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Non-Gaussian Diffusion Imaging with a Fractional Order Calculus Model to Predict Response of Gastrointestinal Stromal Tumor to Second-line Sunitinib Therapy

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Abstract

Purpose—To demonstrate the clinical value of a non-Gaussian diffusion model using fractional order calculus (FROC) for early prediction of the response of gastrointestinal stromal tumor (GIST) to second-line sunitinib targeted therapy.

Materials and Methods—The institutional review board (IRB) approved this prospective study and written informed consents were obtained from all participating patients. Fifteen patients underwent sunitinib treatment after imatinib resistance. Diffusion-weighted imaging (DWI) with multiple b-values was performed prior to treatment (baseline) and two weeks (for early prediction of response) after initiating sunitinib treatment. Conventional MRI images at twelve weeks were used to determine the good and poor responders according to the modified Choi criteria for MRI. Diffusion coefficient D, fractional order parameter β (which correlates with intravoxel tissue heterogeneity), and a microstructural quantity μ were calculated using the FROC model. The FROC parameters and the longest diameter of the lesion, as well as their changes after two weeks of treatment, were compared between the good and poor responders. Additionally, the pre-treatment FROC parameters were individually combined with the change in D (ΔD) using a logistic regression model to evaluate response to sunitinib treatment with a receiver operating characteristic (ROC) analysis.

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Results—Forty-two good responding and thirty-two poor responding lesions were identified. Significant differences were detected in pre-treatment β (0.67 vs. 0.74, $p=0.011$) and D (45.7% vs. 12.4%, $p=0.001$) between the two groups. The ROC analysis showed that D had a significantly higher predictive power than the tumor size change (AUC: 0.725 vs. 0.580; 0.95 confidence interval). When D was combined with pre-treatment β , the AUC improved to 0.843 with a predictive accuracy of 75.7% (56/74).

Conclusion—The non-Gaussian FROC diffusion model showed clinical value in early prediction of GIST response to second-line sunitinib targeted therapy. The pre-treatment FROC parameter β can increase the predictive accuracy when combined with the change in diffusion coefficient during treatment.

Keywords

GIST; Targeted Therapy Response; Diffusion Imaging; FROC Model; Sunitinib

Introduction

Over the past decade, diffusion-weighted imaging (DWI) has been increasingly used in the abdomen, not only for cancer detection and characterization, but also for early evaluation of tumor response to therapies (1–6). For instance, a recent study indicates that apparent diffusion coefficient (ADC) can predict responses of gastrointestinal stromal tumor (GIST) – the most common mesenchymal tumor initiated from the gastrointestinal tract (7) – to first-line imatinib targeted therapy as early as one week after the initiation of treatment (3). The good performance of ADC has been attributed to its association with tissue cellularity. Despite the great success of ADC for treatment prediction, ADC is derived from an overly simplified Gaussian diffusion model, which may not adequately capture a wealth of tissue structural and heterogeneity changes resulting from therapy.

In GIST patients who develop resistance to first-line imatinib and are subsequently treated with second-line sunitinib (8), approximately 40% of patients can develop progressive disease within 3 months (8,9). Unlike lesions prior to first-line imatinib treatment, the progressive GIST lesions to be treated with second-line sunitinib typically exhibit increased and varying degrees of heterogeneity as a consequence of the first-line treatment, resulting in complex tissue structures such as “nodule within a mass” (10,11). This tissue heterogeneity prior to sunitinib therapy may provide a new avenue to predicting treatment response in combination with ADC.

Recognizing that information on tissue microstructures or heterogeneity is not directly provided by the prevailing Gaussian diffusion models, several research groups have proposed more sophisticated non-Gaussian diffusion models (12–22) in an attempt to extract additional tissue structural information. One of these models, known as the fractional order calculus (FROC) model (14,20), features a new parameter – fractional order derivative in space β – which has been linked to intravoxel tissue heterogeneity (20,23–26). The goal of this study is to demonstrate the clinical value of the FROC diffusion model for early prediction of the response of GIST to second-line sunitinib targeted therapy.

