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Rapid Dynamic Contrast-Enhanced MRI for Small Animals at 7T using 3D Ultra-Short Echo Time and Golden-Angle Radial Sparse Parallel MRI

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Abstract

Purpose—To develop a rapid dynamic contrast enhanced (DCE) MRI method with high spatial and temporal resolution for small animal imaging at 7T.

Methods—An ultra-short echo time (UTE) pulse sequence using a 3D golden-angle radial sampling was implemented to achieve isotropic spatial resolution with flexible temporal resolution. Continuously acquired radial spokes were grouped into subsets for image reconstruction using a multicoil compressed sensing approach (GRASP). The proposed 3D-UTE-GRASP method with high temporal and spatial resolutions was tested using 7 mice with GL261 intracranial glioma models.

Results—Iterative reconstruction with different temporal resolutions and regularization factors λ showed that, in all cases, the cost function decreased to less than 2.5% of its starting value within 20 iterations. The difference between the time-intensity curves of 3D-UTE-GRASP and NUFFT images was minimal when λ was 1% of the maximum signal intensity of the initial NUFFT images. The 3D isotropic images were used to generate pharmacokinetic parameter maps to show the detailed images of the tumor characteristics in 3D and also to show longitudinal changes during tumor growth.

Conclusion—This feasibility study demonstrated that the proposed 3D-UTE-GRASP method can be used for effective measurement of the 3D spatial heterogeneity of tumor pharmacokinetic parameters.

Keywords

3D Golden Angle Radial Sampling; GRASP; UTE; Compressed Sensing; Parallel Imaging; DCE-MRI

INTRODUCTION

T₁-weighted dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) has been widely used to assess tissue microenvironment of cancer (1–4) as well as various inflammatory diseases (5–8) in terms of contrast kinetic model parameters, such as the transfer constant (K^{trans}), the plasma volume fraction (v_p), and the extravascular extracellular space volume fraction (v_e) (9,10). However, the ultimate potential of quantitative DCE-MRI methods is often restricted for routine clinical scans as well as preclinical scans, mainly due to the challenge of achieving simultaneous high spatial and high temporal resolution. For small animal imaging, low SNR makes it even more difficult to acquire dynamic MRI data at a high temporal resolution without compromising spatial resolution and/or volumetric coverage.

Compressed sensing (11–13) has emerged as a powerful approach for rapid imaging that exploits image compressibility/sparsity to reduce the number of samples required to reconstruct an image without loss of important information. Compressed sensing can be combined with parallel imaging to further increase imaging speed by exploiting joint sparsity in the multicoil image ensemble rather than in each coil separately (14–17). The additional encoding capabilities of parallel imaging reduce the incoherent aliasing artifacts and thus improve the performance of compressed sensing (15,16). Furthermore, it has been demonstrated that radial k -space sampling is an attractive alternative to conventional Cartesian sampling for compressed sensing, due to the inherent presence of incoherent aliasing artifacts along all spatial dimensions, even for regular undersampling (18–20).

A highly-accelerated dynamic MRI technique called Golden-angle RAdial Sparse Parallel (GRASP) MRI (21,22) is one of the representative examples in which compressed sensing, parallel imaging and golden-angle radial sampling (23) are jointly combined for rapid imaging. Moreover, GRASP offers the possibility of reconstructing flexible temporal frames from the same raw data, this is, with user-defined temporal resolution, frame position, and number of frames. GRASP has been successfully demonstrated in clinical dynamic MRI of the abdomen, breast, head and neck, and heart with significantly improved imaging performance than conventional MRI (24,25). However, there is paucity of studies that utilize such fast imaging methods for small animal imaging.

