Quantitative Perfusion Measurements in Renal Masses with Arterial Spin Labeling and Dynamic Contrast Enhanced MRI at 3T Correlate with Microvessel Density at Histopathology

Yue Zhang[1], Payal Kapur[2,3], Qing Yuan[1], Ananth Madhuranthakam[1,4], Ingrid Carvo[5], Sabina Signoretti[5], Ivan Dimitrov[6], Yin Xi[1], Katherine Wicks[1], Jeffrey Cadeddu[1,3], Vitaly Margulis[3], James Brugarolas[7,8], and Ivan Pedrosa[1,4]

[1]Radiology, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [2]Pathology, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [3]Urology, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [4]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [5]Pathology, Brigham and Women's Hospital, Boston, Massachusetts, United States, [6]Philips Medical Systems, Cleveland, Ohio, United States, [7]Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [8]Developmental Biology, University of Texas Southwestern Medical Center, Dallas, Texas, United States

INTRODUCTION: Renal cell carcinoma (RCC) growth and metastatic potential has been linked tightly to the ability of the tumor to induce formation of new blood vessels (i.e. angiogenesis). While dynamic contrast enhanced (DCE) MRI has been proposed to measure tumor perfusion in a variety of tumors, contraindications to receive I.V. contrast due to impairment in the renal function are common in RCC patients. Furthermore, the contributions of both blood flow and vascular permeability to tissue enhancement may lead to erroneous estimations of tumor perfusion with DCE MRI. Alternatively, quantitative arterial spin labeling (ASL) MRI can be used to measure renal mass perfusion at 1.5T without the need for I.V. contrast[1]. However the correlation between ASL perfusion measurement and pathology-based vascularity measurement, like microvessel density, in renal masses has not been yet described. Moreover, the theoretical advantage of ASL MRI at 3T due to increased signal-to-noise ratio and the prolonged T1 values in tissues has not been investigated. The purpose of this study was to correlate the perfusion of renal masses measured by ASL at 3T to quantitative parameters derived from DCE MRI and validate these results against microvascular density (MVD) measures at histopathology.

MATERIALS AND METHODS

Patients and MRI Protocol: This was a prospective, IRB-approved, HIPAA-compliant study. After signing an informed consent, 36 patients scheduled for surgical resection of a known renal mass underwent 3T dual-transmit MRI with a 16-channel SENSE-XL-Torso coil (Achieva, Philips Medical System, Cleveland, OH). A 2D ASL coronal acquisition (16 label-control pairs and proton density–weighted reference image) was obtained through the kidneys with pseudocontinuous labeling (pCASL), using background suppression and superior saturation of inflowing blood after labeling, and acquiring with a single shot turbo spin echo[2]. Labeling was performed axially 8–10cm above the center of FOV for 1.5 s followed by a 1.5 s post-labeling delay. FOV=40cm×40cm, matrix=176×176, TR=6s. DCE MRI was then performed using a coronal 3D spoiled gradient echo acquisition with a temporal resolution of 5 sec. To minimize respiratory motion during DCE MRI, three consecutive dynamic phases were obtained within each 15-sec breath-held acquisition period. A 15-sec period of free-breathing was allowed between consecutive acquisition periods. Three baseline dynamic phases were acquired, followed by a bolus of 0.1 mmol/kg of gadobutrol (Gadavist; Bayer Healthcare Pharmaceuticals, Wayne, NJ) using a power injector at a rate of 2 cc/sec followed by a 20 cc saline flush at 2 cc/sec. The same MRI sequence was used to generate a T1 map ($T1_0$) prior to contrast injection with three separate acquisitions (flip angles 10°, 5°, and 2°). *Image Reconstruction:* ASL label-control complex data pairs were subtracted and averaged in k-space and then converted to quantitative perfusion (P_{ASL}) maps. DCE images were analyzed using commercial software VersaVue Enterprise (iCAD, Inc., Nashua, NH), to perform voxel-by-voxel fitting with Tofts model and generate quantitative maps of K^{trans}, *Kep*, *Ve,* and *Vp*. The $T1_0$ and initial area under the concentration curve (iAUC) were also calculated. *Image Analysis:* All images were analyzed with a DICOM viewer (Osirix X, version 5.6, 64bit, Bernex, Switzerland). Regions of interest (ROI) of entire tumor, and of high flow and low flow areas within the tumor were drawn on P_{ASL} map and on the DCE-derived maps K^{trans}, *Kep*, *Ve,* and *Vp*, $T1_0$ and iAUC. *Histopathology:* All tumors were classified into one of the following categories: *(a)* low-grade (LG, Fuhrman 1-2) clear cell RCC (ccRCC), *(b)* high-grade (HG, Fuhrman 3-4) ccRCC, *(c)* papillary RCC (pRCC), *(d)* chromophobe RCC (chrRCC), *(e)* oncocytoma (ONC), or *(f)* angiomyolipoma (AML). Immunostaining for CD34 and CD31 were performed for clear cell RCC. Semi-automatic calculation of MVD was performed by matching ROI on CD31 and CD34 stains (Aperio software) to those selected on MRI in the same tumor, and was tabulated as the number of vessels per area (/μm²) within ROI. *Statistics:* The Spearman rank-order correlation was used to assess the correlation between ASL perfusion and DCE parameters, and MVD (p<0.05 considered statistically significant).