Methods

Patients

The institutional review board (IRB) approved this prospective study and written informed consents were obtained from all participating patients. The inclusion criteria for patients were: 1) unresectable or metastatic GIST confirmed by pathology; 2) failure of previous imatinib therapy, as confirmed by CT or MRI; 3) presence of at least one solid lesion larger than 1 cm in diameter or a cystic lesion with wall thicknesses greater than 1 cm (target lesion); 4) sunitinib single-drug targeted treatment (50 mg/day, PO); 5) MR examinations at three time points (pre-treatment, two weeks and twelve weeks after initiation of sunitinib therapy); and 6) confirmation that at least one target lesion could be reliably measured to obtain its longest diameter (LD) and DWI parameters. The exclusion criteria were 1) contraindications for MR examinations; 2) inadequate number of MR examinations during therapy; 3) severe complications due to targeted agent causing interruption of treatment or dosage adjustment; or 4) excessive image quality degradation on DWI.

MR Imaging

All enrolled patients underwent overnight fasting to empty the gastrointestinal tract, and were given 20 mg of anisodamine intramuscularly 15 minutes prior to the MR examination to inhibit the gastrointestinal motility. Pure water (800–1000 mL) was administered orally to distend the gastrointestinal wall for those lesions located at the stomach.

All MR examinations were performed on a 3T MRI scanner (Discovery MR750; General Electric Healthcare, Milwaukee, WI) with an eight-channel phased-array coil. An abdominal T2-weighted (T2W) single-shot fast spin echo sequence (TR/TE = 3000/90 ms; matrix size = 384×256; and field of view (FOV) = 360–400 mm) was applied in a coronal plane to locate the target lesions with a coverage from the top of the diaphragm to the pelvic floor. Based on the coronal images, axial scans covering the target lesions were carried out using a breath-hold T1-weighted (T1W) dual-echo fast spoiled gradient-recalled echo sequence (TR = 200 ms; TE = 1.2 ms for out-of-phase and 2.3 ms for in-phase; flip angle = 85°; matrix size = 320×160; average = 1) and a respiratory-triggered T2W fast recovery fast spin echo sequence (TR = 2 respiratory intervals; TE = 85 ms; matrix size = 320×224; average = 2). The slice thickness and inter-slice gap in all sequences were 5mm and 1mm, respectively.

To apply the FROC model, a set of axial diffusion MR images was acquired using a single-shot spin-echo echo-planar imaging sequence with 11 b-values ($b = 0_1, 20_1, 50_1, 100_1, 300_2, 500_2, 800_2, 1000_4, 1500_4, 2000_6, 3000_8$ s/mm², where the subscript denotes the number of signal averages for the corresponding b-value). At each b-value, a Stejskal-Tanner diffusion gradient was successively applied along the x-, y-, and z-axis to obtain a trace-weighted image in order to minimize the influence of diffusion anisotropy. The other key data acquisition parameters for the diffusion scan were TR/TE = ~4000/97.4 ms, acceleration factor = 2, separation between the two diffusion gradient lobes = 38.6 ms, duration of each diffusion gradient $\delta = 32.2$ ms, FOV = (36–40 cm)², slice thickness = 5 mm, inter-slice gap = 1 mm, matrix size = 128×128, and the scan time = 4–6 min depending on the number of slices to adequately cover the anatomy.

Image Analysis and Therapeutic Response Assessment

According to the FROC model, the voxel intensity in a diffusion-weighted (DW) image is given by

$$S=S_0\exp\left[-D\mu^{2(\beta-1)}(\gamma G_d\delta)^{2\beta}\left(\Delta-\frac{2\beta-1}{2\beta+1}\delta\right)\right] \quad [1]$$

where G_d is the diffusion gradient amplitude, β (dimensionless; $0 < \beta < 1$) is a fractional order derivative that has been linked to intravoxel heterogeneity (20,23,24), μ (in units of μm) is a spatial constant to preserve the nominal units (mm^2/s) of diffusion coefficient D (14,20), and δ and Δ are defined above.

