Dynamic fractal signature dissimilarity analysis for therapeutic response assessment using dynamic contrast-enhanced MRI

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Purpose: To develop a dynamic fractal signature dissimilarity (FSD) method as a novel image texture analysis technique for the quantification of tumor heterogeneity information for better therapeutic response assessment with dynamic contrast-enhanced (DCE)-MRI.

Methods: A small animal antiangiogenesis drug treatment experiment was used to demonstrate the proposed method. Sixteen LS-174T implanted mice were randomly assigned into treatment and control groups ($n = 8/\text{group}$). All mice received bevacizumab (treatment) or saline (control) three times in two weeks, and one pretreatment and two post-treatment DCE-MRI scans were performed. In the proposed dynamic FSD method, a dynamic FSD curve was generated to characterize the heterogeneity evolution during the contrast agent uptake, and the area under FSD curve (AUC_{FSD}) and the maximum enhancement (ME_{FSD}) were selected as representative parameters. As for comparison, the pharmacokinetic parameter K^{trans} map and area under MR intensity enhancement curve AUC_{MR} map were calculated. Besides the tumor's mean value and coefficient of variation, the kurtosis, skewness, and classic Rényi dimensions d_1 and d_2 of K^{trans} and AUC_{MR} maps were evaluated for heterogeneity assessment for comparison. For post-treatment scans, the Mann–Whitney U -test was used to assess the differences of the investigated parameters between treatment/control groups. The support vector machine (SVM) was applied to classify treatment/control groups using the investigated parameters at each post-treatment scan day.

Results: The tumor mean K^{trans} and its heterogeneity measurements d_1 and d_2 values showed significant differences between treatment/control groups in the second post-treatment scan. In contrast, the relative values (in reference to the pretreatment value) of AUC_{FSD} and ME_{FSD} in both post-treatment scans showed significant differences between treatment/control groups. When using AUC_{FSD} and ME_{FSD} as SVM input for treatment/control classification, the achieved accuracies were 93.8% and 93.8% at first and second post-treatment scan days, respectively. In comparison, the classification accuracies using d_1 and d_2 of K^{trans} map were 87.5% and 100% at first and second post-treatment scan days, respectively.

Conclusions: As quantitative metrics of tumor contrast agent uptake heterogeneity, the selected parameters from the dynamic FSD method accurately captured the therapeutic response in the experiment. The potential application of the proposed method is promising, and its addition to the existing DCE-MRI techniques could improve DCE-MRI performance in early assessment of treatment response. © 2016 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4941739>]

Key words: dynamic fractal signature dissimilarity, longitudinal DCE-MRI, tumor heterogeneity

1. INTRODUCTION

As an advanced dynamic MR imaging technique, dynamic contrast-enhanced (DCE)-MRI measures the contrast agent (CA) transfer kinetics between the intravascular and the extravascular spaces in a noninvasive approach. Quantitative pharmacokinetic (PK) and heuristic model-based parameters have been established to characterize *in vivo* microvascular features including blood volume, blood flow, and vascularity permeability.¹ In the context of oncologic diagnosis, DCE biomarkers have been shown to correlate with tumor angiogenesis and pathological grade.^{2,3} DCE-MRI is also capable of assessing and monitoring the treatment effect of radiotherapy, chemotherapy, and antivascular drugs.^{4–7}

Currently, the treatment response of a tumor using DCE-MRI is often evaluated by the morphological descriptors of the tumor volume and first order statistics (mean/median/variance) of the PK parameters within the manually selected regions of interest (ROIs) or over the entire tumor volume.^{8,9} However, these techniques have limited capability to reveal the anatomical and functional heterogeneity information. Tumor neovasculature is often identified by leakiness, abnormal blood flow, and increased vasculature volume fraction. It shows differences within structure and function in the spatiotemporal domain, and the treatment induced function changes may vary across different subregions in the tumor.^{10,11} Recently, texture analysis has been proposed to quantify the tumor heterogeneity. As a general concept, texture in a biomedical

image can be described as the appearance and the structure of pixel arrangements.¹² Texture analysis focuses on the detection and quantification of repeating patterns and nonrandom distributions of pixel intensity values throughout a ROI.¹³ Many texture features have been reported as heterogeneity metrics.^{14–16} In the recently developed concept of radiomics which refers to the automated extraction of image features with great throughput potentials, heterogeneity assessment using texture analysis has been incorporated as a key component for comprehensive data mining and characterization.^{10,17,18}

