

Introducing New DCE Parametric Maps to Quantify Vascular Changes Induced by the Anti-Angiogenic Drug Sunitinib

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Introduction: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is used as a method to evaluate the effect of new anti-angiogenic drugs on the tumor vasculature using gadolinium-DTPA (Gd) as a contrast agent. Anti-angiogenic drugs can inhibit tumor growth by causing destruction of the blood vessels that feed the tumors and hence deprive the tumor cells from nutrients [1]. However, it can affect the normal vasculature of vital organs as well and could cause the blood vessels to become leakier. Extracting information from the DCE data is a complex process requiring an estimation of T1 and then the extraction of contrast agent concentration in the blood. Both K_{ep} and K^{trans} are often sought or the IAUC or median of the CIAUC are used to monitor changes pre and post drug treatment [1]. Often only the first minute of data are used in the processing. We introduce here several new measures of vascular properties (some evaluated from longer time periods). These new measures include blood volume estimates, as well as washout slope. We believe that the measurements derived from the parametric maps can quantify physiological vascular changes in tissue.

Materials and Methods: To evaluate these new measures, we used a preclinical model of human KCI-18 Renal Cell Carcinoma (RCC) cells implanted in the right kidney of immune deficient nude mice. By days 10 to 12, after KCI-18cell injection, mice were divided into four groups, three of them were treated with sunitinib (Pfizer, Inc, New York, NY), at different dosages of 10, 20, or 40 mg/kg per day (SU10, SU20, or SU40, respectively) and the fourth group was treated with vehicle only (control mice). Sunitinib is the most effective drug to date for the treatment of RCC [2]. Treatment with sunitinib was given orally on a daily basis for 7 days, and then mice were imaged by DCE-MRI. MR imaging was performed on a 4.7T scanner (Bruker) with the following parameters: 5 slices, TR=54.7 ms, TE=2.9 ms, two flip angles 5 and 30 degrees, FOV = 32mm x 32mm, slice thickness = 1.5mm with 0.5 mm gap, and matrix size =128x128. The amount of Gd injected was 0.1mmol/kg of body weight. Analysis of the DCE data was done using our home built software SPIN (signal processing in NMR) over 30 time points (7 sec each). Apart from the usual measures of contrast agent uptake (AUC), rate of uptake (SLOPE), peak concentration (PEAK) and time to peak (TTP), we introduced two new measures, 1) the contrast agent uptake to the peak (AUCtp), which can be used to estimate local blood volume, and the rate of clearance (NSLOPE) in the tissue (Figure 1). If one can measure the AUCtp in a local blood vessel, then the ratio of AUCtp(tissue)/AUCtp(blood) represents the fractional blood volume assuming there is no leakage between injection time point and the peak.

Results: Two regions of interest (ROI) representing the periphery and core of kidney tumor (KT) and two ROI's representing the cortex and medulla of normal kidney (NK) were drawn. Each ROI was quantified and the results compared between the four different groups (SU10, SU20, SU40 and control). The low dose of SU10 in the tumor kidney was found to have no effect in both the periphery and core of the tumor compared to the control mice. SU20 and SU40 were found to enhance the blood perfusion to the core and only SU40 was found to increase the uptake rate, peak AUCtp and NSLOPE in the tumor periphery. In the NK, SU10 and SU20 mice have almost the same uptake, rate and peak compared to control NK. However, increasing the treatment dose to 40 mg/kg per day affected the Gd uptake rate, peak and clearance by the cortex and the medulla of NK compared to the control NK (Table 1). These findings were confirmed by histological observations of tissues showing that SU40 caused tumor vessel destruction associated with hemorrhages in KT and dilatation of blood vessels in NK. Mice treated with SU20 had more regularized and thinner vessels in KT and mild dilatation in a few vessels in NK. In contrast, mice treated with SU10 had enlarged abnormal vessels in KT and regular vessels in NK similar to the findings from control mice as recently published [3].