The three parameters (D , β , and μ) of the FROC model were fitted to the multi-b-value diffusion images voxel-by-voxel using a Levenberg-Marquardt nonlinear fitting algorithm (20,27). The initial value of D was determined from a mono-exponential function using the data acquired at low b-values ($< 1000 \text{ sec}/\text{mm}^2$), making it equivalent to ADC to facilitate comparison. After D was determined, β and μ were obtained from fitting to Eq [1] with an initial value of 0.9 and $8 \mu\text{m}$, respectively. A number of other initial β and μ were also investigated and consistent fitting results were achieved irrespective of the initial values. All image processing and analysis were performed using customized software developed in MATLAB (MathWorks, Inc., Natick, MA). The computational time for FROC analysis was approximately 35 seconds per slice on a personal computer with a dual-core CPU (Intel Core i5; 3.30GHz; 16 GB memory) on a Windows 7 operation system.

Aided by and confirmed with T1W and T2W images, regions-of-interest (ROIs) outlining the solid portion of the lesions were placed on the DW images with $b = 1000 \text{ s}/\text{mm}^2$. The largest area of the lesion was determined jointly by two senior radiologists (LT and YSS, with 10 and 15 years of experience in clinical body MR, respectively) who were blinded to the knowledge of good versus poor responders determined by the modified Choi criteria for MRI (see below) (3) at the twelve-week time point. Large areas of cystic or myxoid degeneration/necrosis, if present on the pre-treatment images, were excluded from the ROI across all three time points. The means and standard deviations of D , β , and μ were obtained in the ROIs. For comparison, the longest diameter (LD) of the lesion was also measured on the T2W images.

The mean values of the FROC parameters (D , β , and μ) before treatment (X_{pre}) and two weeks after initiation of sunitinib therapy (X_{week2}) were calculated over the selected tumor ROIs, and used to evaluate a percentage change (ΔX):

$$\Delta X = (X_{\text{week2}} - X_{\text{pre}}) / X_{\text{pre}} \times 100\% \quad [2]$$

where X represents any of the three FROC parameters. Similarly, the changes in tumor size at two weeks (ΔLD) and twelve weeks ($\Delta \text{LD}_{\text{week12}}$) were also computed. We used the modified Choi criteria for MRI (3,28) to determine the response of the tumors to Sunitinib

treatment at the 12-week time point, in which good responders were defined as lesions with at least 10% reduction in LD_{week12} or displaying apparent cystic or myxoid degeneration (similar HU decrease on CT) after twelve weeks of therapy, whereas the other lesions were classified as poor responders.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows (SPSS Inc., Version 22.0; Chicago, IL) with a statistical significance set at $p < 0.05$. Firstly, the normality of the distributions of D , β , μ , LD , D_{pre} , β_{pre} , μ_{pre} , and LD_{pre} were evaluated by a Kolmogorov-Smirnov test. All parameters were compared between the good responder and poor responder groups using a Student's t-test for normal distribution or a Mann-Whitney U-test for non-normal distribution. Using the modified Choi criteria for MRI with imaging data acquired at the twelve-week time point as a standard of reference, receiver operating characteristic (ROC) analysis and the associated area under the ROC curve (AUC) were used to evaluate the performance for predicting the response to sunitinib therapy at the two-week time point.

Secondly, the FROC parameters immediately before sunitinib therapy (D_{pre} , β_{pre} , and μ_{pre}) were used as a pre-condition in conjunction with D in a pair-wise analysis, including (D_{pre} , D), (β_{pre} , D) and (μ_{pre} , D), for predicting response at two weeks. The analysis was done using a binary logistic regression, which assumes that the probability of being a poor responder (denoted by P_0) follows the logistic model:

$$P_0 = \exp(a_0 + a_1 X_1 + a_2 X_2) / [1 + \exp(a_0 + a_1 X_1 + a_2 X_2)] \quad [3]$$

where a_0 , a_1 and a_2 are the regression coefficients that were estimated using a maximum likelihood method (29). P_0 was then used in the ROC analysis and its performance compared with that of using D or LD .