In this study, we have developed a highly accelerated DCE-MRI method using a 3D ultra-short echo-time (UTE) pulse sequence and image reconstruction based on the GRASP method. A 3D UTE pulse sequence was used to continuously acquire images with isotropic high-spatial resolution, which is helpful to measure arterial input functions (AIF) from small vessels and to assess 3D heterogeneity of tissue microcirculation environment. The UTE pulse sequence was also used to minimize the T_2^* effect following contrast injection, which becomes more apparent at higher magnetic fields (26,27), such as 7T. The performance of the proposed imaging method, referred to as 3D-UTE-GRASP DCE-MRI hereafter, has been assessed for quantitative imaging of tumor microcirculation environment in a mouse model of brain tumor.

METHODS

3D Golden-Angle Radial Sampling

A 3D UTE pulse sequence with a golden angle radial reordering scheme was implemented for the proposed 3D-UTE-GRASP DCE-MRI. The 3D k -space trajectory uses center-out radial readouts following the 3D golden angle approach that was suggested by Chan et al (28). The 3D k -space was filled by increasing the azimuth angle (Φ), and alternating the projection direction length (Z) in k_z direction between the upper and lower hemispheres (Figure 1a):

$$\begin{cases} \phi = 2\pi mA \\ Z = (-1)^{m+1} \bmod(mB, 1) \end{cases} \quad [1]$$

where $A=0.6823$, $B=0.4656$, and $m=1, 2, \dots, N_{proj}$ (the number of radial spokes). This scheme approximately filled 3D k -space uniformly as shown in Figure 1c that is comparable to the 3D golden-angle method with full radial readouts (Figure 1d). Density compensation factors were computed using the 3D Voronoi diagram based method (implemented in Matlab with the function *voronoin*), which implements a quick hull algorithm (29) to compute the volume of each sampling point in k -space. Each k -space point volume is then normalized to the maximum voxel volume in each time frame. A 3D random sampling is also shown in Figure 1b for a comparison with the golden angle radial sampling methods, demonstrating that the 3D golden angle sampling provides relatively more uniform sampling of the 3D k -space.

Data Acquisition

Six to eight-week-old C57BL6 mice ($n=7$) were given 1×10^5 GL261 mouse glioma cells suspended in 4 μ L of PBS using a Hamilton syringe for stereotactic intracranial injection. The mice were scanned between post-injection day 14 and day 24 when tumors were observed. One mouse was scanned twice on day 14 and day 18 respectively for longitudinal monitoring of tumor growth. The mice were treated in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and this study was approved by the Institutional Animal Care and Use Committee.

MRI experiments were performed on a Bruker 7T micro-MRI system, consisting of a Biospec Avance III-HD console (Bruker Biospin MRI, Ettlingen, Germany) with an actively shielded gradient coil (Bruker, BGA-12; gradient strength, 600 mT/m) and a ^1H Four-channel phased array receive-only MRI CryoProbe with a volume transmit coil (Bruker, Ettlingen, Germany). Figure 1e shows the images of individual channels of the receive coil and the coil sensitivity maps estimated from the temporal average of all spokes. For MRI scans, general anesthesia was induced by 1.5% isoflurane in air. The animal body temperature was maintained at $34 \pm 2^\circ\text{C}$ during the scan. A bolus of Gd-DTPA in saline at the standard dose of 0.1 mmol/kg was injected through a tail vein catheter, starting 30 seconds after the acquisition of pre-contrast images.

The 3D UTE sequence with 3D golden angle k -space sampling described above was used to acquired dynamic contrast-enhance data. The scan parameters were TR/TE = 4 / 0.008 ms respectively, flip angle (α) = 8.3 degree, image matrix = $128 \times 128 \times 128$, and field of view = $25 \times 25 \times 25 \text{ mm}^3$. The spatial resolution was about $0.195 \times 0.195 \times 0.195 \text{ mm}^3$. This sequence was continuously run for 6 minutes and 51 seconds to acquire 102,712 spokes.