So far, texture analysis has been applied in preclinical and clinical MR studies for computer-aided diagnosis (CADx) and treatment outcome prediction. As for describing local relationships between voxels' gray level intensities, several texture matrices have been defined in 2D and/or 3D for texture feature generation. Among these matrices, the co-occurrence matrix (information about the gray level distribution of pairs of pixels with specified separation and direction) and the run-length matrix (information about the runs of pixels with the same gray level in a specified direction) have been frequently adopted in DCE-MRI analysis.^{19,20} Although the texture features from these two matrices have been hypothesized to be superior in the diagnosis of certain cancers,^{21,22} these features are too simple to capture richer spatiotemporal information.²³ As an alternative strategy, fractal dimension analysis evaluates the spatial heterogeneity by estimating the complexity of ROI at multiple scales with no direct dependence on the gray level intensity values. Several studies using different fractal dimension methods have been investigated in DCE-MRI texture analysis for cancer diagnosis and treatment monitoring.^{9,24,25} These reported studies focused primarily on the evaluation of a chosen contrast-enhanced image volume or PK parametric maps. However, when using a single postenhancement image volume for analysis, the temporal evolution, which is argued as the inherent advantage of the dynamic image acquisition, was not fully utilized; on the other hand, the precision and accuracy of the derived PK parametric maps could be problematic for texture analysis due to the uncertainties in image acquisition and model fitting.²⁶ The dynamics of tumor heterogeneity evolution during the CA uptake may reveal supplementary qualitative and possible quantitative information in addition to classic PK parameters for disease characterization, and it has yet to be well studied.^{27,28} Additionally, few studies have reported the longitudinal change of tumor heterogeneity during the treatment course with multiple post-treatment scans.

In this study, we developed a dynamic fractal signature dissimilarity (FSD) method as a novel texture analysis technique for DCE-MRI therapeutic response assessment. Instead of using the classic PK model fitting approach, the developed dynamic FSD method utilizes the postinjection DCE images within a short time window and evaluates the dynamics of CA uptake heterogeneity during a DCE-MRI exam. In a small animal DCE-study of an antiangiogenesis agent treatment course, we demonstrate the feasibility of the dynamic FSD method in therapeutic response assessment, and we compared its performance against the classic PK analysis and the current fractal dimension techniques.

2. METHODS

2.A. Dynamic fractal signature dissimilarity

In fractal dimension analysis, the complexity of an intensity object defined on the 2D lattice can be described by its extruded 3D surface area.^{24,29} Such surface area originally from a 2D object can be calculated through the 3D Blanket method.³⁰ In this method, the surface area of an extruded 3D surface I is estimated by measuring the volume between two defined "blankets," which are two extruded surfaces that are not further than ε voxels above or below the surface to be measured (Fig. 1). These two surfaces are named as upper blanket $u_\varepsilon(i,j)$ and lower blanket $b_\varepsilon(i,j)$ which are defined as follows:

$$\begin{aligned} u_\varepsilon(i,j) &= \max\{u_{\varepsilon-1}(k,l)\}, \quad \text{with } \|(i,j)-(k,l)\| \leq 1, \\ u_0 &= b_0 = I, \\ b_\varepsilon(i,j) &= \min\{b_{\varepsilon-1}(k,l)\}, \quad \text{with } \|(i,j)-(k,l)\| \leq 1, \end{aligned} \quad (1)$$

where $(i,j),(k,l) \in K^+$ depicts the spatial coordinates. The selection of ε is also called the resolution for blankets calculation and is represented by the voxel numbers. The surface area of I at a certain resolution of ε , $A(\varepsilon)$, is then defined as

$$\begin{aligned} V(\varepsilon) &= \sum \{u_\varepsilon(i,j) - b_\varepsilon(i,j)\}, \\ A(\varepsilon) &= [V(\varepsilon) - V(\varepsilon-1)]/2, \end{aligned} \quad (2)$$

where $V(\varepsilon)$ is the measured volume between the upper blanket $u_\varepsilon(i,j)$ and lower blanket $b_\varepsilon(i,j)$ and $V(0) = 0$. Based on the series $(\varepsilon, A(\varepsilon))$, $S(\varepsilon)$, which we called as fractal signature, is defined as the slope of the best linear fitting of these

Fig. 1. A diagram of a 3D surface (a) and its upper blanket (above the surface) and lower blanket (below the surface) (b).

three points: $(\log(\varepsilon - 1), \log(A(\varepsilon - 1)))$, $(\log(\varepsilon), \log(A(\varepsilon)))$, and $(\log(\varepsilon + 1), \log(A(\varepsilon + 1)))$. The magnitude of $S(\varepsilon)$ can be interpreted as the amount of detailed information on the surface $A(\varepsilon)$ that is lost when the measuring resolution of the Blanket method is worse (i.e., higher value) than ε . When I

comes from a perfect fractal object, $S(\varepsilon)$ should be a constant for all possible ε values.³¹ In order to describe the tumor heterogeneity change during the CA uptake, we proposed the concept of dynamic FSD by comparing the $S(\varepsilon)$ from two DCE tumor volumes that were acquired adjacently,

$$\text{FSD}(t) = \frac{\sum_{n=1}^N w_n \sum_{\varepsilon=2}^{\varepsilon_{\max}-1} \left\{ [S_{n,t}(\varepsilon) - S_{n,t-1}(\varepsilon)]^2 \cdot \log(2\varepsilon + 1/2\varepsilon - 1) \right\}}{\left[\sum_{\varepsilon} \log(2\varepsilon + 1/2\varepsilon - 1) \right] \cdot \left[\sum_n w_n \right]}, \quad t > 0, \quad (3)$$

$$w_n = v_n/V \cdot 1/d_n,$$

where t represents the time point after CA injection and $t = 0$ represents the injection time point, and $S_{n,t}(\varepsilon)$ is calculated by using n th slice of the tumor volume at time point t . The weighting factor w_n accounts for the contribution of the tumor's n th slice toward the $\text{FSD}(t)$ calculation, in which v_n is the subvolume of the tumor's n th slice and d_n is the distance of the n th slice to the tumor's central slice. The location of the central slice was determined by the averaged preinjection volume. For a generated dynamic FSD curve, two heuristic shape features, area under curve (AUC_{FSD}) and maximum enhancement (ME_{FSD}), were selected to characterize the curve feature and were investigated for therapeutic response assessment application.

