MRI contrast agent is associated with nephrogenic systemic fibrosis (NSF) in patients with severe renal failure [6]. Although gadoxetic acid is known to be associated with an intermediate risk for NSF, no NSF associated with gadoxetic acid has yet been reported [22]. No patient in our study had severely reduced renal function, and none of our patients developed NSF during the follow-up period of 4 months. Nevertheless, when re-obtaining AP images because of degraded original AP images, contrast material injection is recommended only for patients with normal renal function and should be carefully considered in patients with renal insufficiency.

Our study had several limitations. First, the study design was retrospective, and the number of patients included was moderate. Second, our study's generalizability is limited to nonobese subjects. Although our results can be applied to Asian subjects with relatively light body weights, further studies are needed to determine whether the benefits of SSAP are also applicable to American and European individuals who have relatively heavy body weights. Third, we performed subgroup analyses only in patients with hypervascular HCCs in their original AP images. Therefore, hypovascular HCCs or HCCs showing insufficient arterial enhancement due to suboptimal dose injection (6 mL) might have been excluded from the study, possibly affecting the detectability of the arterial hypervascularity characteristic of HCC. In addition, we performed quantitative analyses only for patients with HCCs, not for the entire study population. However, analyzing the images of patients with HCCs is significant because appropriate enhancement of AP and HBP images is itself associated with detection and diagnosis of HCC.

In conclusion, AP images obtained after a second injection of a small amount of contrast medium (SSAP) improved image quality compared to the original AP images in patients with substantial or severe motion artifacts on their original AP images. Subtraction images of SSAP maintained the detectability of the arterial hypervascularity characteristic of HCC despite a decrease in arterial enhancement of HCC on the SSAP images. Therefore, a second injection of a small amount of contrast medium can be applied with caution in patients with damaged AP images in gadoxetic acid-enhanced liver MRI, which is critical for the diagnosis of HCC.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Chang Hee Lee.

Conflict of interest The authors declare that they have no competing interests.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology

- Retrospective
- Observational
- Performed at one institution

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