Image Reconstruction

GRASP reconstruction (22) sorts the continuously acquired golden-angle radial data into undersampled temporal frames by grouping certain consecutive radial lines in each frame and uses an iterative algorithm to enforce temporal sparsity constrained by parallel imaging data consistency. The optimization problem to solve GRASP reconstruction is given by:

$$m = \arg \min_m \frac{1}{2} \|F_u C m - y\|_2^2 + \lambda \|\psi m\|_1 \quad [2]$$

where F_u is the undersampled non-uniform Fourier transform defined on the radial trajectory, C are the coil sensitivity maps, m is the dynamic image to be reconstructed, y is the undersampled k - t data (raw data sorted in undersampled temporal frames), λ is a regularization parameter that determines the tradeoff between data consistency and temporal sparsity, ψ is the first-order temporal difference transform, which is used to enforce sparsity. λ is defined as the percentage of maximum signal intensity from corresponding non-uniform FFT (NUFFT) reconstruction of the same temporal resolution. Multiple coil parallel imaging acquisition was implemented in GRASP.

A 3D NUFFT was employed to initialize the 3D GRASP reconstruction. The NUFFT operator was implemented by using the *gpuNUFFT* package (NUFFT implementation on NVIDIA based GPU) (30). Continuously acquired radial spokes were regrouped to 250/500/750/1,000/1,250/2,500 spokes per frame to generate 1/2/3/4/5/10 s/frame temporal resolution, respectively. There was no overlap of spokes used for consecutive frames of the GRASP images at any temporal resolution. The compressed sensing reconstruction was implemented following the same framework of the previously proposed GRASP (22), except that the minimization of Eq. [2] was conducted with the whole 3D data, instead of slice by slice in the stack-of-stars scheme. The 3D GRASP reconstruction was implemented in MATLAB (Mathworks, MA), using a tailored version of the nonlinear conjugated gradient algorithm in (12).

Assessment of Image Quality

The 3D NUFFT image with 38,750 post-contrast spokes (acquired between 50 s and 205 s during the dynamic scan) was used as a reference standard image to assess the influence of the regularization parameter λ on the image quality. The time-intensity curves from regions of interest (ROI) for tumor and arteries in the NUFFT image were used as the references to assess the influence of regularization and temporal resolution on the 3D GRASP image reconstruction. The image reconstruction was repeated with different regularization parameter λ (0.1 % - 20 %) and different temporal resolutions (1 - 10 s/frame = 250-2500 spokes/frame).

Spatial image quality was assessed using mutual information (MI) (31) and structure similarity index (SSIM) (32) with the NUFFT images as the reference standard described above. MI is defined as

$$MI = \sum_{g,r} P_{GR}(g,r) \log \frac{P_{GR}(g,r)}{P_G(g)P_R(r)} \quad [3]$$

where $P_{GR}(g,r)$ is the joint probability distribution of intensity values of GRASP (G) and reference (R) images. $P_G(g)$ and $P_R(r)$ are marginal probability distributions. SSIM is defined as

$$SSIM = \frac{1}{N} \sum_{x,y} \frac{(2\mu_G(x,y)\mu_R(x,y) + C_1)(2\sigma_G(x,y) + C_2)}{(\mu_G^2(x,y) + \mu_R^2(x,y) + C_1)(\sigma_G^2(x,y) + \sigma_R^2(x,y) + C_2)} \quad [4]$$

where $\mu(x,y)$ and $\sigma(x,y)$, local mean and standard deviation weighted by an 11×11 circular-symmetric Gaussian weighting function with standard deviation of 1.5 pixels, normalized to unit sum. C_1 and C_2 , constants were used to avoid instability, $(0.01 \times 255)^2$ and $(0.03 \times 255)^2$, respectively, in this study. MI and SSIM were computed for individual GRASP image frames from the slow washout part (frames 42 - 82) of the DCE-MR images. The NUFFT reference image was reconstructed with all the spokes within the same time period.

Temporal fidelity was assessed by comparing the difference between the enhancement ratio time curves of GRASP and NUFFT reconstructions. The GRASP images were reconstructed with various temporal resolutions (1 - 10 s/frame) and λ (0.1 - 20 %) in order to assess the influence of temporal resolution and λ on the image quality. Due to lack of a ground truth data for high-temporal resolutions used in this study, ROI-averaged NUFFT data were used as reference standards based on a numerical simulation study (Supporting Figures S1 and S2).

