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Evaluation and Prediction of Post-Hepatectomy Liver Failure Using Imaging Techniques: Value of Gadoxetic Acid-Enhanced Magnetic Resonance Imaging

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Despite improvements in operative techniques and perioperative care, post-hepatectomy liver failure (PHLF) remains the most serious cause of morbidity and mortality after surgery, and several risk factors have been identified to predict PHLF. Although volumetric assessment using imaging contributes to surgical simulation by estimating the function of future liver remnants in predicting PHLF, liver function is assumed to be homogeneous throughout the liver. The combination of volumetric and functional analyses may be more useful for an accurate evaluation of liver function and prediction of PHLF than only volumetric analysis. Gadoxetic acid is a hepatocyte-specific magnetic resonance (MR) contrast agent that is taken up by hepatocytes via the OATP1 transporter after intravenous administration. Gadoxetic acid-enhanced MR imaging (MRI) offers information regarding both global and regional functions, leading to a more precise evaluation even in cases with heterogeneous liver function. Various indices, including signal intensity-based methods and MR relaxometry, have been proposed for the estimation of liver function and prediction of PHLF using gadoxetic acid-enhanced MRI. Recent developments in MR techniques, including high-resolution hepatobiliary phase images using deep learning image reconstruction and whole-liver T1 map acquisition, have enabled a more detailed and accurate estimation of liver function in gadoxetic acid-enhanced MRI.
Keywords: Liver cancer; Post-hepatectomy liver failure; MRI; Gadoxetic acid

INTRODUCTION

Hepatic resection is a curative established treatment for patients with primary and metastatic liver tumors [1,2]. However, post-hepatectomy liver failure (PHLF) remains the most serious post-surgical cause of morbidity and mortality despite the improvements in operative techniques and perioperative care [3,4]. The incidence of PHLF can be up to 39.6% in patients who undergo major hepatectomy, and its severity has been reported to be associated with postoperative mortality and morbidity [3-5]. Several risk factors and parameters have been identified to predict PHLF, including biochemical liver function and indocyanine green (ICG) tests [6,7].

Volumetric assessment of the future liver remnant (FLR) is also considered an important factor in the estimation of PHLF, and computed tomography (CT) volumetric analysis is widely used to calculate the FLR [8]. Gadoxetic acid-enhanced magnetic resonance imaging (MRI), which uses a hepatobiliary contrast agent taken up by hepatocytes after intravenous injection, has also been used to predict PHLF by estimating the functional remnant liver volume [9]. Additionally, gadoxetic acid-enhanced MRI can provide several parameters for estimating liver function and is expected to predict PHLF more precisely than only volumetric assessment. In this review, we present the definition of PHLF and the role of imaging examinations in

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its prediction, with a focus on the value of gadoxetic acid-enhanced MRI.

Definition and Risk Factors for PHLF

Several researchers have defined PHLF based on post-operative serum examinations, including total bilirubin and/or prothrombin time. However, as there are various criteria for evaluating PHLF, no definitive criterion has been established. These criteria include complicated formulae and undefined laboratory tests, which limit their utility. Therefore, the absence of a definitive criterion for PHLF was a critical limitation of this study. In routine clinical practice, the Model for End-Stage Liver Disease (MELD) score is a definition calculated from serum creatinine, prothrombin time international normalized ratio (PT-INR), and bilirubin. The '50-50 criterion' (PT < 50% and bilirubin > 50 μmL/L) and peak bilirubin > 7 rule have also been proposed as a simple definition for PHLF. In 2011, the International Study Group of Liver Surgery (ISGLS) defined the severity of PHLF using criteria such as increased INR and concomitant hyperbilirubinemia on or after postoperative day 5 [3]. The ISGLS further classifies the severity of PHLF. Grade A represents a minor temporary deterioration in liver function requiring no change in clinical management. Grade B PHLF results in a deviation from the routine clinical course but is manageable without invasive treatment. Grade C PHLF requires invasive procedures, such as hemodialysis, intubation, mechanical ventilation, extracorporeal liver support, or liver transplantation. Based on the ISGLS criteria, Grade A is defined as mild PHLF, and Grades B and C are considered severe PHLF [3].