2.B. Rényi dimensions

Classic fractal dimension analysis evaluates the spatial heterogeneity by estimating the complexity of ROI at multiple scales with no direct dependence on the gray level intensity values. For a binary object without intensity variation, box counting dimension was proposed to estimate the shape complexity (see Fig. S1 in the supplementary material³² for an example). For intensity objects, Rényi dimensions are a generalization of fractal dimensions as a family of information measurement.³³ It is expressed by summing the Rényi entropy at different scales,

$$d_q = \lim_{s \rightarrow 0} \frac{\log \sum_i p_i^q}{(1-q) \log 1/s},$$

$$d_1 = \lim_{q \rightarrow 1} d_q, \quad (4)$$

where s is the scale resolution (the size of the grid which is imposed on the object for calculation³³) and p_i is the normalized intensity value of i th voxel such that $\sum_i p_i = 1 \forall i$. When substituting $q = 0$ in Eq. (4), the zero order Rényi dimension d_0 is equivalent to the simple box counting dimension. Two Rényi dimensions are often used: d_1 information dimension and d_2 correlation dimension, and $d_1 \geq d_2$. With the consideration of intensity variation, Rényi dimensions are the complexity measurements in terms of both selfsimilarity and pattern irregularity. For objects with

predefined shape, d_1 and d_2 values were reported for objects with larger intensity variations.³⁴ Previous studies reported that d_1 and d_2 values of DCE-MRI parametric maps could reflect the tumor heterogeneity differences between low and high grade gliomas.²⁴ We hypothesize that antiangiogenesis drug treatment would induce changes in spatial heterogeneity statistics of PK parametric maps. As the dynamic FSD analysis was proposed for CA uptake heterogeneity study, we adopted d_1 and d_2 statistics for K^{trans} map analysis in addition to the conventional summary statistics for comparative study purpose. Since d_0 was primarily designed for binary objects, we do not include it in the comparison study.

2.C. Treatment protocol

The diagram of the small animal experiment can be found as Fig. 2. All animal studies were approved by the Institutional Animal Care and Use Committee. Sixteen female *nu/nu* mice with LS-174T (Charles River Laboratories, Wilmington, MA) implanted in the mammary fat pad were followed for four weeks. When tumor volume was approximately 100 μL , the mice were randomly assigned into the treatment ($n = 8$) group or the control ($n = 8$) group. The number of animals in this study was determined based on a power analysis of the population standard deviation estimated from a limited sample size of animals inoculated with the identical tumor cell line in a previous pilot study (see the Appendix for details). A baseline DCE-MRI scan was acquired at day 0. At day 1, the treatment/control group received bevacizumab (Avastin®, Genentech, South San Francisco, CA) or normal saline via an intraperitoneal injection at a dose of 5 mg/kg or 5 ml/kg, respectively. Thereafter, bevacizumab/saline was administered at the same respective dose twice weekly, and

FIG. 2. The diagram of the small animal experiment.

FIG. 3. The workflow of image analysis in this work.

DCE-MRI imaging scans were performed weekly. In this study, the first two post-treatment scans at day 2 and day 9 as well as the baseline scan were evaluated since the therapeutic effects of the treatment group were prominent in terms of tumor growth rate after the first two weeks' treatments.

2.D. Imaging protocol

All DCE-MRI scans were acquired in a 7 T small animal MRI scanner (Bruker BioSpin MRI GmbH, Ettlingen, Germany) equipped with self-shielded gradient coils with a maximum strength of 450 mT/m and a rise time of 110 μ s. An actively detuned volume RF coil (linear transmit, ID = 72 mm) was used in conjunction with a four-element coil (2 $\times$ 2 linear array, 10 $\times$ 10 mm loops) for surface receive. An interleaved ultra-short-echo radial sampling sequence was adopted for 4D reconstruction using a sliding-window keyhole approach as described in the previous work.³⁵ The acquisition parameters were FOV = 20 mm³, matrix = 128³, TR/TE = 5/0.02 ms, NEX = 1, flip angle α = 10°, and temporal resolution = 9.9 s. The varying flip angle method with α = {2°, 10°} was used to measure the native relaxation rate before the CA injection.³⁶ During the scan, animals were positioned in a custom-made MR-cradle and were maintained under anesthesia by isoflurane delivery via a nose cone. The body temperature was controlled between 36 and 37°C by circulating warm water. Breathing was monitored through a pneumatic pillow and was maintained at a rate of 50–60 breaths/min via adjusting isoflurane delivery. An automatic syringe pump (KD Scientific, Inc., Holliston, MA) was used to administer Gd-DTPA (Magnevist, Schering AG, Berlin, Germany) as a bolus via a 27-gauge vein at a dose of 0.5 mmol/kg and a flow rate of 2.4 ml/min. We have verified that the signal from the pulse sequence with the above imaging parameters does not saturate for CA concentration.³⁷ Dynamic imaging was initiated 2 min prior to the CA injection and lasted for approximately 20 min after the CA injection.

