High resolution multi-arterial phase MRI improves lesion contrast in chronic liver disease

Abstract

Purpose: To determine the reliability of arterial phase capture and evaluate hypervascular lesion contrast kinetics with a combined view-sharing and parallel imaging dynamic contrast-enhanced acquisition, Differential Sub-sampling with Cartesian Ordering (DISCO), in patients with known chronic liver disease.

Methods: A retrospective review of 3T MR images from 26 patients with known chronic liver disease referred for hepatocellular carcinoma surveillance or post-treatment follow up was performed. After administration of a gadolinium-based contrast agent, a multiphasic acquisition was obtained in a 28 s breath-hold, from which seven sequential post-contrast image volumes were reconstructed.

Results: The late arterial phase was successfully captured in all cases (26/26, 95% CI 87-100%). Images obtained 26 s post-injection had the highest frequency of late arterial phase capture (20/26) and lesion detection (23/26) of any individual post-contrast time; however, the multiphasic data resulted in a significantly higher frequency of late arterial phase capture (26/26, p=0.03) and a higher relative contrast (5.37+/-0.97 versus 7.10+/-0.98, p < 0.01).

Conclusion: Multiphasic acquisition with combined view-sharing and parallel imaging reliably captures the late arterial phase and provides sufficient temporal resolution to characterize hepatic lesion contrast kinetics in patients with chronic liver disease while maintaining high spatial resolution.
Magnetic resonance imaging (MRI) is playing an increasingly important role in surveillance and diagnosis of hepatocellular carcinoma (HCC), as well as in the monitoring of HCC following local and systemic treatments [1,2]. Prognosis is influenced by the size of the HCC at the time of diagnosis [3], primarily because smaller HCCs are often amenable to treatment by resection, transplantation, or ablation [4].

Effective capture of the late arterial phase is essential for detection of small foci of hepatocellular carcinoma [5-8]; however, determining the precise timing of optimal contrast enhancement for detection of HCC is technically challenging because it is affected by the patient’s cardiac output, choice of contrast agent, contrast injection protocol and imaging protocol [9,10]. More importantly, as with any dynamic MRI application, there is a tradeoff between spatial and temporal resolution.

In clinical practice, a variety of techniques has been applied for late arterial phase imaging, with the majority of them using a 3D spoiled gradient echo pulse sequence with fat suppression. One common approach utilizes a fixed scan delay of 12-20 s after injection of contrast media with a sequential k-space data acquisition to obtain a single arterial phase with the center of k-space being acquired approximately 30 s post-injection [11]. Some single arterial phase approaches employ bolus tracking or a test-bolus injection to optimize the arterial phase timing for each individual patient [12]. Alternatively, lower spatial resolution and/or spatial coverage with multiple temporal phases and a fixed scan delay can be used to increase the probability of capturing the late arterial phase [13]. The acquisition of multiple arterial phases may increase the probability of effective late arterial phase capture, and hence increase the sensitivity of dynamic contrast-enhanced MRI for detecting hepatocellular carcinomas [9,14-16].

Approaches to improving temporal resolution while maintaining relatively high spatial resolution, such as time-resolved imaging of contrast kinetics (TRICKS) [17], Time-resolved angiography with stochastic trajectories (TWIST) [18], and 4D Time-Resolved Angiography using Keyhole (4D-TRAK) [19] are better suited to peripheral angiography than to abdominal imaging due to their sensitivity to motion artifacts and the need for chemically-selective fat saturation or mask subtraction. Furthermore, the keyhole technique samples higher k-space data less frequently, resulting in blurring of small, fast enhancing structures such as small HCCs [20].

Ideally, surveillance for HCC would be performed with an MR sequence capable of both high temporal and high spatial resolution as well as robust fat suppression. Recently, a high spatio-temporal resolution dynamic contrast-enhanced MRI technique called DISCO (Differential Sub-sampling with Cartesian Ordering) was introduced (21) that has four main features: a dual-echo spoiled gradient echo (SPGR) acquisition for Dixon water-fat separation, a pseudo-random variable density k-space segmentation, parallel imaging and view-sharing reconstruction. These four elements provide robust fat-water separated imaging with a temporal resolution of ~4 seconds, allowing the acquisition of seven sequential post-contrast volumes in a single 28 s breath-hold without sacrificing spatial resolution and without the need for mask subtraction.