Identification of the risk factors associated with PHLF is crucial for the appropriate selection of patients and providing information on therapeutic strategies to decrease the incidence and postoperative mortality associated with PHLF. The risk factors for PHLF can be categorized into comorbidities underlying liver disease and perioperative factors [4]. Patient-related factors, including advanced age, male sex, diabetes mellitus, metabolic disorders, malnutrition, renal insufficiency, hyperbilirubinemia, and thrombocytopenia can be associated with an increased but fully uncontrolled risk of PHLF. Perioperative factors can be controlled to minimize the risk of developing PHLF. Surgery-related factors, including excessive blood loss (> 1200 mL), requirement of blood transfusion, prolonged operative time (> 240 min), extended liver resection (> 50% of the liver volume), need for vena cava or other vascular resection, and duration of the Pringle maneuver, are known risk factors for PHLF.

In addition to patient- and surgery-related factors, preoperative risk assessment has important implications for surgical strategies to identify patients at high risk of PHLF. For risk assessment, preoperative liver function using multiple techniques is generally evaluated using clinical factors (presence of chronic liver disease, steatosis, hyperbilirubinemia, and hepatotoxic chemotherapy), laboratory markers (Child–Pugh classification, albumin-bilirubin [ALBI] score, and MELD score), functional tests (ICG test), and the quantity and quality of FLRs. Avoiding liver failure after hepatic resection depends on the regenerative capacity of the remaining liver tissue and the ability to preserve liver function. Noninvasive assessment using the FLR is crucial for surveillance before major hepatic resection, particularly in patients with hepatocellular carcinoma (HCC). Makuuchi's criteria involves integrating the parameters of Child–Pugh classification and ICG plasma disappearance rate (ICG-PDR) to determine the extent of liver resection for HCC [10]. Preoperative assessment of liver function includes ICG and general liver function tests, including Child–Pugh, ALBI, and MELD scores. The extent of hepatic resection must be determined based on the estimated residual liver function.

Role of Volumetric Analysis Using Imaging for Predicting PHLF

Development of PHLF is strongly associated with the volume and function of the FLR, and guidelines have established that the FLR should be preserved as much as possible to prevent PHLF in patients undergoing major liver resection [10,11]. Systematic assessment of the residual liver function during preoperative surgical planning is critical, particularly in cases of baseline liver dysfunction or anticipated extended hemihepatectomy. In general, the required FLR of total liver volume is > 25% for patients with normal liver function, > 30% for patients who receive hepatotoxic chemotherapy (e.g., oxaliplatin and irinotecan), and > 40% for patients with cirrhosis. In patients who do not meet the minimum safe volume threshold of the FLR, portal vein embolization (PVE) can be used to induce atrophy of the embolized liver lobe and compensatory hypertrophy of the FLR [12].

Accurate measurement of liver volume is crucial because

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of substantial variability in liver volume among patients. To calculate liver volume, CT volumetric analysis is an universally accepted method for estimating the FLR. Three-dimensional (3D) post-processing software enables semiautomatic FLR measurements using contrast-enhanced CT images [13]. Deep learning models have recently been developed for the automated or semi-automated segmentation of Couinaud liver segments and FLR for preoperative volumetric assessment [14]. The software also provides visualization of the intrahepatic portal veins and allows precise measurement of the segmental volume of the liver based on the architecture of the intrahepatic vessels. A previous study reported that segment or subsegment volumetry calculated using 3D simulation software highly correlated with the actual resected specimen [15]. An accurate preoperative estimation of the FLR volume is indispensable, and 3D volumetric analysis contributes to precise surgical simulation by drawing and assisting liver surgical planning (Fig. 1).