Results

Lesion Characteristics

In the study, a total of fifteen patients (age range: 25–78 years; median age: 60 years; 8 females, 7 males) was included and one patient was excluded because of severe distortion artifacts on the diffusion images. Among the fifteen patients included, a total of eighty target lesions were identified on the MR images. Six lesions were excluded due to artifacts on DW images or inconsistent appearance across all three time points, and the remaining seventy-four lesions were included in the analysis. There were 4 primary GIST lesions located at the gastrointestinal loci (stomach $n=2$; small bowel $n=2$) and 70 metastatic lesions in the mesentery/peritoneum/omentum ($n=45$), liver ($n=24$), and kidney ($n=1$). According to the modified Choi criteria for MRI, 42 lesions responded well to sunitinib therapy, and 32 lesions poorly. Among the 15 patients, we observed two cases that had lesions with both good and poor responses in the same patient.

Representative FROC Maps

Figure 1 shows a set of images from a representative patient (78-year old male) in the good responder group. Compared to the pre-treatment T2W image (LD = 5.50 cm; Fig. 1-i), there was virtually no appreciable change in tumor size at two weeks (LD = 5.26 cm; Fig. 1-ii), but a substantial decrease after twelve weeks of sunitinib therapy (LD = 3.78cm; Fig. 1-iii). The DW images and the FROC maps before treatment (second row in Fig. 1) and two weeks after treatment (third row in Fig. 1) showed that D ($0.74 \mu\text{m}^2/\text{ms}$ vs. $0.93 \mu\text{m}^2/\text{ms}$) and μ ($7.1 \mu\text{m}$ vs. $7.6 \mu\text{m}$) increased while β (0.69 vs. 0.59) decreased. Figure 2 displays a set of images from a poor responding lesion (55-year old female) whose size continued to increase from 2.75 cm pre-treatment (Fig. 2-i), to 3.02 cm at two weeks (Fig. 2-ii), and 3.51 cm at twelve weeks (Fig. 2-iii). Unlike Fig. 1, the lesion in Fig. 2 showed a decreased D ($0.70 \mu\text{m}^2/\text{ms}$ vs. $0.64 \mu\text{m}^2/\text{ms}$) and μ ($7.5 \mu\text{m}$ vs. $5.6 \mu\text{m}$), and an increased β (0.77 vs. 0.83) after two weeks of sunitinib treatment. The significance of these changes is reported in the following sub-section. It is worth noting that prior to the sunitinib treatment the good responder had a lower β value ($\beta_{\text{pre}} = 0.69$; Fig. 1c) than the poor responder ($\beta_{\text{pre}} = 0.77$; Fig. 2c), suggesting a pre-condition may be exploited in predicting response.

Quantitative Comparison at the Two-week Time Point

Quantitative comparisons of D , β , μ , and LD between pre-treatment and two weeks after treatment are provided in Table 1. Our statistical analyses indicated that β_{pre} and β_{week2} of the good responder group were significantly lower than those of the poor responder group ($p=0.011$ and 0.002 , respectively), reinforcing the observation in Figs. 1 and 2. All other pre-treatment metrics did not show significant difference. Two weeks after the sunitinib therapy, the median value of D increased by 45.7% in the good responder group, as compared to only 12.4% in the poor responder group ($Z=-3.30$, $p=0.001$; Fig. 3). No significant differences were observed in β ($Z=-0.245$, $p=0.807$), μ ($Z=-1.724$, $p=0.085$), or LD ($Z=-1.517$, $p=0.129$), as illustrated in Fig. 3.