Our primary objectives were to establish the reliability of late arterial phase capture and to characterize the enhancement kinetics of hypervascular lesions concerning for hepatocellular carcinoma in patients with known chronic liver disease using a high spatiotemporal multi-phasic acquisition.

Materials and Methods

This study was approved by the institution’s research ethics board.

Patient Population

Dynamic contrast-enhanced MR images from 26 consecutive patients referred for suspected HCC, surveillance for HCC or post-treatment monitoring with positive findings were retrospectively reviewed. All subjects were imaged on a 3T GE MR750 system (GE Healthcare, Waukesha, WI) between December 2011 and March 2012.

MR Imaging Technique

Prior to contrast-enhanced imaging, patients were imaged with a respiratory-triggered T2-weighted fast spin echo sequence (35-44 cm field of view, 6 mm slice thickness, 416 x 224 matrix) and a navigated diffusion-weighted echo planar sequence with multiple b values (35-44 cm field of view, 5 mm slice thickness, 80 x 128 matrix, b values 0, 100, 400, and 800 mm2/s) as per our standard institutional protocol.

The dynamic contrast-enhanced images were acquired with the DISCO pulse sequence, which has been previously described [21]. Briefly, it is a SPGR-Dixon sequence with an elliptically ordered kx-kz that is segmented into four regions: the first representing the center of k-space (labeled A) and the remaining three representing equally distributed pseudo-random sub-samples of the periphery of k-space (labeled B1, B2, and B3) (figure 1). During each breath-hold, the three peripheral k-space segments are alternated with the central portion of k-space (e.g., acquisition order of AB1AB2AB3AB1A). View sharing is restricted to nearest temporal neighbours. Two
dimensional (in $k_x$ and $k_y$) self-calibrated hybrid space parallel imaging (following view-sharing) was incorporated to further accelerate the acquisition. The temporal footprint, or the time taken to acquire all three peripheral k-space segments, was 16.2 s.

Dynamic contrast-enhanced data were acquired in a 28 s long breath-hold with an 18 s scan delay following injection of 0.1 ml/kg gadobenate dimeglumine at 2 cc/sec. These data were reconstructed into seven sequential imaging volumes with a nominal temporal resolution of 4 s. Since an elliptical centric acquisition was used, the center of k-space (A region) was therefore acquired at 18, 22, 26, 30, 34, 38 and 42 s after contrast injection.

Imaging parameters were as follows: 15° flip angle, +/-167 kHz bandwidth, TR/TE1/TE2 4.1/1.2/2.4 ms, 320 x 224 matrix, 35-44 cm field of view, 4 mm slice thickness, 56 slices (interpolated to 2 mm slice spacing for 112 slices), and Auto Calibrating Reconstruction for Cartesian imaging (ARC) parallel imaging with 2 x 2 acceleration. Water-only images were reconstructed using a 2-point Dixon technique with a region-growing algorithm [22], enabling fat suppression at 3T with robustness to $B_0$ and $B_1$ heterogeneity. A 32-channel torso array coil was used with the upper elements enabled for the data acquisition and reconstruction of the abdominal scans.

Following dynamic arterial phase imaging, portal venous and equilibrium phase images were each acquired with a single breath-hold using a commercially available 3D spoiled gradient echo sequence with two-point Dixon water-fat separation (LAVA-FLEX).

**Image Interpretation: Arterial Phase Capture**

The late arterial phase was defined as arterial and hepatic parenchymal enhancement with a blush of contrast in the portal vein. The number of cases with successful capture of the late arterial phase was recorded.