Pharmacokinetic Model Analysis

Pharmacokinetic model analysis with the GRASP reconstructed data was performed to generate the 3D parameter maps of tumors. Arterial Input Function (AIF), $C_p(t)$, was measured from an artery caudal of the eyes with the assumption of blood relaxation time $T_f = 2.1$ s (33) and blood Gd relaxivity $r_f = 4.7$ mM⁻¹s⁻¹ (34). The tissue concentration, $C_{tis}(t)$, was estimated using the generalized kinetic model:

$$C_{tis}(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(u) e^{\left(-\frac{K^{trans}}{v_e}(t-u)\right)} du \quad [5]$$

where v_p and v_e are vascular and extracellular space volume fraction respectively. K^{trans} is transfer constant. Tissue Gd relaxivity was assumed to be $r_1=4.3 \text{ mM}^{-1}\text{s}^{-1}$. Tissue relaxation time was assumed to be $T_1=2.3 \text{ s}$ for tumor and 1.6 s for all other tissues based on our previous *in vivo* studies at 7T (27,35). Contrast agent relaxivity was assumed to be proportional to contrast agent concentration, $R_1(t)=r_1C_{tis}(t)+1/T_1$. Tissue contrast agent concentration to MRI signal conversion can be done from the following equation

$$S(t) = S_0 \frac{\sin(\alpha)(1 - e^{-TR \cdot R_1(t)})}{(1 - \cos(\alpha)e^{-TR \cdot R_1(t)})} e^{-TE/T_2^*} \quad [6]$$

with S_0 represents the fully relaxed signal for a 90° pulse when $TR \gg 1/R_1(t)$. Since for this application, $TE \ll T_2^*$, the exponential term for T_2^* decay can be approximated as 1. It should be noted that, owing to the heterogeneity of tumors, relaxivity constant r_1 may not be a constant. However, for simplicity, it was assumed to be constant within tumor tissue in this study. Parameter estimation was performed with simplex algorithm (36) using Matlab function *fminsearch*. 3D rendering was implemented using Matlab *viewer3d* package (37).

RESULTS

Convergence of Iterative Image Reconstruction

The proposed 3D GRASP reconstruction was repeated with various reconstruction conditions ($\lambda = 0.1 - 20 \%$ and temporal resolution $T = 1 - 10 \text{ s/frame}$) in order to assess the convergence of the iterative algorithm (Figure 2). Convergence was evaluated in terms of the percent change of the cost function given in Eq. [2] between consecutive iterations (Δf). In all cases except $T = 1 \text{ s/frame}$ (Figure 2c), Δf became less than 2.5% within the first 20 iterations (Figure 2b and 2d). Since Δf noticeably slowed down beyond this point in all cases, we selected 2.5% (dashed lines in Figure 2b and 2d) as the stopping point. The Δf curves shown in Figure 2b suggest that λ does not affect the convergence speed when $T = 5 \text{ s/frame}$. For $\lambda = 0.1/0.5/1/2/5/10/15/20 \%$ with $T = 5 \text{ s/frame}$, Δf decreased to 2.5% or lower at 12/13/12/12/10/15/18/15 iterations, respectively. For different temporal resolutions ($T = 1/2/3/4/5/10 \text{ s}$) using regularization $\lambda = 1 \%$, the stopping criterion was reached at 38/21/18/14/12/9 iterations, respectively; the higher the temporal resolution (less number of spokes per frame), the slower its convergence. The convergences of the iterative reconstruction with $T = 5 \text{ s}$ and $\lambda = 1 \%$ in all mice were shown in Figure 2e and 2f, which show a similar convergence behavior in all cases.