For safe liver resection, the identification of both portal perfusion and venous drainage areas is important. Saito et al. [16] reported that the perfusion area of the right anterior segment crossed the superior right hepatic vein and drained into the superior middle hepatic vein in 25% of the patients. Hepatic vein-associated remnant liver ischemia or congestion should be considered when left hepatectomy is performed in such patients because the venous blood regurgitates to the portal vein via the sinusoid in the congested areas resulting in a decrease in portal blood supply [17]. Preoperative detection and identification of the superior right hepatic vein using simulation software are crucial for the precise estimation of the FLR volume after left hepatectomy. The 3D simulation software using contrast-enhanced CT is also useful for laparoscopic liver resection. The 3D simulation of liver resection facilitates intraoperative identification of the vascular and bile duct anatomy and accurately predicts the resected liver volume and surgical margin. Although 3D post-processing software-based CT volumetry is useful for estimating FLR volume following hepatic resection, volumetric assessment for the estimation of future remnant liver function is based on the assumption that liver function is homogeneous throughout the liver segment. Therefore, the combination of volumetric and functional information may be useful for a more accurate evaluation of liver function and estimation of PHLF than morphological analysis.

Value of Gadoxetic Acid-Enhanced MRI for Predicting PHLF

Gadoxetic acid is a hepatocyte-specific magnetic resonance (MR) contrast agent. After intravenous administration, half of the drug is taken up by hepatocytes via the OATP1 transporter and excreted into the bile duct [18]. In the hepatobiliary phase (HBP) images obtained approximately 20 min after administration, uptake into the liver parenchyma can be used to estimate liver function (Fig. 2). The degree of liver parenchymal enhancement decreases as the liver function deteriorates [18]. Haimerl et al. [19] reported that a linear regression model showed a significant correlation between ICG-PDR and gadoxetic acid-enhanced MRI-derived parameters. Haimerl et al. [19] also showed that relaxometry-based parameters were better correlated with ICG-PDR than signal intensity-based parameters.

Various indices have been proposed for the estimation

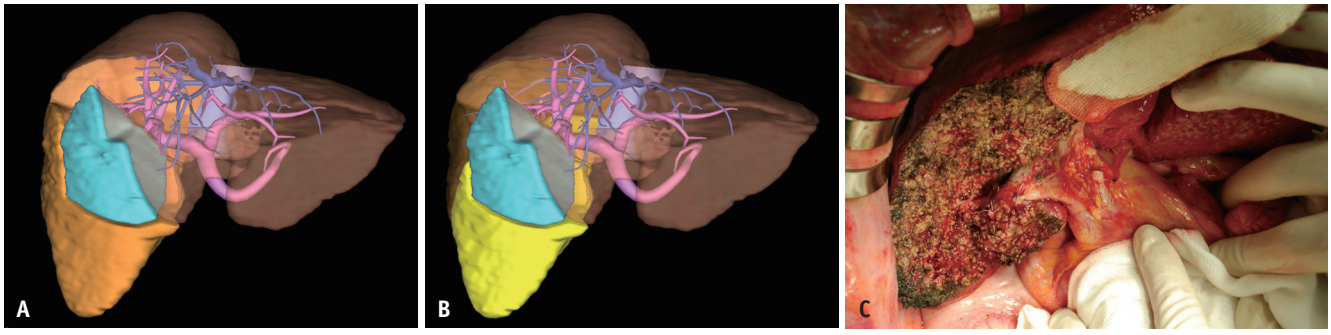

Fig. 1. Hepatic resection of a 60-year-old man (Child–Pugh B patient) with HCC. **A:** First, posterior segmentectomy with S5 partial hepatectomy is conducted; however, the estimated resecting volume is relatively large (543 cm^3) using CT volumetry calculated from 3D simulation software. **B:** Surgical planning changed to S6 subsegmentectomy with S5 partial hepatectomy and the estimated resecting volume decreases (323 cm^3). **C:** Patient receives hepatic resection without significant PHLF, and the resected liver weight (366 g) is considerably similar to the resecting volume (323 cm^3) calculated using CT volumetry. HCC = hepatocellular carcinoma, CT = computed tomography, PHLF = post-hepatectomy liver failure