**Image Interpretation: Detection and Characterization of Hepatic Lesions**

Using the 4D viewer option within Osirix software (Pixmeo, Geneva, Switzerland) [23], regions of interest were drawn on the lesion concerning for HCC and adjacent liver parenchyma. The signal intensity (SI) as a function of time was recorded. The relative contrast was determined by the following formula:

$$\text{relative contrast} = \frac{\text{SI}_{\text{lesion}} - \text{SI}_{\text{liver}}}{\text{SI}_{\text{liver}}}$$
To minimize coil sensitivity-related signal variations, the region of interest placed on the adjacent liver parenchyma was chosen to be at approximately the same location in the anterior-posterior direction as the lesion of interest. Image noise is non-uniformly distributed with ARC parallel imaging; therefore, the conventional definition of contrast-to-noise was not used in our analysis [24]. In the case of multiple lesions, the largest lesion was analyzed, and the maximum lesion diameter in the axial plane was documented.

Lesions were deemed to demonstrate arterial phase enhancement when the relative contrast was greater than 0.15. Using this objective criterion, the time post-contrast injection that identified the lesion of concern for HCC was determined for each case. In addition, the time post contrast that resulted in the highest relative contrast was also recorded for each individual subject.

**Statistical Analysis**

All statistical tests were calculated using the online site for statistical computation, VassarStats.net.

**Results**

**Patient Population**

The 26 subjects consisted of 22 males and four females (mean age 64 years; range 41 – 82 years). Subjects had underlying liver diseases of hepatitis B (six subjects), hepatitis C (12), hepatitis B and C (one), alcohol abuse (two), alcohol abuse and hepatitis C (one), primary biliary cirrhosis (one), hemochromatosis and hepatitis C (one), recurrent pyogenic cholangitis (one) and cryptogenic cirrhosis (one). The mean lesion diameter was 2.7 cm, the median diameter was 1.6 cm and the range was 0.5 – 16.5 cm. The number of lesions less than or equal to 2 cm in diameter was 19/26 (73%).

**Frequency of Capturing the Late Arterial Phase**

The late arterial phase was successfully obtained in all 26 cases (95% confidence interval [CI] 87% - 100%). The frequency of late arterial phase capture for each post-contrast time point is listed in table 1. The images 26 s post-injection captured the highest number (20/26) of late arterial phases (77%, 95% CI 58% - 89%). The frequency of arterial phase capture with the multi-phase acquisition was significantly higher than the frequency of capturing the late arterial phase using the 26 s post-contrast time only (McNemar’s test, p = 0.03). No single time point captured the late arterial phase in all subjects.

<table>
<thead>
<tr>
<th>Seconds post-IV contrast injection</th>
<th>Frequency of late arterial phase capture</th>
<th>95% confidence interval</th>
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</thead>
<tbody>
<tr>
<td>18</td>
<td>19% (5/26)</td>
<td>8-38%</td>
</tr>
<tr>
<td>22</td>
<td>50% (13/26)</td>
<td>32-68%</td>
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<tr>
<td>26</td>
<td>77% (20/26)</td>
<td>58-89%</td>
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<tr>
<td>34</td>
<td>69% (18/26)</td>
<td>50-84%</td>
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<tr>
<td>38</td>
<td>38% (10/26)</td>
<td>22-57%</td>
</tr>
<tr>
<td>42</td>
<td>19% (5/26)</td>
<td>8-38%</td>
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**Detection and Characterization of Hepatic Lesions**

Using a relative contrast of >0.15 as the cut-off, the image volume acquired 26 s post-injection identified 23/26 (88%) lesions. At 22 s post-injection, only 19/26 (73%) lesions were detected. Image volumes obtained at 30 and 34 s post-injection detected 22/26 (85%) and 17/26 (65%), respectively. A graphic representation of the percentage of lesions identified as a function of time is shown in figure 2.

