Sunitinib Induces Reductions in Tumor Vascular Permeability and Intra-tumor Vascular Volume in Renal Cell Carcinoma

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Background: Several anti-angiogenic agents, including sorafenib, sunitinib, and pazopanib, are approved for therapy of renal cell carcinoma (RCC)[1]. DCE-MRI has been shown to be useful for documenting vascular changes in RCC after initialization of this therapy, and pre-therapy DCE-MRI has been shown to be an effective biomarker of tumor response[2,3]. However, variations in kinetic models make comparison of DCE-MRI results between different investigators challenging. We have recently developed radial acquisition methods for DCE-MRI that allow for retrospective image reconstruction at variable time windows[4]. We hypothesize that DCE-MRI with a higher rate of sampling will allow for assessment of plasma volume fraction (V_p), and will alter metrics other DCE-MRI (K^{trans}, k_{ep}, V_e).

Methods: Ten patients with metastatic RCC were studied by DCE-MRI before and early (mean 23 days, range 13-33 days) after initiation of oral Sunitinib therapy. Imaging was performed with 32 slice hybrid radial projection DCE-MRI with golden angle progression over the anatomic area of largest tumor burden (chest, abdomen, pelvis)[4]. Imaging parameters included TR/TE 3.2/1.6 ms, flip 25 degrees, FOV 36-40cm, matrix 192x192, slice thickness 8 mm. Images were reconstructed with KWIC processing using 25 central views, for a temporal resolution of 2 seconds per image set. 4D data sets were reviewed by a radiologist blinded to imaging time point (pre- or post-treatment). Tumors and aorta were manually segmented, with reference to HASTE T2W image sets to exclude neighboring organs or vessels. Pixel-wise enhancement curves were converted to estimated gadolinium concentration using a three-point variable flip angle method for native tumor T_1 measurement[5]. Kinetic modeling was performed with either the routine two-compartment model ("Vp-off"), or with a model including intra-tumoral vascular volume fraction ("Vp-on"). Median pixel values for all tumors assessed were reported. DCE-MRI parameters before and after therapy were compared, as were the effects of the inclusion of a finite vascular volume fraction on the magnitude of both baseline and therapy-induced changes in kinetic parameters. Significance at the p=0.05 level was assessed using the Students t-test, with correction for multiple comparison's using the Holms' procedure.

Results: Results are shown in **Table 1**. Inclusion of V_p significantly altered the absolute magnitude of tumor K^{trans} (p=0.005) and k_{ep} (p=0.009), but not V_e (p=0.44). In several tumors, there was a prominent vascular "peak" in the tumor enhancement curve (**Figure 1**), which provided for assessment of intra-tumoral vascular volume. Using the "Vp-on" model, patient-averaged declines in K^{trans}, k_{ep}, and V_e after therapy were 68% (p=0.003), 53% (p=0.006), and 44% (p=0.014), respectively (**Table 1**). One example of the vascular response to Sunitinib is shown in **Figure 2**. Inclusion of V_p in the DCE-MRI model did not alter the magnitude of therapy-induced changes in K^{trans} and k_{ep}. However, analysis with the "Vp-on" model demonstrated a statistically significant absolute decline in tumor plasma volume by 1.3% (relative decline 52%, p=0.019) following treatment with Sunitinib.

Table 1 Sunitinib effect on tumor DCE-MRI parameters by compartment model

	Two-compartment ("Vp-off") Model			Three-compartment ("Vp-on") Model			
	K^{trans}	K_{ep}	V_e	K^{trans}	K_{ep}	V_e	V_p
Pre-Sunitinib	0.34	1.44	32%	0.20	0.84	32%	2.5%
Post-Sunitinib	0.10	0.60	16%	0.07	0.38	18%	1.2%
Change	-71%†	-44%*	-50%*	-68%†	-53%†	-44%*	-52%*

(K^{trans}, k_{ep} expressed as min^{-1}), *p<0.05 †p<0.01 (pre- vs. post-treatment)

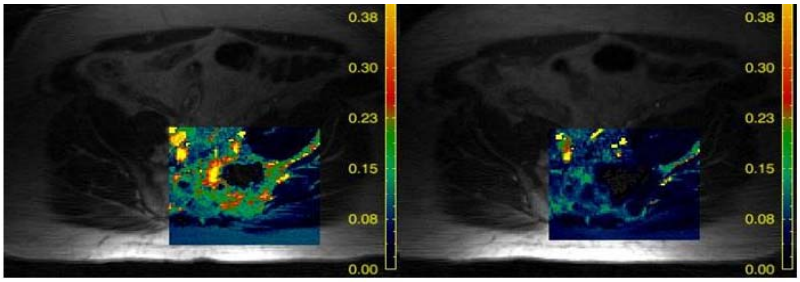

Figure 2: RCC metastasis to the sacrum. DCE-MRI K^{trans} maps ("Vp-on" model), are shown before (left) and after (right) treatment with Sunitinib. K^{trans} response was 76%, with median pixel values of 0.15 min^{-1} (pre-Tx) and 0.03 min^{-1} (post-Tx).

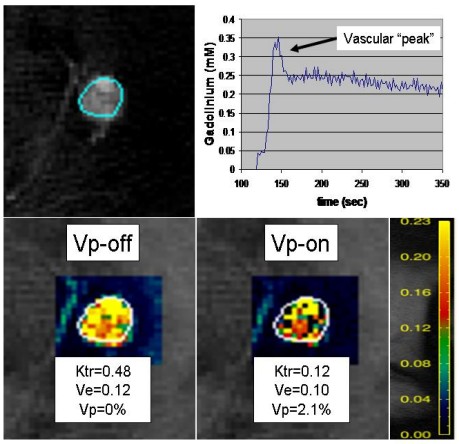

Figure 1: RCC metastasis to the back, with gadolinium-time curve showing vascular "peak". K^{trans} color maps and DCE-MRI modeling results with and without finite tumor vascular volume, demonstrating how K^{trans} results can differ based on choice of kinetic model.

Conclusions: Intra-tumoral vascular volume is a significant contributor to tumor-gadolinium time curves in DCE-MRI of RCC. Inclusion of V_p in DCE-MRI modeling alters tumor K_{trans}, and k_{ep} values. By modeling V_p in DCE-MRI, we were able to document a decline in tumor plasma volume after therapy with Sunitinib, providing an additional imaging biomarker of tumor response to therapy in RCC.

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