2.E. Image analysis

Prior to the image analysis, the tumor volume V was manually contoured and measured based on a stable contrast-enhanced volume. At each scan day, the workflow of image analysis in this work can be summarized in Fig. 3.

In the PK analysis generating the K^{trans} parametric map, the CA concentration $C(t)$ was calculated using

$$C(t) = (R1 - R1_0)/r_1, \quad (5)$$

where $R1_0$ is the native relaxation rate and r_1 is the longitudinal relaxivity ($\approx 3.275 \text{ mM}^{-1} \text{ s}^{-1}$ at 7 T) of the CA. The two-compartment extended Tofts model was used to describe the CA evolution,³⁸

$$C(t) = K^{\text{trans}} \int_0^t C_p(u) \cdot e^{-(K^{\text{trans}}/v_e) \cdot (t-u)} du + v_p \cdot C_p(t), \quad (6)$$

where K^{trans} is the rate constant of CA extravasation from blood plasma to extravascular-extracellular space (EES), and v_p and v_e are the volume fraction of blood plasma and EES, respectively. The arterial input function (AIF) $C_p(t)$ in this study was approximated by a reported population measurement result.³⁹ Equation (5) was then solved on a voxel-by-voxel basis using a linear least-squares method using the full scan time.⁴⁰ The tumor's mean K^{trans} was reported as the primary PK biomarker in this study. Rényi dimensions d_1 and d_2 were recorded as K^{trans} heterogeneity measurement. The K^{trans} coefficient of variation (CV), which is defined as the ratio of standard deviation to the mean, was also reported as a measure of K^{trans} probability distribution dispersion.⁴¹ In addition, K^{trans} kurtosis (measurement of "peakedness" of the probability distribution) and skewness (measurement of asymmetry of probability distribution) were recorded to describe K^{trans} distribution shape features.

In dynamic FSD analysis, the DCE volumes acquired in the first 2-min postinjection time window were adopted for the heterogeneity analysis during the initial CA uptake. The

FIG. 4. An example of pretreatment DCE-MRI scan. (a) Postinjection MR image of a selected slice; (b) the 3D tumor's average CA concentration curve (blue) and dynamic FSD curve; (c) preinjection T_{10} map; (d) AUC_{MR} map generated in the same time window as FSD curve; (e) CA distribution 2 min after injection; and (f) K^{trans} distribution.

minimum ε value [in Eq. (2)] of this work was selected as 1 and $\varepsilon_{\max}$ was empirically chosen as 10. AUC_{FSD} and ME_{FSD} were recorded as primary biomarkers of dynamic FSD analysis.

The AUC_{MR} map, i.e., the AUC map of DCE enhancement image, was generated in the same 2-min postinjection time window as in dynamic FSD analysis. Similar to the PK analysis, the AUC_{MR} tumor mean value, CV, kurtosis, skewness, d_1 , and d_2 were analyzed.

2.F. Statistical analysis

For each post-treatment scan, the Mann–Whitney U -test was used to assess the difference of the recorded quantitative values between treatment and control groups. Significance was determined based on a p -level less than 0.05 with

multicomparison correction if applicable.⁴² Experiments using support vector machine (SVM) in a leave-one-out approach were performed to validate the potential use of the recorded metrics in treatment/control group classification.

3. RESULTS

Figure 4 demonstrates an example of data analysis using a day 0 scan. The tumor heterogeneity can be easily appreciated on postinjection DCE axial image slice (a), AUC_{MR} map (d), and CA concentration map (e). The K^{trans} map shows in (f) which shares some similarities with (d) and (e) in terms of spatial distribution pattern. (b) shows the CA concentration time curve (solid) and dynamic FSD curve (dashed) in the first 2-min postinjection time window. During the initial CA

FIG. 5. The comparisons of tumor volume V and its relative value between treatment/control groups during the treatment course. * indicates that statistically significant difference was found between treatment/control groups.

uptake stage, the dynamic FSD curve had a prominent peak following the CA injection, while the FSD values after the peak were relatively small and stable.

Figure 5 demonstrates the tumor volume V changes during the study. At day 0, the initial tumor volumes of the treatment and control group were 115 ± 41 and 91 ± 37 μL , respectively. As the treatment course continues, the tumor in the treatment group grew slower than the tumors in the control group. The effect of the bevacizumab was more obvious on the comparison of the relative value (defined as the ratio of day 2/9 value to the reference day 0 value) of V . After three administrations, the relative V in the control group was significantly higher than that in the treatment group ($p = 0.002$) at day 9.

