ORIGINAL ARTICLE

Assessment of image quality using gadobenate dimeglumine and gadoxetic acid contrast agents for hepatocellular carcinoma evaluation in magnetic resonance liver imaging

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Abstract:

Gadolinium-based contrast agent (GBCA) has a valuable role for optimizing the detection of lesions in contrast-enhanced Magnetic Resonance Imaging (MRI) examination. This study aimed to evaluate the image quality using liver specified GBCA; gadobenate dimeglumine and gadoxetic acid contrast agents for hepatocellular carcinoma (HCC) assessment in MR liver imaging. MR images of twenty-two (n=22) HCC patients who underwent either one of the liver-specified GBCA-enhanced MRI at 1.5T were retrospectively assessed. Qualitative and quantitative assessments were performed by three blinded review independent observers and by using image quality parameters; signal noise ratio (SNR) and contrast noise ratio (CNR), respectively between HCCs and liver parenchyma. Cohen's Kappa analysis showed that the inter-reviewer agreements of HCC presence and confidence level using gadobenate dimeglumine were "entirely agree" and "fairly disagree", respectively, while “fairly agree" and "moderately agree” were observed for gadoxetic acid, respectively. The SNR and CNR of both contrast enhanced images were not statistically significant each other ($p > 0.05$). Gadobenate dimeglumine-enhanced and gadoxetic acid-enhanced MR images had similar image quality for HCC assessment. The advantages of each contrast agents should be taken into consideration to optimize the detection and characterization of HCC in contrast-enhanced MR imaging for improved clinical management of HCC.

Keywords: gadobenate dimeglumine contrast agent; gadoxetic acid contrast agent; hepatocellular carcinoma; MRI

1. INTRODUCTION

Liver lesions are one of the most common cancer occurrences worldwide [1]. The primary type of hepatic lesions that commonly encountered is hepatocellular carcinoma (HCC). The importance of early detection and accurate characterization of HCC had been emphasized for successful therapy and overall patients' survival [2]. The use of current radiological imaging techniques such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) have essential roles in detecting early HCC lesions thus providing effective treatment options and surveillance [3]. Currently, ultrasonography has become a primary imaging technique essentially for early detection of HCC with the combination of serial alpha-fetoprotein (AFP) as a standard HCC biomarker, and it acts as basis surveillance for HCC [4]. However, advances well-defined dynamic imaging technique such as MR imaging is highly advocated for further evaluation of HCC when patients with elevated AFP and new suspicious lesions are reported in ultrasound study.

In MRI, optimal image quality facilitates small anatomical structures and pathologies depiction and enhances the diagnostic ability of images [5]. Increased signal intensity and improved image contrast at higher MR field are the methods to enhance the image quality [5]. Gadolinium-based contrast agents (GBCA) are commonly used in clinical practice for enhancement of structures anatomically and physiologically due their paramagnetic characteristic which altering the relaxation properties of water protons during scanning, thus producing contrast changes in tissues [5]. Liver-specified GBCA has been developed to optimize morphological assessment as well as to provide physiological information of the liver and associated blood vessels [6]. Currently, two types of liver-specified GBCA that most commonly used are gadobenate dimeglumine (Gd-BOPTA, Multihance®) and gadoxetic acid (Gd-EOB-DTPA,

Primovist®, Eovist®) [7]. Gadobenate dimeglumine and gadoxetic acid are bimodal chelated GBCA which have kinetic properties that comprise to a distribution phase and elimination phase, corresponding to the multiphasic and hepatocyte phase in hepatobiliary imaging [6].This study aimed to evaluate the image quality between gadobenate dimeglumine and gadoxetic acid at hepatocyte phase qualitatively and quantitatively.

2. MATERIALS AND METHODS

2.1 Patient Population

This retrospective study was approved by institutional review board of the participating institution (NMRR-19-571-46982 (IIR)). Twenty-two (n=22) MR images of patient who underwent contrast-enhanced abdominal MRI for suspected/known HCC from January 2014 to January 2019 in the Department of Diagnostic Imaging of a government hospital and met the inclusion criteria were reviewed. These patients were confirmed of having HCC based on ultrasonography findings and elevated level of AFP.

2.2 Hepatic MR Imaging

Abdominal MR imaging was performed using a 1.5 T system and 6-channel phased array body coil. Contrast-enhanced MR protocol was performed using bolus injection of either 0.1 mmol/kg gadobenate dimeglumine (Multihance®) at 2.0mL/s injection rate or 0.025 mmol/kg gadoxetic acid (Primovist®) at 1.5mL/s injection rate, followed by a 20mL saline chaser administered at 2mL/s. The acquisition protocol included three consecutive post-contrast administration phases, which were arterial, portal venous and delayed phases and followed by hepatocyte phase.

