Predicting Response to Sunitinib Second-line Therapy in Gastrointestinal Stromal Tumors Using Non-Gaussian Diffusion MRI

Yi Sui[1,2], Lei Tang[3], Kejia Cai[2,4], Shun-Yu Gao[3], Frederick C. Damen[2,4], Ying-Shi Sun[3], and Xiaohong Joe Zhou[2,5]

[1]Bioengineering, University of Illinois at Chicago, Chicago, IL, United States, [2]Center for MR Research, University of Illinois Hospital & Health Sciences System, Chicago, IL, United States, [3]Radiology, Peking University Cancer Hospital & Institute, Beijing, China, [4]Radiology, University of Illinois Hospital & Health Sciences System, Chicago, IL, United States, [5]Departments of Radiology, Neurosurgery and Bioengineering, University of Illinois Hospital & Health Sciences System, Chicago, IL, United States

PURPOSE: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors originating from the gastrointestinal tract [1]. Typically the first-line treatment of GIST uses imatinib mesylate, a tyrosine kinase inhibitor, to block tumor-cell proliferation. However, more than half of the patients show tumor progression within two years of initiating imatinib therapy [2]. For patients with imatinib-resistant progressive lesions, the second-line treatment using sunitinib maleate, a multi-targeted tyrosine kinase inhibitor, has shown greater progression-free survival and overall survival rates [3]. Despite the success, ~40% patients receiving sunitinib therapy still show disease progression within 12 weeks [4]. As such, assessment of early response is crucial not only for allowing timely initiation of alternative treatment, but also for minimizing the adverse effects of ineffective therapy. Traditionally therapeutic response is assessed by the change of tumor size, which may not be observable until weeks or even months after the treatment. Recently diffusion-weighted imaging (DWI) was demonstrated as a promising tool for detecting treatment-induced tissue changes, as reflected by apparent diffusion coefficient (ADC), much earlier than tumor volume can provide [5]. Although the conventional ADC value, derived from a simple mono-exponential diffusion model, is useful for assessing the treatment efficacy following imatinib therapy [5], its applicability becomes questionable for monitoring the second-line treatment with sunitinib, since the imatinib-resistant GIST lesions typically show a large degree of intravoxel heterogeneity beyond what a single ADC value can characterize. The purpose of this study is, therefore, to use a non-Gaussian diffusion model, known as the fractional order calculus model (FROC) [6–8], to assess the early response to sunitinib second-line treatment in imatinib-resistant progressive GIST lesions.

METHODS: ***Patients***: Sixteen (16) GIST patients (8 males, 8 females; age range = 25–78 years; median age = 60 years), who failed previous imatinib treatment and underwent sunitinib single drug targeted treatment, were enrolled in the study with IRB approval and written informed consent. ***Imaging:*** Images were acquired on a 3T MRI scanner (GE MR750; GE Healthcare, Milwaukee, WI) with an 8-channel phased array coil at three time points: prior to treatment (baseline), 2 weeks (for prediction), and 12 weeks (for determination of the response) after sunitinib treatment. The imaging protocol included anatomical imaging, and diffusion EPI (TR/TE = 4000/97.4 ms, FOV = 34 × 34 cm^2, matrix = 128 × 128, scan time = 4-6 min) with 11 b-values up to 3000 s/mm^2. The slice thickness was 5 mm for all sequences. ***FROC Model Fitting:*** The multi-*b*-value diffusion data were fitted to the FROC model using the following equation: $S/S_0 = \exp\{-D\mu^{2(\beta-1)}(\gamma G_d \delta)^{2\beta}[\Delta-(2\beta-1)\delta/(2\beta+1)]\}$, where D is diffusion coefficient (similar to ADC); β, the spatial fractional order, is related to the degree of intravoxel heterogeneity; and μ, a spatial quantity in units of μm, is related to the diffusion mean free length [6]. All image processing and fitting were performed using Matlab (Mathworks Inc, MA). ***Tumor Response Assessment:*** Tumor ROIs were placed on diffusion images at b-value of 1000 s/mm^2 where tumors were best identified. Based on the imaging findings at 12 weeks after sunitinib treatment, the patients were classified as good response if the target lesions had a 10% or greater reduction in the longest diameter (LD), or displayed apparent cystic or myxoid degeneration; otherwise, they were considered as poor response. To predict earlier response, the values of D, β, μ and LD at week 2 were calculated over the whole tumor regions, and the percentage change was calculated by $\%\Delta X = (X_{wk2} - X_{pre})/ X_{pre} \times 100\%$, where X_{wk2} and X_{pre} are the diffusion parameters (D, β or μ) or LD at week 2 and pre-treatment, respectively. ***Statistical Analysis:*** The percentage changes were compared using Mann-Whitney U test with $p < 0.05$. Areas under the curve (AUC) were obtained from ROC analysis to evaluate the performance of LD, individual FROC parameters as well as the combination of all FROC parameters (binary logistic regression) in predicting the therapeutic response. All statistical analyses were carried out using SPSS software (SPSS Inc., Chicago, IL).

