Non-invasive quantification of anti-angiogenic therapy by contrast enhanced MRI in experimental pancreatic cancer

Hans-Juergen Raatschen[1], Christian Olaf Schoenfeld[1], Birgit Hotz[2], and Hubert G Hotz[2]

[1]*Diagnostic and Interventional Radiology, Hannover Medical School, Hannover, Germany,* [2]*General, Vascular and Thoracic Surgery, Charité Universitätsmedizin Berlin, Berlin, Germany*

Purpose:

MRI is a pivotal pillar in the follow-up of cancer: However, conventional MR imaging techniques are not well suited for assessing early changes in tumor vascularization during angiogenesis-inhibition.
The purpose of this study was to measure effects of different angiogenesis inhibitors on the microvasculature of orthotopically implanted pancreatic cancers by dynamic, contrast-enhanced MRI in order to establish a non-invasive technique for monitoring antiangiogenic cancer treatment response.

Materials and Methods:

Fragments of DSL-6A/C1 pancreatic cancers were orthotopically implanted in the pancreatic tail of 109 Lewis rats. Three weeks later, antiangiogenic treatment was initiated by intraperitoneal administration of bevacizumab (n=38) and suramin (n=27), while the control group (n=44) remained untreated. 24 hours, 1 week and 4 weeks after treatment initiation, a dynamic, albumin-(Gd-DTPA)-enhanced MRI was performed. Estimates of fractional tumor plasma volumes (fPV, %) and vascular permeability (KPS, ml/min/100cc) were calculated based on the dynamic MRI data by using a two-compartment pharmacokinetic model.

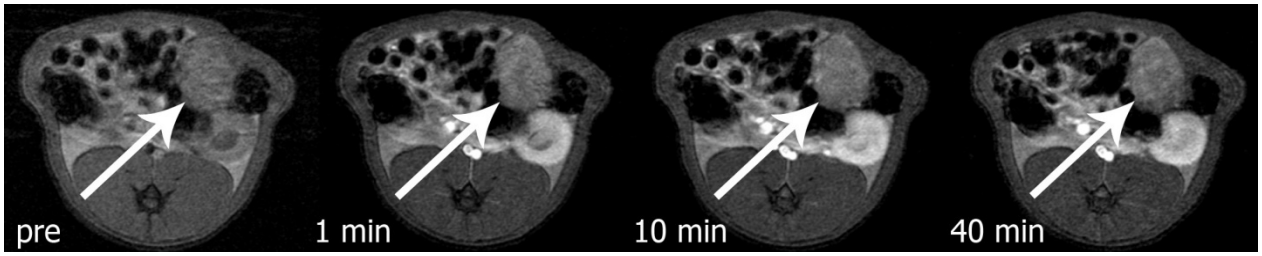

Figure 1: Representative dynamic T1-weighted images of an orthotopically implanted pancreatic cancer after 4 weeks of angiogenesis inhibition (suramin)

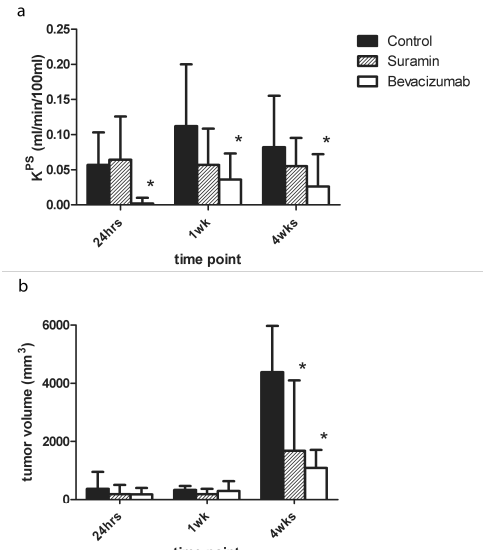

Figure 2: MRI-assayed permeability (a) and tumor volumes (b) of control and angiogenically inhibited pancreatic cancers at different timepoints.

Results:

At 24 hours, KPS was significantly reduced in the bevacizumab group compared to the control and suramin group (0.002 ± 0.008; 0.057 ± 0.046 and 0.064 ± 0.062 (mean ± SD); p<0.001). After one and four weeks, KPS was significantly smaller in the bevacizumab group compared to the control group (0.036 ± 0.037 vs. 0.112 ± 0.088; p < 0.01 and 0.026 ± 0.046 vs. 0.082 ± 0.074 respectively; p < 0.05)
At one week, fPV was significantly larger in control tumors compared to the bevacizumab and suramin group (15.10 ± 9.97; 6.25 ± 2.74 and 7.47 ± 3.44 respectively; p < 0.01). At 24 hours and four weeks, differences in fPV among control, bevacizumab and suramin groups were not significant (4.84 ± 3.11; 7.06 ± 5.42; 6.00 ± 4.08 and 5.21 ± 3.37; 5.03 ± 2.80; 4.11 ± 3.9; p = 0.53 and p = 0.64).Tumor volumes at 24 hours and one week were similar among the two treatment groups and the control group: 130.4 ± 206.2; 186.8 ± 320.7; 368.0 ± 587.2 mm3 (p = 0.41), and 178.9 ± 286.6; 116.6 ± 166.6; 276.0 ± 150.6 mm3 (p = 0.40). After four weeks, tumor volumes were significantly larger in the control group compared to the bevacizumab and suramin group: 4380.3 ± 1590.6; 869.6 ± 717.2 and 1676.5 ± 2424.1 mm3 (p<0.001)

Conclusion:

Pharmacokinetic analysis of dynamic, albumin-(Gd-DTPA)-enhanced MRI appears to be a sensitive method to quantify angiogenesis-inhibiting effects of bevacizumab and suramin well before changes in tumor volumes can be detected and thus might be a useful addition to morphological MRI in the follow-up of antiangiogenic cancer treatment.