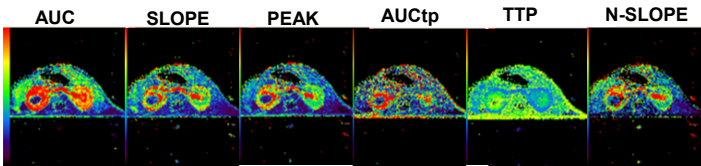


Figure 1: The DCE parametric maps are obtained from Gd concentration curves. They show the total contrast agent uptake (AUC), rate of uptake (SLOPE), peak concentration (PEAK), uptake to the peak (AUCtp), time to peak (TTP) and the rate of Gd clearance (NSLOPE) in the tissue.

Discussion and Conclusions: SU40 had a dramatic effect on SLOPE, PEAK and NSLOPE indicates that this dose is high and caused significant vascular damage. On the other hand, the SU20 data from KT showed results similar to healthy NK, indicating that this dose is safer and regularized the tumor vessels. Our result on the pre-clinical RCC tumor model demonstrates that DCE parametric maps have the potential to assess the effect of anti-angiogenic drugs on blood flow and vascular changes in tumors as well as normal tissues. The two new parametric maps introduced here AUCtp and NSLOPE provided further guidance as to what could be considered normal versus abnormal tissue response to anti-angiogenic therapy.

References:

1. TE. Yankeelov and JC. Gore. *DCE-MRI in Oncology: Theory, Data Acquisition, Analysis, and Examples*. Curr Med Imaging Rev. 2009; 32, 91–107.
2. RJ Motzer et al. *Activity of SU11248 in patients with metastatic RCC*. J Clin Oncol.2006; 24, 16–24.
3. GG. Hillman et al. *DCE-MRI of Vascular Changes Induced by Sunitinib in Papillary RCC Xenograft Tumors*. Neoplasia 2009; 11, 910–920.

A) Kidney Tumor:

Parametric maps:		AUC	SLOPE	PEAK	TTP	AUCtp	NSLOPE
Region:							
Periphery	Control	931 ± 257	26 ± 3	7 ± 0.4	110 ± 10	25 ± 4	16 ± 3
	SU10	759 ± 148	21 ± 6	6 ± 2	132 ± 17	31 ± 11	9 ± 3
	SU20	862 ± 109	20 ± 2	5 ± 0.6	99 ± 4	14 ± 2	11 ± 0.6
	SU40	1093 ± 87	37 ± 10	9 ± 3	103 ± 11	27 ± 10	25 ± 9
Core	Control	251 ± 152	10 ± 1	2 ± 0.6	153 ± 2	15 ± 4	5 ± 0.3
	SU10	206 ± 80	6 ± 1	2 ± 0.7	146 ± 15	14 ± 8	3 ± 0.2
	SU20	484 ± 29	13 ± 6	3 ± 0.8	130 ± 29	16 ± 5	9 ± 6
	SU40	508 ± 209	18 ± 10	5 ± 2.5	142 ± 22	25 ± 4	12 ± 10

B) Normal Kidney:

Parametric maps:		AUC	SLOPE	PEAK	TTP	AUCtp	NSLOPE
Region:							
Cortex	Control	660 ± 231	22 ± 0.1	5 ± 0.2	99 ± 4	17 ± 3	14 ± 0.1
	SU10	657 ± 80	18 ± 0.8	4 ± 0.4	112 ± 14	18 ± 6	9 ± 1
	SU20	814 ± 74	19 ± 2	4 ± 0.5	100 ± 3	14 ± 1	11 ± 2
	SU40	904 ± 72	33 ± 12	7 ± 3	94 ± 6	19 ± 8	20 ± 11
Medulla	Control	659 ± 159	16 ± 0.2	5 ± 0.3	122 ± 17	23 ± 7	11 ± 3
	SU10	503 ± 120	13 ± 0.8	3 ± 0.5	131 ± 13	21 ± 8	7 ± 1
	SU20	664 ± 64	14 ± 0.3	4 ± 0.3	108 ± 8	15 ± 3	10 ± 2
	SU40	673 ± 149	20 ± 6	5 ± 1	102 ± 3	16 ± 3	13 ± 3

Table 1: The characteristic tables are obtained from quantification of DCE-parametric maps and represent values obtained from the tumor core and its periphery (A) and the cortex and medulla of normal kidney (B).