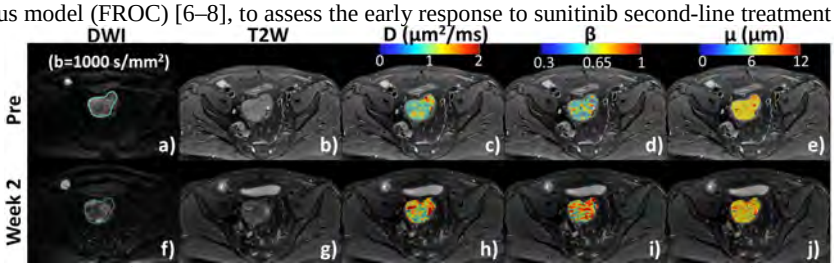

Fig. 1 Images from a representative good responder prior to (top row) and two weeks after (bottom row) sunitinib treatment. ROIs (green) were drawn on DWIs (b=1000 s/mm^2) (a, f). T2w PROPELLER images showed no significant change in tumor size (b, g), while FROC parameter values (c-e, h-j) had an observable increase in tumors after two weeks treatment.

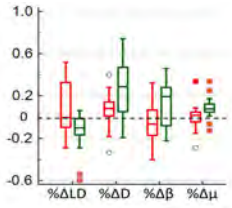

Fig. 2 Boxplots of percentage changes of LD and FROC diffusion metrics (D, β and μ) between poor (red) and good (green) responders. All parameters showed statistical significance between two groups ($p<0.03$)

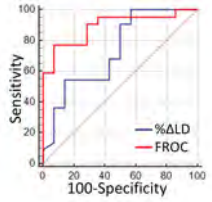

Fig. 3 ROC curves of percentage changes of LD (AUC=0.732), and the combination of D, β and μ. (AUC=0.893).

RESULTS: Eighty-four (84) target lesions were identified from the 16 patients, and their D, β and μ values were reliably measured at all three time points. Based on the imaging results at 12 weeks, 48 lesions responded well, and 36 lesions responded poorly to sunitinib therapy. Figure 1 shows images from a representative good responder prior to and two weeks after sunitinib treatment. ROIs were drawn on DWIs (Figs 1a, f). No significant change in tumor size was found on T2w images (Figs 1b, g), while increased FROC parameter values (Figs 1c-e, h-j) were observed in tumors after two weeks treatment. Figure 2 illustrates boxplots of the percentage change in LD and FROC parameters for the responder and non-responder groups, where significant differences were observed in %ΔD (28% vs 8%, p = 0.032), %Δβ (20% vs -6%, p = 0.013), %Δμ (8% vs 2%, p = 0.004), as well as %ΔLD (-9.9% vs -0.1%, p=0.02). Comparing with the conventional predictor %ΔLD (AUC=0.732), the combination of all three FROC parameters illustrated substantial improvement (AUC=0.893) in predicting the response as early as 2 weeks into the sunitinib treatment (Fig. 3).

DISCUSSION: The FROC diffusion model produced a new set of parameters for predicting the response of sunitinib treatment at as early as week 2. The differences between groups in two FROC parameters (%ΔD and %Δβ) (20-26%) were considerably larger than that of %ΔLD (9.8%), providing a more sensitive means for early therapy prediction. Furthermore, by combining all three FROC parameters, the FROC model outperformed LD in predicting sunitinib treatment responses. Although a large number of patients are helpful to further validate the findings, our results suggested that diffusion imaging with high b-values and a non-Gaussian model can provide valuable information for early response prediction of sunitinib targeted therapy of GIST.

REFERENCES: 1. Corless et al., Nat. Rev. Cancer; 2011. 2. Demetri et al., Lancet; 2013. 3. Demetri et al., Lancet; 2006. 4. Demetri et al., Lancet; 2006. 5. Tang et al., Radiology; 2011. 6. Zhou et al., MRM; 2010. 7. Magin et al., J Magn Reson; 2008. 8. Sui et al., ISMRM; 2012.