The assessment of early vascular effects of the angiogenesis inhibitor sunitinib in renal cell carcinoma (RCC) by DCE-MRI and diffusion weight MRI (DWI) at 3 Tesla.

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Introduction: Sunitinib is an oral angiogenesis inhibitor, used as first line treatment in patients with metastatic renal cell cancer (RCC). Tumor neovasculature is characterized by increased vessel density, increased permeability and high interstitial fluid pressure. A successful antiangiogenic treatment is expected to result in stabilization of the vasculature and a reduction in permeability and in interstitial fluid pressure, resulting in a decrease of the size of the leakage space. Also, it can induce necrosis. This study aims to assess the early vascular effects of sunitinib in RCC patients with a dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted imaging (DWI) at 3 Tesla (T) .

Patients and Methods: In eight patients with progressive RCC with abdominal lesions, DCE-MRI and DWI measurements were performed at baseline, on days 3 and 10 after start of sunitinib, using a 3 T Siemens MR system (TrioTim, Siemens, Erlangen, Germany). After conventional T1- and T2-weighted imaging, three echo-planar DWI sequences were obtained during 22 second breath-holds after maximal expiration, using three gradient factors (b=50, b=300 and b=600 s/mm^2). Sequence parameters were: TR 1800 ms, TE 62 ms, FoV 360x317 mm, matrix 100x88, 13 slices of 10 mm thickness and parallel factor 2. Apparent diffusion coefficient (ADC) maps were calculated and analyzed from these, for tumor ROIs and ROIs containing healthy liver tissue. DCE-MRI was performed after 15 ml 0.5M Gadolinium (Gd)-DTPA was administered intravenously in 6 seconds by a Spectris^{TM} MR injection system. Using a 2D T1-weighted fast low-angle shot (FLASH) gradient echo sequence with a time resolution of 2 seconds Gd-DTPA uptake in the tissue was monitored. A vascular input factor (VNF) was determined from pixels in the spleen. Sequence parameters were: TR 39 ms, TE 2.08 ms, α 45°, FoV 350x263 mm, matrix 256x103, slice thickness 7mm, 8 slices. DCE-MRI data were acquired with a temporal resolution of 2 seconds for 5 minutes.. We obtained pharmacokinetic maps for k_{ep} and K^{trans} as described previously, using data from the first 90 seconds. (1) From each map, the mean k_{ep} and K^{trans} of the whole tumor or metastasis was determined. To assess tumor heterogeneity, histogram analyses were performed. After the dynamic T1 measurements, a second bolus of 15 ml 0.5M Gd-DTPA was administered iv in 3.75 seconds followed by dynamic T2* weighted echo-planar measurements during 90 seconds. Sequence parameters were: TR 1000 ms, TE 23 ms, α 90°, FoV 320x180 mm, 4 slices of 10 mm. T2* data will be analyzed and presented at a later stage. For follow-up scans slice positions were matched with the first session using anatomical hallmarks as a reference. VEGF plasma levels were measured day 0, 3 and 10.

