Discrimination of Renal Cell Carcinoma Subtypes with dynamic contrast-enhanced perfusion MRI and Pharmacokinetic Modeling

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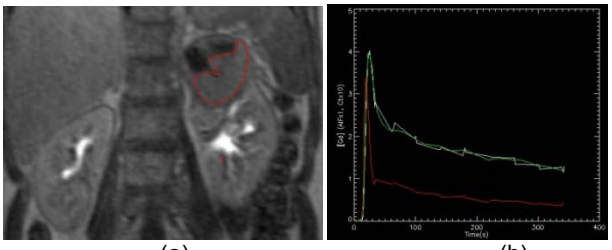
Introduction: Renal cell carcinoma (RCC) is a heterogeneous disease with multiple subtypes unique in their histopathologic features, clinical manifestation, prognosis, and response to therapeutic regimens [1]. Currently, surgery is the treatment for all RCC irrespective of subtypes, but multiple therapeutic options including less aggressive options such as ablation and active surveillance are being investigated in management of localized RCC. Non-invasive assessment of RCC subtype may help in future management of this disease by allowing for patient and tumor specific therapy. Several prior studies [2, 3] have demonstrated that dynamic contrast-enhanced MRI (DCE MRI) is a useful modality for evaluating RCC as it provides physiological information on tumor vascularity and microvessel permeability [3]. However, the role of these parameters (derived from pharmacokinetic model analysis) in discriminating RCC tumor subtype has not been investigated. Hence, the purpose of our study was to investigate the feasibility of pharmacokinetic model parameters, such as transfer constant (ktrans), extravascular extracellular volume fraction (ve), and plasma volume fraction (vp), for discrimination of RCC subtypes.



(a) (b)

Figure 1 GKMv model analysis applied to RCC tumor. (a) ROI drawn around solid portion of clear cell RCC. (b) GKMv model analysis of tumor DCE-MRI data (white line) using individual AIF (red), yielding best-fit model (green). Note both tumor data and model fit are scaled by 10 times for display.

Materials and Methods: In this HIPPA compliant prospective study, patients with known or suspected renal tumors underwent preoperative DCE-MRI at 1.5T. Patients who underwent surgery and had DCE data available for analysis were included. Imaging was performed at 1.5T (Siemens Magnetom Avanto, Erlangen, Germany) with body array coil. DCE-MRI data with a high temporal resolution (1.2 s/frame) was acquired using a 3D TWIST (Time-resolved angiography With Interleaved Stochastic Trajectories) pulse sequence (voxel resolution 1.56 x 1.56 x 2.5 mm, TR = 2.33 ms, TE = 0.77 ms, FA = 12º). Prior to contrast injection, 5 frames were acquired within a breath-hold. After injection of 4cc of Gd-DTPA (Magnevist, Bayer, Wayne, NJ) at 2cc/second by a power injector and with 5 second scan delay. 21 frames (3D volume) through the kidneys were acquired in a long 30 second breath-hold followed by 5 frames per breath-hold every 30 seconds for total of 5 to 6 minutes. Post- processing was performed using custom made IDL software. Dynamic contrast enhanced images were co-registered using SPM (UCL, UK) to minimize the motion artifact. A single radiologist manually drew regions of interest (ROI) around the renal tumor on a single coronal image. A different reader manually drew a separate ROI in the lumen of the aorta to measure individual arterial input function (AIF). The generalized kinetic model with vascular term (GKMv) [4] was used for pharmacokinetic model analysis with the assumption that T1 = 1.2 s for lesion, T1 = 1.2 s for plasma, and the Gd relaxivity in plasma and lesion is 4.1 mmol/L^{-1}s^{-1}. Model parameter estimation was performed using the Simplex method by minimizing the residual sum of squares between the data and model prediction. The difference between groups was assessed using a 2-tailed t-test with unequal variance.

Table 1 Results of GKMv model analysis for each RCC subtype.

	clear cell	oncocytic	papillary
Ktrans (/min)	0.91±0.70	2.20±1.96	0.11±0.12
ve	0.23±0.18	0.26±0.19	0.21±0.07
vp	0.16±0.14	0.33±0.33	0.09±0.08

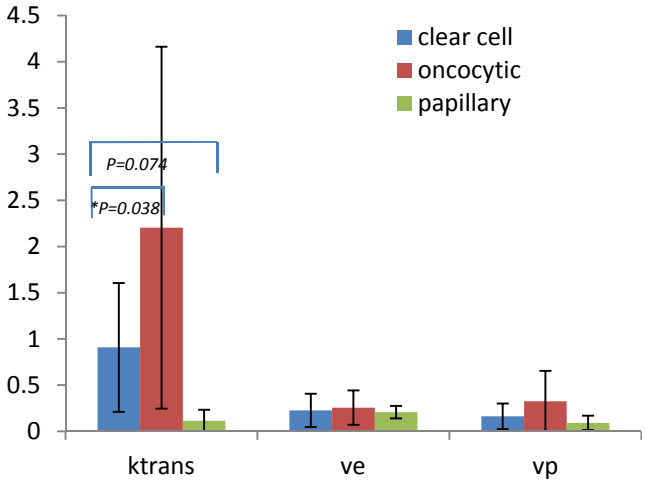


Figure 2 Comparison of GKMv model parameters between three subtypes of RCC.

Results and Discussion: 23 tumors (in 22 patients) were evaluated. At histopathology there were 14 clear cell RCC, 6 oncocytic tumors, and 3 papillary RCC. Figure 1a shows an example of ROI drawn around the solid portion of tumor on a single coronal slice. Figure 1b is the result of fitting GKMv model in which AIF (red), measured data in tumor (white), and best model fit (green) are depicted. Table 1 displays the results of ktrans, ve, vp for each RCC tumor subtype; these results are summarized graphically in Figure 2. Significant differences were found in ktrans between clear cell RCC and oncocytic RCC (p = 0.038) and between clear cell and papillary RCCs (p = 0.074). Papillary RCC has lower vp than both oncocytic and clear cell RCCs (p= 0.41 for clear cell vs. papillary; p=0.28 for oncocytic vs. papillary). However, the results were not statistically significant likely due to the small sample size. The large variability in the oncocytic group might be because we included both oncocytoma and chromophobe in this group. To our knowledge, the present study is the first attempt to use DCE-MRI and pharmacokinetic model to differentiate RCC subtypes. In the future, we will study other advanced models such as the shutter speed model, as well as other methods of data processing such as voxel based analysis.

References: 1. Sun et al, Radiology 2009; 250(3):793-802. 2. Rosen et al, Clin Cancer Res 2007; 13:770s-776s. 3. Notohamiprodjo et al, J Magn Reson Imaging 2010; 31(2):490-501. 4. Tofts, J Magn Reson Imaging 1997; 7:91-101.