Influence of Regularization Factor λ

GRASP images reconstructed using different regularization factors ($\lambda = 0.1 - 10 \%$) and $T = 5 \text{ s/frame}$ (1,250 spokes/frame) were compared with the reference standard image that was reconstructed using NUFFT with 38,750 spokes) (Figure 3). Representative GRASP images are shown in Figure 3a, along with the NUFFT image for the same temporal resolution and the reference image, which shows that the images appear less blurry with larger λ values. The similarity between GRASP images and the reference image was assessed in terms of SSIM and MI (Figure 3b). In general, with the increase of λ , both SSIM (increased from

0.74 to 0.82) and MI (increased from 2.16 to 2.42) monotonically increased. This indicates that the image quality improves with more weight on regularization along the temporal dimension. However, Figure 3c demonstrates that the average signal enhancement curve of a lesion is affected by λ ; the larger the λ , the more its temporal smoothing in general. The normalized DCE-MRI signal intensity showed good consistence for the regularization parameter, λ , range of 0.1%~2.0% as shown in Figure 3c. When λ is greater than 5%, the normalized signal DCE-MRI dynamics are way off the NUFFT reconstruction reference, which indicates too much temporal regularization along temporal direction. In terms of the distance between the GRASP reconstructed curves and the NUFFT reference reconstruction (Figure 3d), the curve with $\lambda = 1\%$ is the closest one to the reference data, as it can also be observed in Figure 3c.

Influence of Temporal Resolution

Figure 4a shows the GRASP reconstructed images for different temporal resolutions ($T = 1/2/3/4/5/10$ s/frame and $\lambda = 1\%$). The ROI-averaged signal enhancement curve from the NUFFT images was used as a reference standard intensity curve. All the enhancement curves are close to the reference curve with consistent delayed signal enhancement level at the end of the curve. However, the signal enhancement level near the peak varied depending on the temporal resolution. The signal enhancement curves with $T = 1$ s/frame in both tumor and vessel ROIs showed the largest differences from the reference curve around the peak, as expected due to the higher temporal resolution requirement and thus higher acceleration. Among the different temporal reconstructions assessed in this study, the ones with $T = 4$ and 5 s/frame were the closest to the reference curve.

Contrast kinetic model analysis

Figure 5a shows 3D rendering of the maximum intensity projection at different time points, the baseline (15 s), the AIF peak (35 s), the tumor peak (75 s) and the washout end (405s). Figure 5b shows an artery (red) used to measure AIF (Figure 5c) and a sample tumor pixel (blue) where its enhancement curve was shown in Figure 5d, along with a model fit. This analysis was repeated for all pixels in the imaging field of view to generated 3D maps of K^{trans} , v_e and v_p . With the 3D isotropic resolution of the data, the parameter maps can be shown in any planes, including axial, sagittal, and coronal as demonstrated in Figure 6.

One of the possible applications of the proposed 3D DCE-MRI method is to monitor tumor growth in 3D. Figure 7a and 7b show a same tumor at two time points, Day 14 and Day 18, without treatment, demonstrating that the heterogeneous tumor growth in all three dimensions. The total number of voxels in the tumor was 345 on Day 14 and 913 on Day 18, with the corresponding volume of 2.57 mm^3 and 6.80 mm^3 , respectively. This indicated a tumor growth of 1.64 times in four days. Figure 8 shows the histograms of tumor pharmacokinetic parameter $K^{trans}/v_e/v_p$. The median K^{trans} increased from $0.20 \pm 0.20 \text{ min}^{-1}$ on Day 14 to $0.25 \pm 0.07 \text{ min}^{-1}$ on Day 18. The interstitial volume fraction increased from 0.25 ± 0.21 on Day 14 to 0.33 ± 0.10 on Day 18. The vascular space volume fraction remained similar with 0.10 ± 0.06 on Day 14 and 0.09 ± 0.04 on Day 18.