2.3 Qualitative Image Analysis

Seven (n=7) gadobenate dimeglumine –enhanced images and fifteen (n=15) gadoxetic acid contrast-enhanced images were analysed. The anonymized MR images were randomly reviewed by three senior medical officers who have four to five years' experience in MR images interpretation on a 1536 x 2048 pixels MRI image viewing workstation (RadiForce RX360; EIZO Corporation; Hakusan, Japan) in a blinded fashion. Image analysis was based on axial and coronal images of the region of interest. The reviewers were blinded whether the images they would review were gadoxetic acid-enhanced images or gadobenate dimeglumine-enhanced images. Each reviewer recorded confidence level score to each HCC lesion by using a four-point score scale as [1: not an HCC lesion, 2: possibly an HCC lesion, 3: most probably an HCC lesion and 4: definitely an HCC lesion] and stated the segment location of the HCC lesions. Then, the image quality was further characterized based on four categories: lesion visibility, lesion delineation, lesion and liver parenchyma differentiation and diagnostic usefulness.

The identification number, location and diameter of the lesions were recorded to achieve accurate correlation between the reference standard and the scored lesions findings. Further description of the location and size of the lesion within each liver segment were documented in the case of the patients with multiple lesions visualized in the same segment.

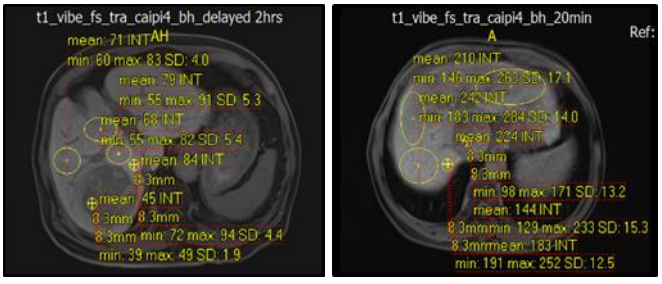
2.4 Quantitative Image Analysis

Signal intensity (SI) values with their standard deviations (SD) for the HCC metastases regions and overall liver parenchyma were assessed by regions-of-interest (ROI) on the MR images confirmed by a radiologist. If heterogeneous lesions were visualized, the selected ROIs were ensured to be in the more homogeneous areas. Areas of haemorrhage and intra-tumoral necrosis were excluded from the ROIs. No ROI was placed in any liver parenchyma areas containing large vessels or artefacts. For every different imaging phase in each patient, the ROIs were mirrored. HCC lesions and liver parenchyma signal-to-noise ratios (SNR) were calculated as follows (Figure 1) [8]:

$$SNR_{\substack{\text{HCC and liver}\\ \text{parenchyma}}} = \frac{SI^{\text{HCC and liver parenchyma}}}{SD_{noise}} \quad (2.1)$$

Subsequently, the HCC-to-liver contrast-to-noise ratios (CNR) were manually calculated for contrast-enhanced arterial through hepatocyte as follows where SI_{liver} was the mean SI of the background liver parenchyma (Figure 1) [9]:

$$CNR_{HCC\text{-}to\text{-}liver} = \frac{SI_{HCC} - \overline{SI}_{liver}}{SD_{noise}} \quad (2.2)$$



(a) (b)

Figure 1: Quantification of regions-of-interest (ROI) in the sites of liver pacenchyma and lesion in (a) gadobenate dimeglumine-enhanced image and (b) gadoxetic acid-enhanced image

2.5 Statistical analysis

Statistical analysis was performed by comparing the contrast enhancement in the HCC and liver parenchyma as well as the HCC-to-liver contrast as dependent variables, in both the gadoxetic acid and gadobenate dimeglumine groups as independent variables. Qualitative image analysis was performed by using Cohen's Kappa statistics for the level of agreement between inter-reviewer analyses. The level of agreement between the three reviewers was evaluated based on the confidence level to measure on how the contrast agents optimally and accurately demonstrated every HCC lesion. For quantitative image analysis, the SNR and CNR of each contrast agent-based image were compared using Mann-Whitney U-test. All statistical analyses were performed using IBM SPSS Statistics software version 21.0 (SPSS, New York, US) with $p < 0.05$ were deemed as statistically significant.

3. RESULTS AND DISCUSSION

3.1 Qualitative Analysis

The results showed two out of four HCC lesions were identified by each reviewer in gadobenate dimeglumine-enhanced images while five out of eight HCC lesions were identified by each reviewer in gadoxetic acid-enhanced images. The confidence level of HCC lesions among the reviewers (R1, R2, R3) showed there was fair disagreement for gadobenate dimeglumine-enhanced images ($\kappa = -0.33$) and moderate agreement for gadoxetic acid-enhanced images ($\kappa = 0.55$) (Table 1).