The K^{trans} analysis results are summarized in Fig. 6. The tumor mean K^{trans} evolution during the treatment course is presented in Fig. 6(a). At day 0, there was no significant difference between the treatment/control groups K^{trans} value. After three treatment deliveries at day 9, the treatment group had a significantly smaller K^{trans} value than the control group ($p = 0.021$). The relative K^{trans} of the two cohorts at both day 2 and day 9 had no significant difference in (b). Similarly, the K^{trans} CV, kurtosis, and skewness showed no significant difference between the two cohorts at both post-treatment days in (c)–(e). In contrast, the classic fractal dimensions d_1 ($p = 0.013$) and d_2 ($p = 0.028$) of K^{trans} map reflected significant difference between the treatment/control group at day 9 in (f) and (g). The AUC_{MR} analysis results are presented in Fig. 7 with the same layout as Fig. 6. Of the investigated metrics, none of them showed significant differences between the treatment/control groups at day 2/day 9.

Figure 8 presents the dynamic FSD analysis results. Figures 8(a) and 8(b) show the dynamic FSD curves at all scan days of two selected animals from the treatment group and control groups, respectively. As can be seen, the dynamic FSD curves shared common features with an enhancement peak following the CA injection and a relatively stable postpeak tail. The longitudinal change of AUC_{FSD} and its relative value are presented in Figs. 8(c) and 8(d). Both cohorts had reduced AUC_{FSD} value after the treatments, and the relative AUC_{FSD} values showed significant differences between the two cohorts

at both day 2 ($p = 0.029$) and day 9 ($p = 0.005$), suggesting the bevacizumab treatment effect. Figures 8(e) and 8(f) illustrate the comparison of ME_{FSD} and its relative values between treatment/control groups. At day 0, the baseline ME_{FSD} values of the control group were higher than those in the treatment group with wider distribution, though the difference was not statistically significant. The relative ME_{FSD} values in the treatment group were significantly higher than the control group values at both day 2 ($p = 0.005$) and day 9 ($p = 0.008$).

The results of treatment/control groups' classification experiments using SVM are summarized in Table I. When mean K^{trans} was used as the sole input elements, the classification accuracy at day 9 was 68.8%, and if K^{trans} CV was added to the input, the accuracy was improved to 75.0% at day 9. If classic fractal dimensions d_1 and d_2 were selected as the input elements, the achieved accuracies were promising at both day 2 (87.5%) and day 9 (100%). Compared to the results using K^{trans} metrics, the classification accuracies using AUC_{MR} metrics were generally lower than the corresponding statistics of K^{trans} results, and AUC_{MR} metrics demonstrated higher classification accuracies at day 2 rather than day 9. In contrast, the classification accuracies were as high as 93.8% at both day 2 and day 9 using the metrics from the dynamic FSD analysis. The 93.8% classification accuracy day 2 made the dynamic FSD method advantageous in the early detection of therapeutic response during the treatment course. Comparing to conventional K^{trans} statistics (mean value and CV), the functional heterogeneity information (K^{trans} d_1 and d_2) as well as the investigated dynamic CA uptake heterogeneity information (dynamic FSD parameters) could be superior in the detection of antiangiogenesis therapeutic effect.

4. DISCUSSION

For effective therapeutic response assessment, a dynamic FSD method was developed to better characterize the CA uptake heterogeneity information during a DCE-MRI scan. This method was evaluated in a longitudinal small animal study which involved the use of bevacizumab, a recombinant humanized monoclonal IgG₁ antibody that selectively binds to

FIG. 6. The longitudinal change of mean K^{trans} (a), relative K^{trans} (b), K^{trans} CV (c), K^{trans} kurtosis (d), K^{trans} skewness (e), K^{trans} d_1 (f), and K^{trans} d_2 (g). * indicates that statistically significant difference was found between treatment/control groups.

and neutralizes the functional activity of vascular endothelial growth factor (VEGF).⁴³ Such neutralization can lead to the reduction of tumor vascularization function and subsequent tumor growth.⁴⁴ Traditionally, the lesion size of a solid tumor is one of the main metrics for the assessment of treatment response.⁴⁵ The decrease of lesion volume reflects an effective response and would be the desirable treatment outcome. In this study, the application of bevacizumab caused a decrease of tumor growth rate, though the complete tumor regression was not achieved. As a noninvasive measurement of vascular functional information, DCE-MRI has served as a helpful imaging tool in the treatment evaluation and novel antiangiogenesis drug development. The classic PK parameter K^{trans} describes the combined information of capillary wall surface, capillary permeability, and blood flow from blood vessel to tissue and has served as the primary quantitative biomarker of DCE-MRI analysis. Many studies have reported a decreased regional mean K^{trans} value after the bevacizumab application or its combination with other treatment regimens.^{46–49} The relative K^{trans} in reference to the baseline value has also been

adopted in treatment assessment studies. However, the relative K^{trans} in this experiment did not show significant differences between treatment/control groups after the treatment.

