High Resolution pHe Imaging of Tumors

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Introduction: The microenvironment within tumors is significantly different from that in normal tissues. A major difference is the chaotic vasculature of tumors, which results in unbalanced blood supply and significant perfusion heterogeneities. As a consequence, many regions within tumors are transiently or chronically hypoxic. This exacerbates tumor cells' natural tendency to overproduce acids, resulting in very acidic extracellular pH (pH_e) values. The hypoxia and acidity of tumors have important consequences for anti-tumor therapy and can contribute to the progression of tumors to a more aggressive metastatic phenotype [1]. Methodologies to image the spatial distribution of tissue pH_e would have considerable biomedical and clinical relevance in such cases because they would enable the noninvasive assessment of disease extent, progression, and response to therapy. To this end, we have developed methods to measure pH_e using the pH-sensitive contrast reagent (CR), GdDOTA-4AmP^{5-} (4AMP). The R_1 relaxation enhancement produced by 4AMP depends on both concentration and pH_e. Therefore, in order to calculate the pH_e, independent measurement of the CR concentration is needed.

Methods: The current experimental protocol addressed this matter by using the pH-insensitive CR, GdDTPA^{2-}, which was injected prior to the pH-sensitive 4AMP, assuming that both CRs have identical pharmacokinetics. The distribution of the pH-insensitive agent can be used to predict the concentration of the pH-sensitive agent and, from this, the r_1 of the pH-sensitive agent was calculated and used to estimate the pH_e. The current approach differed from previously reported dual injection methods [2, 3] in that the CR were infused and the data were collected using radial acquisition to reduce the effect of organ motion. This improved method has been performed in both intracranial C6 gliomas in rats, and in mouse kidneys, which are described here.

Results: A pixel-by-pixel analysis (Fig.1) demonstrated robust correlations between the pharmacokinetics of two CRs injected sequentially. Fig.2. shows T1-weighted images (a, b) and T1 maps (c, d) before and after infusion of CR. From these data, the (e) CR concentrations were calculated and used to calculate (f) pH maps.

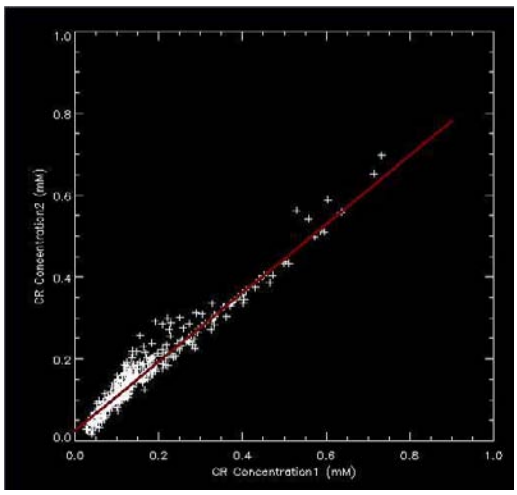

Fig.1. Pixel by pixel correlations between the pharmacokinetics of two successive perfusion of GdDTPA^{2-} within kidney shows robust linear relationship.

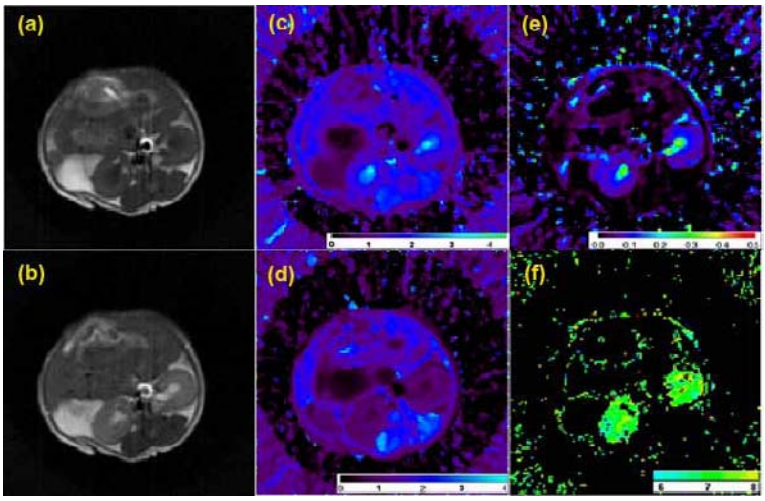

Fig.2. (a) T1-W image before CR injection; (b) T1-W image after CR injection ; (c) T1 Map before CR injection ; (d) T1 Map After CR injection ; (e) Concentration Map of CR; (f) The pHe map of kidney.

Conclusions: The pH_e maps are in good agreement with values reported by Raghunand et al. [2] in normal kidney. The binary phase injection approach showed robust correlations between the pharmacokinetics of two contrast reagent and allowed pH_e maps to be obtained with improved spatial resolution, compared to dual injection and spectroscopic methods described previously [2, 3]. However, the current protocol still suffers from long experiment time, which needs to be improved with the aim of implementing this technique in a clinical setting. For this reason, continued research toward the development of single injection pH_e imaging method is warranted.

References: [1] Gatenby and Gillies, Nature Rev. Cancer *4:* 891-899, 2004; [2] Raghunand, MRM, *49*:249-257, 2003. [3] Garcia-Martin, MRM 55:309-315, 2006