ROC Analysis

The AUC values from the ROC analysis on D , β , μ , and LD after two weeks of therapy are listed in Table 2. Consistent with the results in Fig. 3, D showed statistical significance ($p=0.001$) for predicting response to sunitinib therapy and improved the AUC from 0.580 to 0.725 when compared to the conventional criterion relying on LD which did not exhibit statistical significance ($p=0.243$). When D was combined with any of the three pre-treatment FROC parameters, the AUC was increased from using D alone (Table 2). The combination (β_{pre} , D) produced the largest AUC (0.843) and far outperformed either D (AUC $D=0.725$, $Z=3.09$, $p=0.002$) or LD (AUC $LD=0.580$, $Z=2.26$, $p=0.02$) for predicting response at the two-week time point as demonstrated in Fig. 4. β_{pre} was plotted against D for all 74 lesions in Fig. 5 where the good responder and poor responder groups were best separated by a line ($4.3 D - 9.63\beta_{\text{pre}} + 5.98 = 0$) corresponding to a probability of $P_0=0.5$ in the logistic model in which β_{pre} and D were independent variables.

Discussion

Accurately evaluating response to targeted therapy at the earliest time point is one of the most important aspects in treating unresectable GIST tumors. Using a non-Gaussian FROC diffusion model, we have demonstrated that the combination of a pre-treatment parameter β_{pre} and a treatment-induced diffusion coefficient change ΔD can considerably improve the accuracy over the approach of using ΔD alone or relying on tumor size change in predicting GIST response to second-line sunitinib therapy. More importantly, the present study has demonstrated the feasibility of predicting the response in as early as two weeks following the initiation of sunitinib treatment, a reduction of up to ten weeks as compared to the conventional approach of measuring tumor size change in three months, which is used by both RECIST and Choi criteria (28). These results enabled by a novel diffusion imaging method are significant, as earlier and more accurate prediction would allow the non-responding GIST patients to timely switch to alternative therapies and minimize treatment toxicity.

Previous studies have shown that change in ADC can be a sensitive and early marker for assessing GIST response to first-line imatinib treatment (3,30–32), consistent with a growing number of publications illustrating the role of ADC for monitoring cancer therapy (1,2,6,33–37). Among them, one study (3) demonstrated that ADC increases significantly after only one week of first-line imatinib treatment of GISTs in the good responders. A substantial increase in diffusion coefficient ($\sim 45.7\%$ in Fig. 3) was also observed in our study in lesions responding favorably to the second-line sunitinib therapy. Interestingly, unlike the previous study (3) which reported no increase (or decrease) in ADC in poor responders to the first-line imatinib treatment, we observed a moderate increase in ΔD ($\sim 12\%$ in Fig. 3) among GISTs who responded poorly to the second-line sunitinib therapy, leading to a compromised performance of using ΔD alone to separate the good responder from poor responder groups (AUC = 0.725; Fig. 4).

The compromised performance of ΔD (or ΔADC) for predicting response to sunitinib therapy is likely caused by pre-existing conditions as a result of prior first-line treatment. Lesions undergone imatinib treatment can become heterogeneous even if they did not show significant reduction in size (3,28). The β parameter in the FROC diffusion model has been reported to be inversely related to the degree of intravoxel heterogeneity (14,20,23–25,38). Prior to the second-line sunitinib treatment, significant difference in β value (i.e., β_{pre}) was observed between the good responder and poor responder groups (Table 1), suggesting the existence of a possible pre-condition. This pre-condition was carried over throughout at least the first two weeks of sunitinib treatment, which explains the significant difference in β_{week2} that mirrors β_{pre} (Table 1) but no significant change in $\Delta \beta$ (Fig. 3 and Table 2).

By taking advantage of this pre-condition, the combination of β_{pre} and ΔD produced the best performance with an AUC of 0.843 (Fig. 4 and Table 2) and a predictive accuracy of 75.7% (56/74). If a lesion is more heterogeneous prior to sunitinib treatment (i.e., lower β_{pre}), a smaller increase in ΔD during treatment would indicate a good response. One possible explanation is that more heterogeneous lesions can be mixed with inactive regions such as cyst or necrosis whose diffusion property does not change much during the course of

treatment, resulting in an overall smaller change in D when these lesions respond to targeted therapy.

The pre-condition may also exist in D_{pre} and μ_{pre} as demonstrated in Table 2. However, these pre-conditions were much weaker than β_{pre} which itself showed a moderate AUC value of 0.671 (data not included in Fig. 4 for simplicity). Any pre-condition reflected by D_{pre} is likely related to tissue cellularity, but not to the degree of tissue heterogeneity in GIST following the first-line targeted therapy. According to the FROC model, μ is strongly coupled with D (14,20), explaining the similar behavior between D and μ observed in this study (Table 1). One important exception is that D showed a significant predictive power, whereas μ did not (Fig. 3).