Results and discussion: In eight RCC patients (7 clear cell and one papillary RCC), treatment with sunitinib did not result in significant changes in mean k_{ep} (s^{-1}) and K^{trans} (s^{-1}) values in tumors or healthy liver tissue on days 3 and 10. However, in six patients, the difference in mean k_{ep} values at day 10 exceeded the previously determined repeatability coefficient (at 1.5 T) (2). We did not observe a significant k_{ep} and K^{trans} histogram shift in tumor or healthy liver ROIs. Two patients (6 and 7) showed an increase in tumor mean k_{ep} values (fig. A). Pt 6 had objective progressive disease five weeks after start of treatment based on RECIST CT evaluation. All other patients, including pt 7, showed stable disease at CT evaluation after two cycles of treatment. In two patients (pt 1 and 2) a remarkable increase in k_{ep} values was observed in healthy liver tissue while in tumors their k_{ep} values decreased (fig. A). However, with DWI we observed a significant increase in ADC (x10^{-6} s/mm^2) from baseline (mean 1174, range 868-1373) to day 3 (mean 1315, range 1008-2097, p=0.036) with a subsequent significant decrease to day 10 (mean 1154, range 824-2005, p= 0.029)(fig. B). Baseline and day 10 ADC values did not significantly differ (p >0.1). This indicates reduced restriction of brownian motion of water molecules on day 3, possibly due to edema or the development of necrosis. We hypothesize that the subsequent decrease in ADC on day 10 is the result of development of organized necrosis and therefore a reduction in the interstitial space. Further exploration of the used time schedule is necessary. Remarkably, in the patient with papillary RCC (pt 2), no changes in ADC were observed. VEGF plasma levels indicate a near significant increase from baseline to day 10 (mean 0.55 ng/ml to 1.24 ng/ml, p=0.062). Correlation with treatment outcome follows.
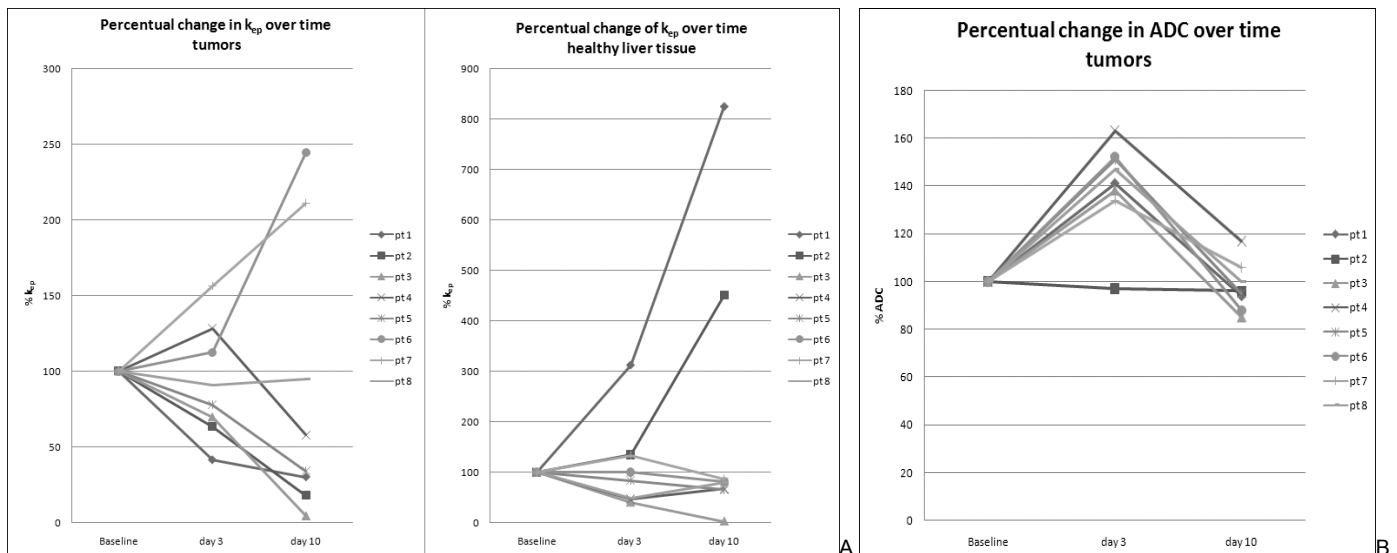
A. Percentual change of k_{ep} over time in tumors and healthy liver tissue. B. Percentual change in ADC in tumors.

Conclusions: This is the first report of DWI results in RCC patients at 3 T. Treatment with sunitinib provokes significant increases in ADC after 3 days, with recurrence to baseline values at day 10. This is possibly due to the development of edema and necrosis. In this limited number of patients, no significant changes in both mean k_{ep} and K^{trans} values, as well as in the histogram results were found, although in individual patients some trends indicative for early vascular effects of sunitinib were observed. In the early development of new drugs, especially targeted therapy, incorporation of DWI besides DCE-MRI is warranted to get more insight in the behavior of tumors.

(1) Van Laarhoven, H. et al. J Magn Reson Imaging 2003 Sep;18(3):315-20. (2) Desar, I. et al. Abstract ISMRM 2010.