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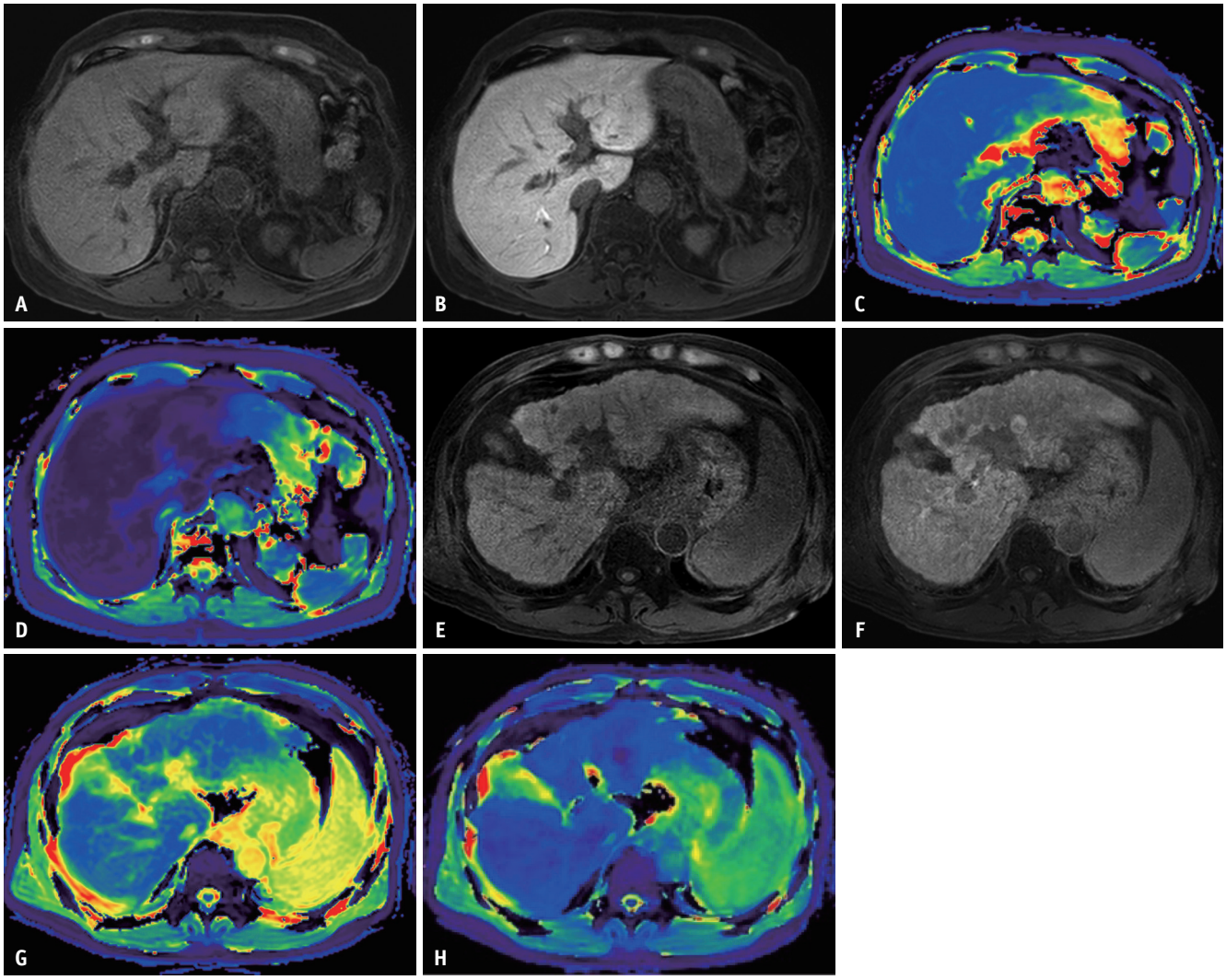