The strong coupling between D and μ was recognized at the beginning of FROC model development (14,20). Mathematically, these two parameters cannot be determined independently. Our strategy to solve this issue was to fit D by a mono-exponential function using low b -values ($b < 1000 \text{ sec/mm}^2$) where the nominal diffusion process is dominant. Once the diffusion coefficient was determined, μ and β were obtained from a non-linear fitting according to Eq. [1]. This approach makes D equivalent to ADC, allowing the FROC model to be used without losing any potential benefits afforded by ADC. Additionally, this approach also allows exploring the potential role of μ in microstructural characterization, as indicated in previous studies (14,20). An alternative way to decouple D and μ is to fix μ to a specific value, such as 1. Given the potential benefits of treating μ as a variable, we did not explore this alternative strategy in this study.

The FROC model represents a special case of a more generalized continuous-time random-walk (CTRW) model that recognizes intravoxel diffusion heterogeneity in both time (denoted by α) and space (denoted by β) (17). To accurately estimate α , diffusion measurements need to be performed by varying not only diffusion gradient amplitude, but also the diffusion time. In a clinical setting, this can be rather difficult to implement, constrained by the echo time to preserve the signal-to-noise ratio (SNR), the total scan time, and the limited gradient strength on a clinical scanner (e.g., 50-80 mT/m). In addition, non-linear fitting to determine the parameters in the CTRW model has been shown to be more sensitive to noise in the image as compared to the FROC model. For these reasons, our study was limited to the FROC model by assuming $\alpha = 1$.

Another limitation of this pilot study is the small number of patients. Although we analyzed multiple lesions from several patients and observed that lesions in the same patient could have differing responses, in general lesions from the same patient tend to react to targeted therapy in the same way. Thus, treating multiple lesions from the same patient as independent samples has only a moderate impact on improving the statistical power. Additionally, we used modified Choi criteria for MRI at twelve weeks as a “gold standard” to determine good versus poor responders in this pilot study. The applicability of this standard in the context of second-line sunitinib therapy may require validation by a correlation with long-term prognosis such as progression-free survival and the overall survival.

In conclusion, our study has demonstrated that changes in diffusion coefficient can be a predictive indicator for early response to second-line sunitinib therapy of GIST. More importantly, the change in diffusion coefficient during treatment can be combined with a tissue heterogeneity parameter β prior to treatment to considerably improve prediction of good versus poor responders only two weeks after initiating the treatment, yielding an AUC of 0.843 and an accuracy of 75.7% (56/74). These results indicate that high b-value diffusion imaging with a non-Gaussian FROC model has the potential of predicting the response of GIST to second-line Sunitinib targeted therapy earlier (e.g., 2 weeks) than the present approach, and more accurately than using ADC alone.

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Figure 1.

The T2W images (first row) obtained from a good responder (78-year old male) show that the tumor size measured by LD did not have appreciable change from pre-treatment (i; 5.50cm) to week two (ii; 5.26cm), but a substantial decrease after twelve weeks (iii; 3.78cm) of sunitinib treatment. The second and third rows display DW images and the FROC maps (overlaid on the T2W images) obtained prior to (a-d) and two weeks after (e-h) sunitinib treatment, respectively. ROIs (green) were drawn on the DW images (b=1000 s/mm²; a, e) and propagated onto the FROC parameter maps (b-d, and f-h). D (0.74 μm²/ms vs. 0.93

$\mu\text{m}^2/\text{ms}$) and μ (7.1 μm vs. 7.6 μm) increased along with a decrease in β (0.69 vs. 0.59) after two weeks of treatment.

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Figure 2.