Table 1: Confidence level of HCC lesions detection by the three reviewers in gadobenate dimeglumine and gadoxetic acid enhanced MRI protocols

Protocol	R1 – R 2	R2 – R 3	R1 – R 3	κ
Gadobenate dimeglumine-enhanced MRI	1.00	-1.00	-1.00	-0.33
Gadoxetic acid-enhanced MRI	1.00	0.33	0.33	0.55

The result indicates that gadoxetic acid-enhanced images are better than gadobenate dimeglumine-enhanced images in detecting the presence the HCC lesions at hepatocyte phase. This finding is consistent with the previous literature [8]. Image acquisition of hepatocyte phase for suspected or diagnosed HCC has important role to confirm the presence of HCC and provide reliable diagnosis [9]. The degree of hepatocellular enhancement of lesions in the hepatocyte phase depends on the expression and activity of different molecular transporters and also depending on the underlying cytogenetic profile of the individual. This explains the liver lesions heterogeneity with regard to their hepatocellular phase intensity enhancement [10]. Liver-specified uptake rate for gadoxetic acid was 50% of the injected dose as compared with a maximum of 4% for gadobenate dimeglumine [11]. Therefore the enhancement rate of intracellular hepatocytes is higher using gadoxetic acid as compared to gadobenate dimeglumine.

On the contrary, gadobenate dimeglumine contrast agent was proven to give a good characterization of lesions in dynamic phases (arterial, portovenous and delayed) [12]. Multistep carcinogenesis would cause increasing tumoral arterial blood supply hence resulting for increased enhancement during arterial phase imaging [12]. Moreover, gadobenate dimeglumine is known for its superior ability to demonstrate HCC capsules as compared to gadoxetic acid [13].

3.2 Quantitative Analysis

For quantitative analysis, the median SNR and CNR showed no statistically significant difference in both gadobenate dimeglumine-enhanced images and gadoxetic acid-enhanced images ($p > 0.05$) as shown in Table 2.

Table 2: Median (interquartile range) of SNR and CNR analysis of HCC lesions in gadobenate dimeglumine and gadoxetic acid enhanced MRI protocols

Protocol	SNR	CNR	p-value
Gadobenate dimeglumine-enhanced MRI	41.45 (20.74)	-8.30 (8.44)	0.924
Gadoxetic acid-enhanced MRI	36.89 (11.39)	-6.84 (4.42)	0.447

Our study showed the performance of contrast enhancement of both contrast agents is not varied significantly to each other as indicated by SNR and CNR values. It has been reported both contrast agents are equivalent in diagnostic performances, with gadoxetic acid acquires optimal parenchymal enhancement in 20 minutes as compared with 3 hours in gadobenate dimeglumine [14]. Both agents provided comparable enhancement of liver parenchyma during the maximum accumulation in hepatocytes phase [15]. In this study, all hepatocyte phase sequences were acquired at 20 minutes after injection, indicating that rapid parenchymal washout of the GBCA has occurred. This subsequently results in insufficient enhancement of liver parenchyma relative to the HCC lesions in gadoxetic acid enhanced.

As image quality in both gadobenate dimeglumine-enhanced and gadoxetic acid-enhanced images had been proved equivalent to each other, other clinical related factors such as risk to patient, time consuming and cost should be taken into consideration. Hence optimization of contrast enhancement with least risk would be practiced in each clinical site thus facilitating for more accurate detection and diagnosis. Similarly, gadobenate dimeglumine and gadoxetic acid have been proven to have an intermediate risk of nephrogenic systemic fibrosis [16]. However, US Food and Drug

Administration had approved that 0.025 mmol/kg of gadoxetic acid was already sufficient to detect and characterize HCC in hepatocyte phase, in which 0.1mmol/kg of gadobenate dimeglumine was needed to obtain similar result [6]. Nevertheless, gadoxetic acid is superior to gadobenate dimeglumine vascular signal enhancement in dynamic phase (arterial, portovenous and delayed phases). Our MR contrast-enhanced protocol demonstrated shorter acquisition time in gadoxetic acid contrast study to achieve optimum HCC lesion enhancement in comparison with gadobenate dimeglumine contrast study. To reach optimum hepatocyte-specific plateaus enhancement, 60-90 minutes are required for gadobenate dimeglumine and 15-25 minutes for gadoxetic acid [7]. Furthermore, it has been reported about only 0.6 – 4% of gadobenate dimeglumine is cleared via biliary excretion as compared to 50% of gadoxetic acid [6]. Finally, gadobenate dimeglumine also was excellent in the visualization of HCC capsule appearances as compared to gadoxetic acid in hepatocyte phase due to its prolonged extracellular effect and with a hepatocellular uptake which started later than 40 min after injection [13].

In summary, gadoxetic acid contrast agent is preferable for the evaluation of focal malignancies within the liver parenchyma and intracellular characteristics of the liver while gadobenate dimeglumine contrast agent is valuable for the identification of vascular abnormalities in dynamic phases and detection of HCC capsules in the hepatocyte phase. However, with the advantages of rapid acquisition time and low nephrogenic risk patients, gadoxetic acid is preferable in routine clinical practice.

4. CONCLUSION

Gadobenate dimeglumine-enhanced and gadoxetic acid-enhanced MR images had similar image quality at hepatocyte phase qualitatively and quantitatively. The advantages of both gadolinium-based contrast agents should be taken into consideration to optimize the detection and characterization of HCC in contrast-enhanced MR imaging for improved clinical management of HCC.

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