

Clinical Translation of VSI using Ferumoxytol: Feasibility in a Phase I Oncology Clinical Trial Population

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Introduction

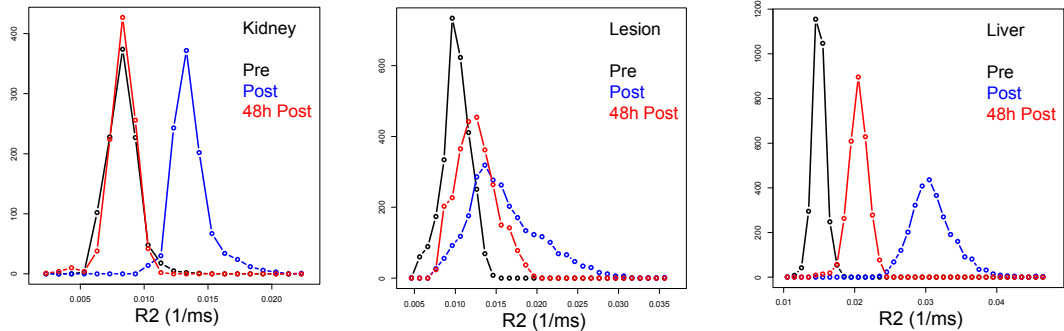
Vessel size imaging (VSI) is a technique that allows vascular parameters such as tumor blood volume, vessel density (Q), and average vessel size to be derived noninvasively. VSI has been successfully implemented pre-clinically using ultrasmall paramagnetic iron oxide (USPIO) intravascular contrast agents such as ferumoxytol[1,2,3]. Clinical imaging with this USPIO agent has focused primarily on evaluating perfusion/permeability in CNS lesions[4]. We evaluated the feasibility of acquiring VSI measures using ferumoxytol in a Phase I population of patients with advanced solid tumors, in particular, liver metastases, and compared the VSI parameters to pre-clinical estimates also obtained with ferumoxytol.

Methods

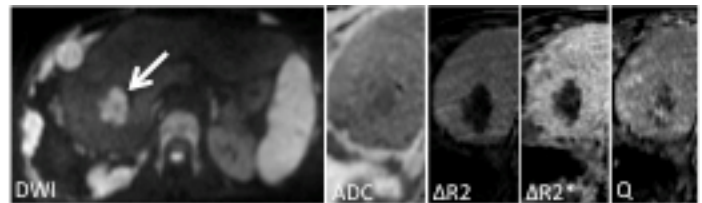
Multi-echo turbo-spin echo/FSE sequences were used to acquire maps of transverse relaxation rate, R_2 , before and after ferumoxytol injection. Similarly R_2^* maps were created based on multi-slice multi-echo gradient echo sequences. Diffusion weighted images were also acquired and used to calculate ADC maps. Maps of vessel density, $Q=(\Delta R_2/(\Delta R_2^*)^{2/3})$, were also generated. Preclinical protocols were implemented on an Agilent 4.7T system; 4 mice with xenograft tumors were imaged prior to, 3, 23, 43, 63 min and 24 hours after injection with 6 mg Fe/kg of ferumoxytol. Clinical protocols were implemented on Siemens and GE 1.5T MR scanners using standard pulse sequences. Three colorectal patients (7 targeted liver lesions in total) were imaged prior to, ~5 min after and 48 hrs after injection of 3 mg Fe/kg ferumoxytol. Scanning was conducted at screening, as part of a phase I clinical trial protocol. All protocols were approved by local Institutional Review Boards.

Results and Conclusions

Representative histograms from one patient show the evolution in R_2 as a function of time in the kidney (left, showing recovery of signal at 48 hrs), liver lesion (center), and normal liver (right, showing delayed recovery due to iron uptake).



Diffusion weighted image (arrow indicates lesion) and representative maps from same patient: DWI, ADC (median tumor $1.07 \times 10^{-3} \text{ s/mm}^2$), ΔR_2 , ΔR_2^* , and Q, left to right.



Despite using half the ferumoxytol dose by weight, % changes from baseline (pre-injection) for both R_2 and R_2^* were much greater in the human liver lesions than in the xenograft tumors as shown in Table 1.

Table 1: % Change from Pre-Injection values of R_2 and R_2^* as a function of time after injection in mouse and human. N= number of lesions analyzed.

		Post Injection		24h Post Injection		48h Post injection	
		mean (SD)	N	mean (SD)	N	mean (SD)	N
Mouse	R_2	13 (3)	4	-2 (1)	3		
	R_2^*	15 (3)	4	-13 (11)	3		
Human	R_2	37 (13)	7			30 (17)	4
	R_2^*	166 (41)	7			98 (48)	4

Q (vessel density)	
mean (SD)	
Mouse	0.0713 (0.0053)
Human	0.0298 (0.0098)

Table 2: Mean values of Q in xenograft and human liver lesions.

Lesion to lesion variability was higher (as expected), partly due to the fact that lesions were not segmented into viable/necrotic tissue prior to analysis, as was done with xenografts. Recovery time course changes are likely affected by lesion heterogeneity, but can also be partially attributed to differences in species half-lives. Table 2 shows estimates of vessel density (Q); mean values in liver lesions are lower than in xenografts due to the greater increase in ΔR_2^* in these lesions after ferumoxytol injection.

These data demonstrate the feasibility of clinical VSI using stock pulse sequences, and provide valuable information for the further refinement of the imaging protocol using ferumoxytol in a Phase I population. In addition, the high level of ferumoxytol in the normal liver does not seem to prevent the measurement of VSI metrics in liver metastases.

References [1] Tropres et al, MRM 2004; 51:533-541. [2] Ungersma et al, MRM 2010; 63:1637-1647. [3] Varallyay et al, J. Cer.Blood Flow and Met. 2009; 29:853-860. [4] Neuwalt et al, Stroke 2011; 42:1581-1588.