Fig. 2. T1-weighted images and color-coded T1 maps on precontrast and hepatobiliary phase images for patient with normal and impaired liver function. **A-D:** An 81-year-old woman with pancreatic ductal adenocarcinoma. The good liver parenchymal enhancement in the HBP **(B)** compared with the precontrast T1-weighted image **(A)** suggests preserved liver function (calculated liver-to-muscle ratio = 2.83, liver-to-spleen ratio = 2.41, relative liver enhancement = 1.16, and contrast enhancement index = 2.16). T1 maps in precontrast **(C)** and HBP **(D)** images show a strong uptake of gadoxetic acid contrast agent (reduction rate of T1 value = 0.64 and ΔR1 value = 2.28). **E-H:** A 64-year-old man with hepatocellular carcinoma caused by hepatitis C virus infection. Surface irregularities and atrophy of the liver suggest advanced fibrosis or cirrhosis. Poor liver parenchymal enhancement in HBP **(F)** compared with the precontrast T1-weighted image **(E)** suggests impaired liver function (calculated liver-to-muscle ratio = 2.10, liver-to-spleen ratio = 1.26, relative liver enhancement = 0.62, and contrast enhancement index = 1.64). T1 maps in precontrast **(G)** and HBP **(H)** images show faint uptake of gadoxetic acid contrast agent (reduction rate of T1 value = 0.38 and ΔR1 value = 0.69). HBP = hepatobiliary phase

of liver function using gadoxetic acid-enhanced MRI, including signal intensity-based methods and MR relaxometry (Table 1). Signal-intensity-based methods using gadoxetic acid-enhanced MRI are easily applicable for estimating the regional liver function [19]. Maintaining the consistency of liver enhancement over serial examinations is important in signal intensity-based measurements. However, signal intensity is a relative value that depends on technical parameters, including magnetic field strength, receiver coils, B1-field heterogeneity, pulse sequence, reconstruction method, and MRI system manufacturer. Therefore, signal intensity correction adjusted for pre- and post-contrast images using the signal intensities of various reference organs is required. The major methods for signal intensity correction include the relative enhancement of HBP images considering the liver-to-muscle ratio or liver-to-spleen ratio. A previous study demonstrated that these parameters were consistent across serial examinations, scanner types, and field strengths

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Table 1. Summary of signal intensity and relaxometry methods for estimating liver function

Indices	Required phase	Reference tissue	Formula
Signal intensity-based method			
Liver-to-muscle ratio	HBP	Spleen	SI_{HBP} of the liver/SI_{HBP} of the muscle
Liver-to-spleen ratio	HBP	Muscle	SI_{HBP} of the liver/SI_{HBP} of the spleen
Relative liver enhancement	Pre, HBP	None	(SI_{HBP} of the liver - SI_{pre} of the liver)/SI_{pre} of the liver
Contrast enhancement index	Pre, HBP	Muscle	(SI_{HBP} of the liver/SI_{HBP} of the muscle)/(SI_{pre} of the liver/SI_{pre} of the muscle)
Hepatic uptake index	HBP	Spleen	Liver volume × [(SI_{HBP} of the liver/SI_{HBP} of the spleen) - 1]
MR relaxometry method			
Reduction rate of T1 value	Pre, HBP	None	($T1_{pre}$ of the liver – $T1_{HBP}$ of the liver)/$T1_{pre}$ of the liver
ΔR1 value	Pre, HBP	None	$1/T1_{HBP} - 1/T1_{pre}$
Hepatocyte uptake ratio	Pre, HBP	Spleen	$\psi_{spleen}/(1 - \psi_{liver}) \times (\Delta T1_{spleen}/\Delta T1_{liver} - \psi_{liver}/\psi_{spleen})$