RESULTS: ASL was successful in 30 patients. MVD measurements were acquired in 16 clear cell RCCs. **Fig.1** shows representative ASL *and* DCE-derived perfusion maps in the same patient, and corresponding pathology images. Significant correlations are found between P_{ASL} and K^{trans} in entire tumor and in high flow region (**Table 1**). Perfusion related measurements, P_{ASL}, K^{trans} and *Kep*, also correlate with MVD measurement based on CD34 and CD31. **Fig.2** shows scatterplots between perfusion related measurements and MVD based on CD31.

Spearman correlation	K^{trans}	*Kep*	MVD_{CD34}	MVD_{CD31}
P_{ASL} for entire tumor	ρ=0.48,P=0.0091	ρ=0.46,P=0.0121		
P_{ASL} for high flow	ρ=0.43,P=0.0331	ρ=0.52,P=0.0081	ρ=0.51,P=0.0083	ρ=0.66,P=0.0002
K^{trans}			ρ=0.41,P=0.0005	ρ=0.61,P=0.0011
Kep			ρ=0.42,P=0.0347	ρ=0.64,P=0.0006

Table 1: Spearman correlation coefficients (ρ) and P values.

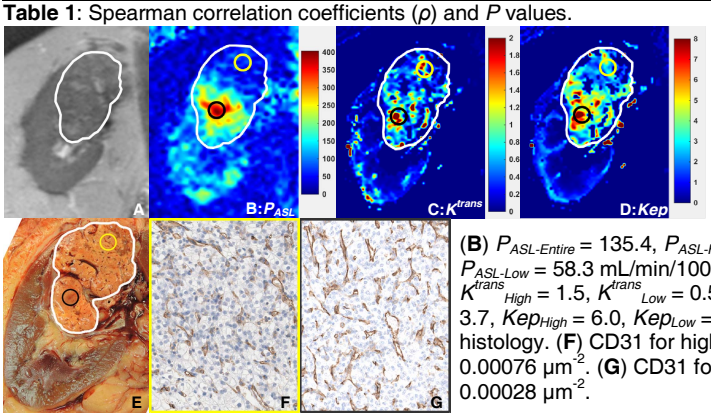
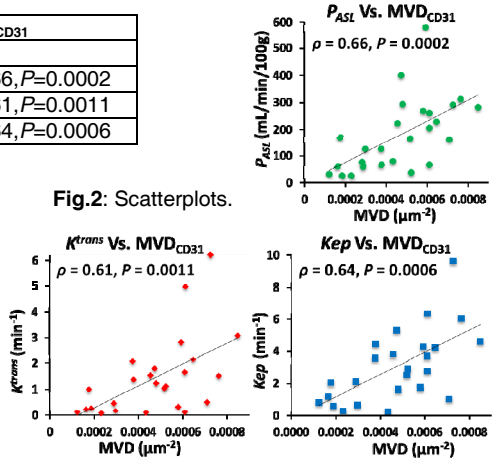


Fig.1: A patient with LG ccRCC (white circle). Small black circle indicated high flow region and yellow circle indicated low flow (**B**) $P_{ASL\text{-}Entire}$ = 135.4, $P_{ASL\text{-}High}$ = 311.6 and $P_{ASL\text{-}Low}$ = 58.3 mL/min/100g. (**C**) K^{trans}_{Entire} = 0.8, K^{trans}_{High} = 1.5, K^{trans}_{Low} = 0.5 min^{-1}. (**D**) Kep_{Entire} = 3.7, Kep_{High} = 6.0, Kep_{Low} = 2.1 min^{-1}. (**E**) Gross histology. (**F**) CD31 for high flow area, MVD= 0.00076 μm^{-2}. (**G**) CD31 for low flow area, MVD= 0.00028 μm^{-2}.

Fig.2: Scatterplots.



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CONCLUSION: ASL MRI at 3T allows for noninvasive assessment of tumor perfusion in renal masses without the need for administration of exogenous contrast agent. The perfusion measurements by ASL and DCE MRI in entire tumor and in high flow region correlate with MVD at histopathology.