DISCUSSION

With the development of fast imaging techniques such as compressed sensing and parallel imaging, it has become feasible to apply high spatial and temporal resolution DCE-MRI for clinical evaluation of suspicious lesions (22,38,39). Such rapid imaging methods can provide quantitative pharmacokinetic parameters that can be used as biomarkers for tumor microenvironment and tumor growth or treatment response. In this study, a 3D GRASP method was implemented by using a UTE sequence and extending the GRASP imaging method (22) from 2D golden angle sampling in plane with stack-of-stars volumetric sampling to 3D golden angle sampling. It was demonstrated that the proposed method can highly accelerate DCE-MRI to achieve a high temporal resolution with an isotropic high spatial resolution for small animal imaging at 7T where it is crucial to minimize the T_2^* effect. The results of this study suggested that the 3D-UTE-GRASP MRI data can be used for contrast kinetic analysis with direct AIF measurement in small animal imaging studies.

While compressed sensing reconstruction has been increasingly used for DCE-MRI, it remains challenging to select the required reconstruction parameters. One of the major challenges is how to select the regularization parameter λ that determines the trade-off between the data consistency and the sparsity constrain. Despite its importance, there is no consensus to date on how to determine the optimal λ for different clinical applications, since the value of λ depends on the noise level which changes for different acquisitions. We found that, among the λ values investigated, the best results in terms of temporal fidelity were achieved around $\lambda = 1\%$ of the maximum signal intensity in the NUFFT image reconstructed with the same temporal resolution. In the GRASP-MRI with the stack-of-stars scheme (22), $\lambda = 5$ was chosen as the optimal parameter for the dynamic images with 21 spokes/frame. Then the λ was adjusted for other temporal resolutions proportionally to the pseudo-noise level. Since the regularization strength needs to be adaptively changed depending on the noise level, λ can also be defined in terms of the noise level (40). In other compressed sensing studies (41,42), λ was empirically determined as 0.5 or 0.005. These studies with relatively small regularization factors suggest that the data consistency term should be emphasized more than the sparsity term in general. However, it remains unclear how these regularization factors from different studies are compared to each other as they are not defined in the same way. Further study is warranted to establish a more systematic and quantitative way to determine the regularization factor.

The golden angle acquisition scheme has been used for k -space sampling in different ways. One of the commonly used methods is the stack-of-stars scheme that employs 2D golden angle radial sampling in k_x - k_y plane combined Cartesian encoding in k_z direction (22,43). Alternatively, golden angle sampling can also be used for 2D phase encoding with Cartesian readouts in the third dimension (44,45). Castets et al (46) used a disk-like spiral trajectory in a 2D plane and rotate the plane in 3D k -space with a golden angle separation to realize 3D under-sampling. In all cases, the common goal is to achieve incoherent sampling of k -space for successful compressed sensing reconstruction. Hence, a 3D golden angle scheme would be most effective for incoherent sampling of the 3D k -space. Various 3D golden angle samplings have been used for 3D radial acquisition in previous studies mostly for motion tracking (47–52). In this study, we demonstrated that a relatively uniform yet incoherent

sampling of the 3D k -space could be achieved using a 3D golden angle scheme of half projections alternating between upper and lower hemispheres. The proposed scheme provided an isotropic 3D coverage/resolution for DCE-MRI studies in which a high 3D spatial resolution was acquired along with a high-temporal resolution in order to measure complex tumor heterogeneity. While the k -space sampling scheme used in this study was achieved by modifying the methods used in previous studies (47–50), future studies can be conducted to optimize the k -space sampling strategy depending on the specific applications or the expected dynamic pattern of the target signal, such as wash-in and wash-out phases in DCE-MRI.