$\Delta T1_{spleen}$ and $\Delta T1_{liver}$ indicate the difference in T1 values of the spleen and liver, respectively, between precontrast and HBP images. ψ_{spleen} and ψ_{liver} are the water content of the spleen and liver, respectively.
HBP = hepatobiliary phase, Pre = pre-contrast, SI = signal intensity, MR = magnetic resonance

[20]. Relative liver enhancement and contrast enhancement index, employing pre-contrast and HBP images, were used to evaluate the degree of enhancement. In contrast, the hepatocellular uptake index (HUI) is a semiquantitative method for estimating liver function using compound parameters that combine liver volume and the uptake of a gadoxetic acid contrast agent [21]. Remnant HUI is an index of gadoxetic acid uptake by the hepatocytes. Kim et al. [22] investigated whether gadoxetic acid-enhanced MRI was useful in predicting PHLF compared with FLR alone and a combination of FLR and ICG-PDR in 73 patients with HCC who underwent hepatectomy. PHLF grades are significantly associated with remnant HUI-related parameters with higher diagnostic accuracy. In addition, the functional liver imaging score (FLIS), which introduces three imaging features including enhancement quality, rate of biliary contrast excretion, and persistence of signal intensity in the portal vein, is a simple and easy way to estimate liver function in gadoxetic acid-enhanced MRI. Luo et al. [23] examined whether FLIS could predict PHLF in 502 patients with HCC and found that FLIS was an independent predictor of PHLF rather than laboratory markers or ICG-PDR.

For the prediction of PHLF, a systematic review showed that gadoxetic acid-enhanced MRI-derived functional volumetry exhibited a higher predictive capacity than volumetric assessment alone and could serve as a promising imaging biomarker [24]. Because gadoxetic acid-enhanced MRI-derived parameters can estimate segmental liver function, they may be useful in situations with potentially heterogeneous liver function throughout the liver. PVE induces the atrophy of embolized liver segments and compensatory hypertrophy of non-embolized liver segments, resulting in heterogeneous liver function. Theilig et al. [25] evaluated the predictive ability of gadoxetic acid-enhanced MRI for PHLF in 36 patients who underwent liver resection after right PVE. A reduction in the relative enhancement of the remnant liver after PVE, rather than a serum examination or volumetric analysis, can predict PHLF. Portal vein tumor thrombus (PVTT), which frequently develops in HCC, also decreases the portal venous flow caused by tumor filling. These patients have relatively poor liver function, and ICG-PDR results are occasionally unreliable because of the arterioportal shunt. A previous study reported functional heterogeneity in patients with HCC and PVTT [26]. The liver-to-muscle ratio in the occluded areas of the liver was significantly lower than that in the non-occluded areas, indicating that gadoxetic acid-enhanced MRI could visualize functional heterogeneity within the liver, even in patients with PVTT. Tsujita et al. [27] investigated the utility of gadoxetic acid-enhanced MRI in predicting PHLF in patients with HCC and PVTT. The liver-to-spleen ratio of the remnant liver was significantly higher than that of the resected liver, and remnant HUI was an independent predictor of severe PHLF. Therefore, evaluating changes in the uptake of gadoxetic acid contrast agents within the liver may provide a more accurate determination of the surgical indication by estimating the FLR function in HCC patients with PVTT. The function of the congested segments secondary to outflow obstruction in the remnant donor liver can also be evaluated using gadoxetic acid-enhanced MRI [28]. This study verified that gadoxetic acid uptake decreased in congested segments of the remnant right liver after left hepatectomy in a living

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donor. In 32 living donor subjects, the liver-to-muscle ratio in segments 5 and 8 decreased by 30% compared with that before left hepatectomy.