We also observed the high functional heterogeneity within the tumor. As an example, the hot spots in a 2D K^{trans} distribution obtained before the treatment at day 0 as shown in Fig. 4(d) were surrounded by low K^{trans} intensity regions. As the tumor evolves, the periphery and the core of the tumor may have different enhancing rates during the CA uptake with very different K^{trans} distribution.^{50,51} To account for the problem, some studies evaluated the treatment response in the separated tumor subregions,^{52,53} while some studies utilized the K^{trans} histogram information involving kurtosis and skewness.⁵⁴ In this work, the K^{trans} kurtosis of both the treatment and the control group increased along with the experiment, which indicated that K^{trans} distribution evolved toward leptokurtosis (high “peakedness”). This observation does not fully support some previous studies in which the increase of kurtosis was correlated with the tumor chemotherapy response.⁵⁵ The observed skewness in this work was all positive, and this

FIG. 7. The longitudinal change of mean AUC_{MR} (a), relative AUC_{MR} (b), AUC_{MR} CV (c), AUC_{MR} kurtosis (d), AUC_{MR} skewness (e), AUC_{MR} d_1 (f), and AUC_{MR} d_2 (g).

means that the observed K^{trans} distributions' peaks were with low intensity region with a longer tail at the high intensity region. The increase of skewness may reflect the shift of K^{trans} peak value toward the lower intensities. So far, few studies have been reported regarding the longitudinal change of K^{trans} distribution shape descriptor including kurtosis and skewness after therapy. This renders the kurtosis and skewness preliminary and challenging in DCE-MRI therapeutic response assessment.

The classic fractal dimensions d_1 and d_2 based on the K^{trans} map reflected significant difference between the treatment/control groups at day 9. As quantitative metrics describing the object complexity, high d_1 and d_2 values were associated with high degree of heterogeneity. Previous studies reported increased K^{trans} d_1 and d_2 values after the simulated treatment using digital tumor phantom.²⁴ One of the contributions of our work is the longitudinal study of classic d_1 and d_2 change using *in vivo* small animal data. When using K^{trans} d_1 and d_2 values for treatment/control groups' classification, the accuracy was as high as 100% at day 9

after three treatment deliveries. These pilot results suggest the great potential of classic fractal dimension analysis in monitoring antiangiogenesis drug treatment response. In this work, the treatment group K^{trans} d_1 and d_2 values were higher than the control group values. The increases of treatment group d_1 and d_2 values in the previously reported study were not observed probably due to the incomplete tumor regression. Nevertheless, the capability of heterogeneity information from fractal dimensions in therapeutic response assessment was demonstrated as is complementary information to the classic PK analysis.

The dynamic FSD analysis is a novel image texture analysis method which is very different from the classic PK analysis. The study outcomes from the treatment/control groups demonstrated significant differences for certain dynamic FSD features right after the first treatment delivery (day 2). In contrast, the therapeutic effect of the treatment group for the PK parameter K^{trans} and its heterogeneity measurement was not obvious until three treatments were delivered (day 9). The treatment/control group classification accuracy at day 2

FIG. 8. The demonstration of dynamic FSD analysis. (a) and (b) Dynamic FSD curves on all scan days of a treatment group animal and a control group animal [the day 0 curve in (b) has been shown in Fig. 3(b)]; (c) and (d) the longitudinal change of AUC_{FSD} and its relative value; (e) and (f) the longitudinal change of ME_{FSD} and its relative value.

using the selected dynamic FSD parameters was higher than the accuracy using the classic texture analysis metrics based on K^{trans} , and the corresponding accuracies at day 9 were comparable. These results from dynamic FSD analysis can be attributed to the description of CA uptake heterogeneity dynamics which cannot be captured by conventional PK model analysis. This dynamic FSD analysis also demonstrated several technical advantages for potential clinical application. Since it utilizes the DCE images rather than the model fitting of CA concentration distributions, a measurement of the arterial input function is not needed. Also, the calibration scans for the native relaxation calculation are not required. In some clinical DCE-MRI applications with low temporal resolution, such as breast DCE-MRI for early stage diseases, the saved scan time is considerable.⁵⁶ In addition, the dynamic FSD

analysis only requires a short scan time immediately after the CA injection, while the PK analysis needs longer postinjection scan time for accurate model fitting. This shorter scan time could potentially reduce the effects of intrascan motion due to the patient discomfort after a certain time. Nevertheless, we acknowledge the indispensable role of classic PK model analysis as the derived PK parameters can be correlated with physiological process. At this preliminary stage, we would like to present our dynamic FSD method as a supplementary tool for DCE-MRI analysis. Although the proposed dynamic FSD method showed its advantages over the PK analysis in early therapeutic effect detection at day 2, it might be too early to use this novel method as the sole DCE-MRI analysis method in the replacement of classic PK analysis. Potential retrospective and preferable perspective clinical study comparing this novel

TABLE I. The results of treatment/control groups' classification using SVM.

SVM input	Classification accuracy	
	Day 2 (%)	Day 9 (%)
K^{trans}	Mean K^{trans}	37.5
	Rev. mean ^a K^{trans}	68.8
	(Mean K^{trans} , CV)	42.9
	(Kurtosis, skewness)	50.0
	(d_1 , d_2)	75.0
AUC _{MR}	Mean AUC _{MR}	43.8
	Rev. mean AUC _{MR}	43.8
	(Mean AUC _{MR} , CV)	64.3
	(Kurtosis, skewness)	28.6
	(d_1 , d_2)	31.3
Dynamic FSD	(AUC _{FSD} , ME _{FSD})	43.8
	(Rev. AUC _{FSD} , rev. ME _{FSD})	18.8
		56.3
		25.0
		93.8
		92.9

^aTwo day 0 scans were excluded in the analysis due to uncertain CA injection dose.

method against classic PK analysis would be helpful in the determination of its role in potential clinical application.