Image reconstruction with undersampled data has been widely used to shorten scan times. Among various highly-accelerated MR imaging approaches (11–22), the proposed method in this study is based on GRASP (22) that have been successfully demonstrated for various clinical imaging applications (53). It has been shown that the GRASP MRI provides the image quality required for clinical reading while providing a sufficiently high temporal resolution to detect early contrast arrival in tumors compared with the surrounding tissue. In breast cancer, it was demonstrated that a high temporal resolution was required to better quantify the wash-in phase of the contrast enhancement and to differentiate between benign and malignant lesions (40). However, it still remains challenging to achieve a high temporal resolution if the number of slices is large. The GRASP MRI method uses the stack-of-stars scheme with the slice portioning in the inner most loop of the pulse sequence. In such method, the number of slices sampled in the inner most loop can be a limiting factor to achieve a high temporal resolution with a large volume coverage (i.e., a large number of partitions), as it is necessary to maintain a certain number of spokes per frame to achieve a reasonable image quality. This issue can be resolved by using a 3D golden-angle sampling approach as the slice partitioning dimension is also sparsely sampled. The current study with the proposed 3D-UTE-GRASP DCE-MRI method demonstrates the feasibility of achieving a high temporal resolution without compromising the coverage or resolution in all three dimensions, which can be useful in breast and body imaging applications or in high-resolution brain imaging.

Another key advantage of using the 3D-UTE-GRASP DCE-MRI method developed in this study is the inherent isotropic spatial resolution. It was demonstrated that the 3D DCE-MRI data with an isotropic spatial resolution provide a unique opportunity to visualize and assess the 3D spatial distribution of tumor contrast kinetic properties (Figure 6) and their changes (Figure 7 and Figure 8). Tumor heterogeneity is a hallmark of an aggressive tumor and treatment resistance. Texture analysis of tumor is a rapidly growing area of active research to quantitatively measure the spatial distribution and to identify textual features that can be used as imaging markers of tumor aggressiveness and treatment response (54–57). While an isotropic high resolution is preferred for such texture analyses (58), it is often not available as conventional MR images typically have the slice thickness larger than the in-plane resolution. This issue can be resolved by using our 3D-UTE-GRASP DCE-MRI method with an isotropic spatial resolution. In the present study, we presented histograms to summarize the distributions of the contrast kinetic properties (Figure 8). It can be extended to assessment of 3D textural features in future studies.

In this proof-of-concept study, the proposed imaging method was tested using a small number of mice with one murine tumor model in the brain. The flexible image reconstruction capability of the method can be useful in imaging tumors outside the brain, such as in the flank or mammary fat pad, that are more prone to motion artifact. Limitation of the study also includes using a highly sensitive cryogenic coil that is not commonly used in other small animal imaging sites. Further studies are warranted to repeat the study with conventional coils. Another limitation of the study was that the flip angle used for the 3D UTE sequence was not optimized. The flip angle of 8.3° was the maximum flip angle allowed in the UTE sequence provided by the scanner manufacturer. The scan protocol, including flip angle, can be further optimized in terms of image quality and contrast depending on specific DCE-MRI applications. It was beyond the scope of our study to assess the effect of motion on the proposed method. Since our UTE sequence samples the center of k -space at each echo readout, we expect that our method has the typical reduced motion sensitivity of radial sequences. In addition, high temporal resolution images can be used to resolve the actual motion during the scan and can provide an opportunity to use an image registration method for reducing motion artifacts. The image reconstruction technique can be further improved by combining with a motion-compensated method as demonstrated by Feng et al (59,60).

To conclude, it has been demonstrated that DCE-MRI studies with small animals can be conducted with (i) highly-accelerated imaging acquisitions with a high spatial and temporal resolution, (ii) negligible T_2^* effect, (iii) reduced partial volume effect, and (iv) variable temporal resolutions that can be tailored according to different needs. The results from this study demonstrated that the proposed 3D-UTE-GRASP method can be useful in effective measurement of the 3D spatial heterogeneity of tumor pharmacokinetic parameters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

3D golden angle sampling and parallel imaging. (a) modified 3D radial spokes in k -space with azimuth angle $\Phi = 2\pi mA$ and projection length (Z) in k_z direction being the modules one of mB , for $m = 1, 2, \dots, 102712$ spokes with 2D golden angle means, $A = 0.6823$ and $B = 0.4656$. Distribution of 400 projection tips for the random (b), modified (c) and original (d) 3D golden angle sampling. The green areas are computed voronoi regions for k -space sampling density compensation. (e) Demonstration of images of individual channels of the receive coil and the coil sensitivity maps estimated from the temporal average of all spokes.