Recent advances in deep learning-based image reconstruction have accelerated the acquisition time and reduced the image noise without compromising image contrast, leading to accelerated acquisition and high image quality in liver MRI [29]. Deep learning image reconstruction enables the acquisition of high-resolution HBP images, thereby providing more detailed anatomical information and may be advantageous for precise segmentation and calculations. In terms of a "one-stop shop" of preoperative simulation, gadoxetic acid-enhanced MRI might be the most important imaging examination for detecting tumors, simulating vessel and bile duct anatomy, and estimating remnant functional reserve, which warrants further

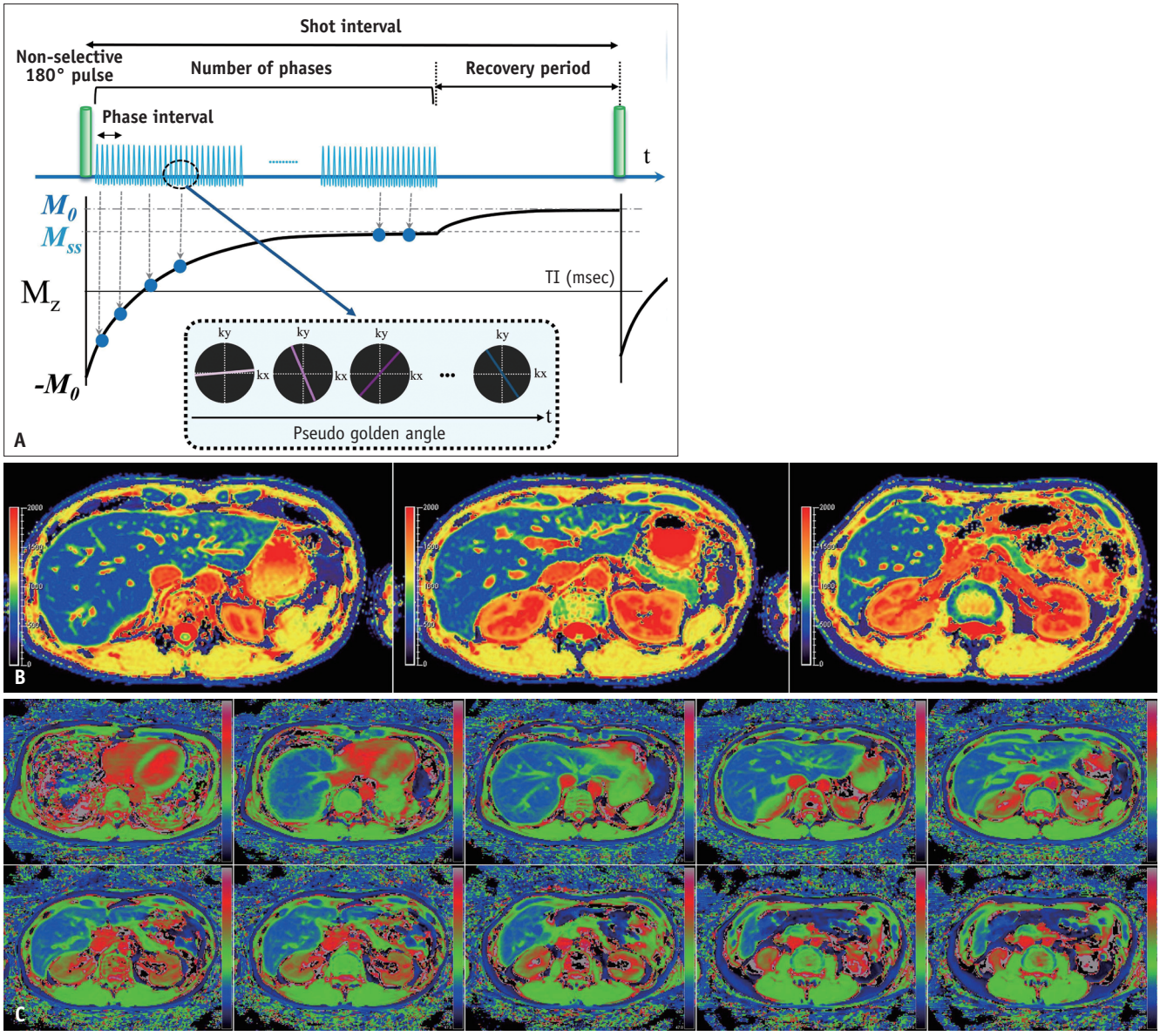

Fig. 3. Representative case of free-breathing 3D Look-Locker sequence in comparison with modified Look-Locker inversion recovery.
A: Details of free-breathing 3D Look-Locker sequence with radial sampling acquisition. After applying a non-selective inversion pulse, T1-turbo field echo radial sampling acquisition is obtained. Echo is continuously acquired with the specific phase interval; images are created for each TI by setting the phase interval and separating the k-space trajectory of the acquired data. Modified Look-Locker inversion recovery (MOLLI) images **(B)** and free-breathing 3D Look-Locker images **(C)** in a healthy volunteer. MOLLI captures three slices using electrocardiography synchronization and pulse wave synchronization with breath-hold, whereas free-breathing 3D Look-Locker captures the whole upper abdomen in 5 min without synchronization or breath-hold.

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investigations.

The usefulness of MR relaxometry has been proposed by several researchers, and T1 relaxometry is the most reliable quantitative method for the estimation of liver function using gadoxetic acid-enhanced MRI [30,31]. The T1 value is an absolute value at the same static magnetic field strength, and a linear relationship exists between the relaxation rate (R1 = 1/T1 value) and concentration of the contrast agent, whereas signal intensity-based methods are not linearly related to the hepatocyte uptake of the contrast agent (Fig. 2). Reduction rate of the T1 value or ΔR1 value ($1/T1_{HBP} - 1/T1_{pre}$) are popular indices that can theoretically measure the concentration of