The dynamic FSD analysis uses the postinjection DCE images and evaluates the heterogeneity evolution during a very short CA uptake time window. The derived FSD value is a quantitative metric that describes the heterogeneity differences of two volumes. In a dynamic FSD curve, a higher FSD value means that the tumor CA distribution pattern at this point has a higher degree of difference from the CA distribution pattern at the prior time point. In other words, a higher FSD value means bigger morphological change of DCE image resulted by CA uptake, which is equivalent to higher CA uptake heterogeneity. As indicated by the blue curve in Fig. 4(b), the tumor heterogeneity changed dramatically at the initial CA uptake and remained relatively stable during the continuing steady CA uptake. During the experiment, we found that steady CA uptake could be observed in all analyzed DCE scans during a short time window after injection, while the CA washout dynamic varies after the initial uptake with many early washout cases. As a result, we selected the first 2 min postinjection time for the analysis to keep the focus on the study of CA uptake heterogeneity. In the classic PK analysis, the rate constant K^{trans} models the CA uptake from blood plasma to EES, yet the heterogeneity of CA uptake may not be fully described by the K^{trans} distribution. Some other quantities, including water molecule concentration and native longitudinal relaxation rate, may have indirect effect on the CA uptake heterogeneity. As an alternative strategy, the FSD value directly quantifies the CA uptake heterogeneity and may contain additional information than K^{trans} heterogeneity measurement. It could be an interesting future work to investigate the selected dynamic FSD features in a longer time window; however, the tumor heterogeneity dynamic would be affected by both uptake and washout processes and potentially be heavily regulated by other PK parameters besides K^{trans} . Simulation studies based on digital dynamic phantom would be useful toward revealing the complicated

relationship between dynamic FSD features and multiple classic PK parameters.

During the longitudinal study, as the tumor treatment response may differ in tumor subregions, particularly the periphery and center regions, the tumor CA uptake pattern may change in both spatial and temporal domains and thus lead to the amplitude and shape change of the dynamic FSD curve, including peak position, peak width, and amplitude variation of the postpeak tail. In Eq. (3), the FSD value at a certain time point can be interpreted as the weighted average of $S(\varepsilon)$ series. As an example, Fig. S2 in the supplementary material shows the plots of $A(\varepsilon)$ and $S(\varepsilon)$ of the animal shown in Fig. 4. $S(\varepsilon)$ can also be interpreted as the evaluation of frequency component of the intensity distribution. Specifically, high magnitude of $S(\varepsilon)$ at small ε relates to prominent “high-frequency” gray level variations, while high magnitude of $S(\varepsilon)$ at large ε relates to substantial “low-frequency” patterns of the gray level distribution. Compared to Fourier analysis, the curve fitting approach in $S(\varepsilon)$ generation could be less sensitive to “bad” voxels with very high/low intensities and thus be potentially robust for image texture analysis and pattern recognition with high noise level.³⁰

In Figs. 8(a) and 8(b), the change of dynamic FSD curve shape can be observed. We believe that AUC_{FSD} and ME_{FSD} could be used to represent shape features of a dynamic FSD curve. At day 0, the treatment/control groups showed discrepant (though not statistically significant) ME_{FSD} and AUC_{FSD} distributions. Since the group assignment was randomized, this observation may suggest the large individual variability of CA uptake. The use of relative ME_{FSD} and relative AUC_{FSD} could reduce the individual variability and describe the reliable therapeutic response information. For a future study of individual CA uptake variability, a larger small animal population is in demand to maximize the treatment/control group separation based on the results in Figs. 8(d) and 8(f) for better statistical persuasiveness. In addition, Kaplan–Meier outcome analysis would be helpful in determining the clinical benefit of the CA uptake heterogeneity information from the proposed dynamic FSD analysis.

Based on the observation of sharp peaks right after the CA injection, we speculate that the performance of the proposed dynamic FSD method may be affected by the temporal resolution. To verify this hypothesis, we did an additional comparison study by generating the FSD curve at simulated 19.8 s (×2) and 29.7 s (×3) temporal resolutions in the same 2-min time window. Specifically, each FSD value was calculated using two DCE volumes that were acquired with 19.8 or 29.7 s intervals. Figure 9 shows the comparison of the dynamic FSD curves using different temporal resolutions from the same scan shown in Fig. 4(b). As can be seen, three curves generated with different temporal resolutions shared similar shape patterns with a prominent peak after the immediate CA injection and a relatively stable tail in the following CA uptake. At the simulated 19.8 s temporal resolution, the maximum enhancement of the FSD curve (green) was found at the same position as the original FSD curve (red). Similarly, the curve generated with 29.7 s temporal resolution (blue) demonstrated