**Relative Contrast**

There was considerable inter-subject variation in the time that provided the highest relative contrast, and each of the seven post-contrast times provided the optimal relative contrast in at least one subject (figure 3). The time of peak relative contrast between the lesion and background liver parenchyma ranged widely and occurred 18-42 s post-gadolinium administration: 26 s post-injection afforded the best relative contrast in 35% (9/26) cases, the most of any single time point; however, 65% of lesions were better appreciated at another time point, illustrating the variability in optimal enhancement delay time across patients and the benefit of multi-phase acquisitions. The relative contrast 26 s post-gadolinium was 5.37 +/- 0.97 (standard error of the mean). If the time point that provided the best relative contrast was selected on a per subject basis, the average relative contrast was 7.10 +/- 0.98 (t-test (p<0.01).

In several instances, the lesion was seen to arterially enhance, become iso-intense to liver, and then wash out, all in a 28 s breath-hold. Rapid contrast kinetics were well characterized and were seen in both suspected recurrent (figure 4) and de novo HCC (figure 5). In tumors that exhibited rapid enhancement and washout, the window of time available to capture the late arterial phase was decreased, and the importance
FIGURE 2. Percentage of lesions with lesion-to-background liver contrast > 0.15 as a function of time post contrast administration.

FIGURE 3. Distribution of highest lesion-to-background liver contrast as a function of time post contrast administration.
FIGURE 4. 55 year-old male with hepatitis B and previous TACE for HCC. A large region of rapid arterial enhancement and washout was concerning for tumour recurrence. A large region of concern for recurrent HCC, identified using of rapid arterial enhancement, exhibited washout that began before the end of the 28 s acquisition. This example illustrates how rapid tumoral enhancement kinetics can be well characterized with DISCO.

FIGURE 5. Images from a 69 year-old male with hepatitis C, hemochromatosis and history of right partial hepatectomy for HCC. The 8 mm lesion in the subcapsular left lobe (arrow) arterially enhanced and washed out in one 28 s breath-hold. This pattern of enhancement is consistent with HCC. The patient went on to receive treatment with transarterial chemoembolization and was disease-free at the 3-month follow up examination (not shown).
FIGURE 6. Images from a 56 year-old male with hepatitis C. A 16 mm lesion in the left lobe exhibited subtle arterial enhancement that can be appreciated on phases 1-5 (arrow in b and f); however, the lesion is essentially isointense to the remaining liver on subsequent phases. Washout was demonstrated in the portal venous phase (not shown). This example highlights the benefit of multiple arterial phases, especially in a nodular, cirrhotic liver, where a lesion can be difficult to distinguish from background nodularity without the benefit of an optimized arterial phase. This patient did not undergo treatment, and at 3 month follow up imaging (not shown), this lesion had increased 50% in size and multifocal HCC was present.

FIGURE 7. The arterial phase demonstrated multiple small arterially enhancing lesions consistent with HCC (a). One of the small lesions in the left lobe is highlighted with an arrow. High spatial resolution images were required to adequately visualize these small lesions, many of which were subcentimeter in size. Although these lesions were small, their presence was significant, as illustrated by an image from the 3-month follow up examination, which revealed interval growth of all the tumors (b).
of high temporal resolution became evident. Multiple arterial phases were found to be especially beneficial in nodular, cirrhotic livers, where a lesion could be difficult to distinguish from background nodularity without the benefit of an optimized arterial phase, particularly if it exhibited only mild hypervascularity (figure 6). High spatial resolution images allowed routine visualization of small, sub-centimeter foci of arterial enhancement with portal venous washout that were concerning for HCC (figure 7).

Discussion
Reliable capture of the late arterial phase is critical for the diagnosis of hepatocellular carcinoma. In this study, the potential benefit of a multiphasic arterial acquisition has been shown in a population of patients with chronic liver disease. Use of all the multiphasic data resulted in a significantly higher frequency of late arterial phase capture and a higher relative contrast compared to the single best phase (which occurred 26 s post-gadolinium administration).

A limitation of this study is that it was small and retrospective; however, it does demonstrate the feasibility of routine use of a multi-phasic arterial acquisition in patients with chronic liver disease in the clinical environment. Other promising multi-arterial phase techniques have been developed, some of which have been used in volunteers or in a small number of patients but have not been implemented in clinical practice [25].