Figure 2.

Convergence of compressed sensing reconstruction iterations. (a) With temporal resolution $T = 5$ s, vary regularization parameter $\lambda = 0.1/0.5/1.0/2.0/5.0/10/15/20$ %, plot the cost function value .vs. number of compressed sensing reconstruction iterations. (c) With regularization parameter $\lambda = 1$ %, vary temporal resolution $T = 1.0/2.0/3.0/4.0/5.0/10.0$ s, plot the cost function value .vs. number of compressed sensing reconstruction iterations. (b) and (d) show the corresponding cost function decrease % ratio, with 2.5 % stopping criterion (black dashed line) reached by all the iterations. (e) and (f) show the convergence of compressed sensing reconstruction iterations for multiple animals ($n=7$, M1 ~ M7, with M2 scanned twice). Temporal resolution of $T = 5$ s and regularization parameter $\lambda = 1$ %.

Figure 3.

Demonstration example of 3D-UTE-GRASP reconstructed images and tumor ROI DCE-MRI dynamics ($T = 5$ s). (a) Reference image (using post-contrast 38,750 spokes from 50 s to 205 s) with tumor ROI (blue), NUFFT reconstruction of the dynamic datasets (using 1,250 spokes/frame), and GRASP reconstructions with different regularization λ (using 1,250 spokes/frame). (b) SSIM and MI vs. different λ s. (c) Normalized signal enhancement curves of tumor ROI average from NUFFT reconstruction (assumed to be the reference) and different λ s. (d) Sum of squares between different λ reconstructed curves and NUFFT reconstructed reference.

Figure 4.

Demonstration example of 3D-UTE-GRASP reconstruction with different temporal resolutions ($\lambda = 1\%$). (a) Reconstruction with temporal resolution $T = 1/2/3/4/5/10$ s with tumor ROI (blue) and vessel ROI (red). (b) Normalized signal intensity curves for tumor ROI for different temporal resolutions and NUFFT reconstructed reference, and zoom in for contrast uptake region (10 s ~ 50 s) (c). (d) Normalized signal intensity curves for vessel ROI for different temporal resolutions and NUFFT reconstructed reference, and zoom in for contrast uptake region (10 s ~ 50 s) (e).

Figure 5.

Demonstration example of 3D rendered DCE-MRI dynamics and signal intensity curve (tumor and AIF) for DCE-MRI pharmacokinetic model analysis. (a) 3D maximum intensity projection (MIP) rendering of DCE-MRI dynamics (reconstructed with $T = 5$ s and $\lambda = 1$ %) at different stages: baseline (15 s), AIF peak (35 s), tumor enhancement peak (75 s), and washout end (405 s). Tumor enhancement ratio was multiplied by 2 for better visualization of tumor. (b) Vessel pixels (red) used for AIF and tumor pixel (blue) for sample tumor enhancement curve. (c) MRI measured AIF from vessel pixel. (d) Sample tumor pixel enhancement curve (blue cross) and GKM model fitting (green solid). The triangle, square, cross, and circle marked the corresponding time points in (a).

Figure 6. Pharmacokinetic model parameter color maps of tumor center slices in coronal/axial/sagittal planes. The coronal/axial/sagittal images in gray scale were reconstructed with 1,250 spokes/frame ($T = 5$ s) and $\lambda = 1$ %.

Figure 7. Demonstration example of using 3D-UTE-GRASP for longitudinal study ($T = 5$ s and $\lambda = 1$ %). Day 14 (a) and day 18 (b) scans with coronal/axial/sagittal zoom in tumor maps and corresponding pharmacokinetic parameter color maps.

Figure 8.

Demonstration example of using 3D-UTE-GRASP for longitudinal study ($T = 5$ s and $\lambda = 1$ %). Whole tumor $K^{trans}/v_e/v_p$ histogram comparison between day 14 and day 18 (Figure 7.).