FIG. 9. The comparison of dynamic FSD curves generated using the original 9.9 s temporal resolution (red), simulated 19.8 s (green), and 29.7 s (blue) temporal resolutions. The red curve was shown in Fig. 6(b).

its maximum as its first datum but with a 9.9 s shift due to the limited temporal resolution. The comparison of ME_{FSD} and AUC_{FSD} statistics from the simulated 19.8 and 29.7 s temporal resolutions can be found in Figs. S3 and S4 in supplementary material,⁵⁷ respectively. At simulated 19.8 s temporal resolution, significant differences of relative ME_{FSD} between treatment/control groups were found at both day 2 and day 9, but significant differences of relative AUC_{FSD} between two groups were only found at day 9; in contrast, when the temporal resolution was reduced to 29.7 s, significant differences of relative ME_{FSD} and relative AUC_{FSD} between two groups were observed only at day 9. The SVM results of treatment/control groups' classification using simulated dynamic FSD parameters are summarized in Table S1 in the supplementary material.⁵⁷ For a short summary, as the temporal resolution degrades, the classification at both post-treatment scan days became less accurate. These results suggest that high temporal resolution is favored for the dynamic FSD method. However, the performance of the dynamic FSD method at low temporal resolution could be improved because the spatial resolution can be enhanced during the low temporal resolution scan. In this retrospective simulation study, the benefit of enhanced spatial resolution cannot be addressed. We believe future perspective experiments would be helpful for the comprehensive demonstration of the dynamic FSD method at low temporal resolutions.

Another interesting future work is the improvement of the 3D Blanket method which is used in FSD calculation. In 3D Blanket method, a 2D intensity object is extruded as 3D surface and the calculation is conducted in a 3D fashion. In this work, we calculated the FSD value of a 3D intensity object (i.e., the tumor) as a weighted average of 2D slices' FSD values, and this approach was reasonable and yet empirical.^{11,27} It might be appealing to extrude the 3D intensity object as a 4D surface for a possible "4D Blanket Method." Future works about the dynamic FSD analysis on a basis of 4D surface fractal analysis will explore these possibilities.

5. CONCLUSION

In this work, a dynamic FSD method was developed for DCE-MRI therapeutic response assessment. Unlike the classic DCE-MRI analysis based on PK model fitting, the proposed dynamic FSD method is a novel image texture analysis technique which quantitatively evaluates the CA uptake heterogeneity dynamics based on DCE images. In a small animal antiangiogenesis drug treatment experiment, the selected parameters from the dynamic FSD method demonstrated significant differences between treatment/control groups as early as after first treatment delivery; in contrast, the classic PK parameter K^{trans} and its heterogeneity measurement from classic texture analysis reflected the significant differences between treatment/control groups only after three treatment deliveries. After first treatment delivery, the treatment/control group classification using the selected parameters from the dynamic FSD method achieved highest accuracy in comparison with the classifications using existing metrics. These results suggest that the proposed dynamic FSD analysis is promising in monitoring antiangiogenesis treatment response. Future works about the mathematical framework and large scale experiments might be essential toward the clinical application of the proposed method.

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APPENDIX: POWER ANALYSIS FOR DETERMINING SAMPLE SIZE

Power analysis is a common statistical approach for determining the sample size needed to test a null hypothesis with a given significance level. This approach requires an estimation of the effect size (difference in group means normalized by the standard deviation of the whole population). The number of animals per groups is found by⁵⁸

$$n = \frac{2\sigma^2(z_{(\alpha/2)} + z_{(1-\beta)})^2}{(\mu_1 - \mu_2)^2}, \quad (A1)$$

where σ is the population standard deviation, $(\mu_1 - \mu_2)$ is the difference between group means, α is the significance level, and $(1 - \beta)$ is the power. For a significance level of 0.05 and power of 0.8, the standard normal deviates are equal to $z_{(\alpha/2)} = 1.96$ and $z_{(1-\beta)} = 0.842$ for a two-sided test.

In our power analysis, the pharmacokinetic parameter used to compute the sample size was K^{trans} . This choice was mainly driven by the fact that our group has an extensive experience in the study of the bias and uncertainty of K^{trans} .³⁷ The statistical variation of the PK parameters presented in the current work is under investigation. The effect size was estimated from a pilot study with the same experimental

TABLE II. Mean K^{trans} in tumor volume for each animal in the control and treatment group at day 17. At this time-point, the difference between group means was the largest observed in the pilot study. The data here are used to estimate the effect size and to calculate sample size.

	K^{trans} in control group (min^{-1})	K^{trans} in treatment group (min^{-1})
Animal 1	0.1805	0.0598
Animal 2	0.1298	0.1256
Animal 3	0.1258	0.0426
Animal 4	0.1821	0.0884
Group mean K^{trans}	0.1546	0.0791
Std. dev	0.0510	

design as described in the paper. A limited number of animals ($n = 4/\text{group}$) were followed longitudinally and the difference between group means was chosen as the largest difference observed in the pilot study (day 17). The standard deviation was then estimated from the pooled data at the same time-point. Table II summarizes the data from this time-point.

Using the data in Table II, the number of animals/group is estimated to be about 7.2. This value was rounded up to improve statistical power.

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