gadoxetic acid contrast agent (Table 1). However, gadoxetic acid must be considered to be distributed within both hepatocytes and vascular components in the HBP images. Yoon et al. [32] evaluated hepatocyte uptake ratios calculated from T1 mapping to estimate liver function and clinical utility in 50 patients with HCC. The hepatocyte uptake ratio negatively correlated with liver function, as measured by ICG-PDR, and exhibited good performance in identifying patients with contraindications to major hepatectomy. However, MR relaxometry has limitations in terms of the acquisition number of slices and long breath-hold time for acquisition. The advent of motion correction sequences using radial sampling has enabled the MR of the upper abdomen without breath-hold [33]. A free-breathing 3D look-locker sequence with radial sampling acquisition was developed that allowed T1 map acquisition of the entire liver without breath-holding [34]. Although this technique is not available for any MR machine, it is expected to provide a more accurate assessment of whole-liver function than other T1 relaxometry methods. Future studies are required to determine its clinical utility by comparing the currently implemented T1 mapping with whole-liver T1 mapping for predicting PHLF in patients who undergo hepatic resection (Fig. 3).

CONCLUSION

The extent of hepatic resection is an important preoperative factor for predicting PHLF, and volumetric assessment using contrast-enhanced CT traditionally contributes to surgical simulation by estimating the residual liver function. In contrast to volumetric assessment, gadoxetic acid-enhanced MRI offers additional information on individual hepatocyte function, leading to a more precise evaluation even in cases with heterogeneous liver function. Recent developments in MR techniques have enabled a more detailed and accurate estimation of liver function using gadoxetic acid-enhanced MRI.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Keitaro Sofue. Resources: Eisuke Ueshima, Shohei Komatsu, Takeru Yamaguchi, Shinji Yabe. Software: Ryuji Shimada. Supervision: Masatoshi Hori, Takamichi Murakami. Writing—original draft: Keitaro Sofue, Ryuji Shimada. Writing—review & editing: Eisuke Ueshima, Shohei Komatsu, Takeru Yamaguchi, Shinji Yabe, Yoshiko Ueno, Masatoshi Hori, Takamichi Murakami.

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