Our multi-phasic arterial acquisition was not directly compared with a more conventional arterial phase acquisition because this comparison has been previously published [ref]. A comparison of DISCO with a spoiled gradient echo sequence (LAVA-FLEX) in a small group of patients demonstrated no significant differences in quality of fat suppression, artifact severity or overall image quality [21] and significantly increased the frequency of late arterial phase capture in a series of patients who received gadoxetate disodium (Gd-EOB-DTPA, gadoteric acid, Eovist or Primovist, Bayer HealthCare) [26]. In our study, the optimally-timed single phase was determined from analysis of the dynamic data, something that is not available for a conventional single-phase acquisition. This presents something of a “best case” scenario for a single phase; in reality, the benefits of multiphasic acquisition may be even more apparent, although this will need to be investigated in future trials. Comparison of the multiphasic data to a single time point contained within that data set served to illustrate that lesion enhancement kinetics vary substantially between subjects and that even an optimally-timed single arterial phase could fail to detect a small subset of lesions. Furthermore, the time of peak lesion-to-background-liver contrast ranged widely, and multiphase arterial imaging allowed this parameter to be optimized for each individual subject. This variability may be due to inter-subject differences in hepatic circulations times and/or heterogeneity in the vascular supply or underlying biology of the arterially enhancing lesions. In practical terms, this may necessitate radiological review of all post-contrast phases despite the large number of images acquired. DICOM viewing software that allows scrolling as a function of either time or spatial location may facilitate analysis of these large data sets.

Other groups have reported inter-subject variation in hepatic circulation times, and hence variable timing for optimal lesion detection [27]. Low et al. found that younger patients required a shorter scan delay than older patients [9]. Kagawa et al. showed a significant difference in the time of initial HCC enhancement between patients previously treated with transarterial chemoembolization and those who were treatment naïve [10]. Future work could involve further characterization of contrast kinetics as a function of lesion size, treatment status, or underlying liver disease.

Patients with cirrhosis may have difficulty holding their breath, which was a concern with our protocol given the 28 s breath hold [28]. In some instances, the image quality in the last two phases was compromised by motion. The arterial phase had been captured in all subjects by 34 s post-contrast, although in some subjects the maximum lesion-to-background-liver contrast occurred at 38 or 42 s post-contrast. In the future, motion artifacts could be reduced by acquiring a fewer number of arterial phases, with the knowledge that occasionally this compromise may result in a decreased lesion-to-background-liver contrast.

Imaging is becoming critical in diagnosis of HCC and can obviate the need for biopsy under certain circumstances [29]. It is important to focus efforts to improve diagnosis with technological advances in MRI, and several other multi-phase sequences have been proposed. These include CAIPIRINHA-Dixon-TWIST VIBE [30], temporal resolution acceleration with constrained evolution reconstruction (TRACER), which samples k-space with a 3D stack of variable density spirals to obtain a high temporal frame rate [31], high spatio-temporal resolution liver imaging performed with time-resolved three-dimensional radial MR and fluoroscopic triggering [32], and liver imaging in free-breathing subjects using a combination of compressed sensing, parallel imaging and golden-angle radial sampling [25]. Compared with the complex reconstruction schemes proposed in [32] and [25], DISCO reconstruction, due to its Cartesian sampling, is fairly rapid, online and well-suited for clinical adoption.
This technique has the potential for detailed evaluation of hemodynamics within focal liver lesions and a prospective study with a larger number of patients with chronic liver disease at risk for HCC should be performed to further elucidate the value of multiphasic imaging in identifying liver lesions.

Conclusion

Dynamic contrast-enhanced multiphasic acquisition, combining a 3D SPGR-Dixon sequence, parallel imaging and view-sharing, reliably captures the late arterial phase and provides sufficient temporal resolution to characterize hepatic lesion contrast kinetics in patients with chronic liver disease while maintaining high spatial resolution and robust fat saturation.

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References