The T2W images (first row) obtained from a poor responder (55-year old female) shows the tumor size measured by LD had a slight increase from pre-treatment (i; 2.75cm) to week two (ii; 3.02cm), but a substantially increased after twelve weeks (iii; 3.51cm) of sunitinib treatment. The second and third rows display DW images and FROC maps (overlaid on the T2W images) obtained prior to (a-d) and two weeks after (e-h) sunitinib treatment, respectively. ROIs (green) were drawn on the DW images ($b=1000 \text{ s/mm}^2$; a, e) and propagated onto the FROC parameter maps (b-d, and f-h). D ($0.70 \mu\text{m}^2/\text{ms}$ vs. $0.64 \mu\text{m}^2/\text{ms}$) and μ ($7.5 \mu\text{m}$ vs. $5.6 \mu\text{m}$) decreased along with an increase in β (0.77 vs. 0.83) after two weeks of treatment. These trends were opposite to those in Fig. 1.

Figure 3.

Boxplots of percentage change in D, β , μ and LD between pre-treatment and two weeks into sunitinib therapy for both good responder (blue boxplot) and poor responder (red boxplot) groups. D in the good responder group (median of D: 45.7%) was significantly larger (* $Z=3.3$, $p=0.001$) than that in the poor responder group (median of D: 12.4%). No significant differences were found in β ($Z=-0.39$, $p=0.69$), μ ($Z=-1.72$, $p=0.09$), and LD ($Z=-1.17$, $p=0.24$).

Figure 4.

The ROC curves of ΔLD , ΔD , and the combination of β_{pre} and ΔD . The corresponding AUC values are listed in Table 2. The combination of β_{pre} and ΔD gives the largest AUC (0.843).

Figure 5.

A scatter plot of β_{pre} , ΔD for both good responder (blue circles) and poor responder (red crosses) lesions. The good responder and poor responder groups are best separated by the black dash line ($4.3 \Delta D - 9.63 \beta_{pre} + 5.98 = 0$), corresponding to a probability of $P_0=0.5$ in the logistic regression model with β_{pre} and ΔD as independent variables.

Table 1

Summary of the FROC parameters and LD (mean $\pm$ standard deviation) of the good responder and poor responder groups at two time points using a student t-test

Parameter	Time point	Good responder (n=42)	Poor responder (n=32)	t	P
D ($\mu\text{m}^2/\text{ms}$)	Pre	1.08 $\pm$ 0.45	1.15 $\pm$ 0.46	0.677	0.500
	Week 2	1.65 $\pm$ 0.94	1.33 $\pm$ 0.66	1.661	0.101
β (a.u.)	Pre	0.67 $\pm$ 0.12	0.74 $\pm$ 0.08	2.619	0.011
	Week 2	0.71 $\pm$ 0.15	0.80 $\pm$ 0.09	3.298	0.002
μ (μm)	Pre	7.62 $\pm$ 0.87	7.99 $\pm$ 0.95	1.756	0.083
	Week 2	8.63 $\pm$ 1.46	8.58 $\pm$ 1.20	0.172	0.864
LD (mm)	Pre	44.2 $\pm$ 25.8	34.7 $\pm$ 27.2	1.527	0.131
	Week 2	41.9 $\pm$ 26.0	35.0 $\pm$ 25.5	1.135	0.260

FROC: fractional order calculus; LD: longest diameter.

Table 2

AUC values (mean $\pm$ standard deviation), 95% confidence intervals, and asymptotic significance (p-values) of using changes in various metrics after two weeks of therapy for predicting sunitinib treatment response.

metrics	AUC	95% confidence interval	Asymptotic significance (p-value)
LD	0.580 ± 0.068	0.447 – 0.713	0.243
D	0.725 ± 0.059	0.609 – 0.840	0.001
β	0.527 ± 0.068	0.394 – 0.659	0.694
μ	0.618 ± 0.066	0.489 – 0.746	0.085
(D _{pre} , D)	0.728 ± 0.058	0.614 – 0.841	0.001
(β _{pre} , D)	0.843 ± 0.047	0.751 – 0.935	<0.001
(μ _{pre} , D)	0.777 ± 0.053	0.672 – 0.882	<0.001

AUC: area under curve; LD: longest distance.