

Chronic and acute anti-angiogenic treatment effects detected by arterial spin labeling in mouse tumor

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Introduction

Tumor blood flow is an important marker of angiogenesis which is a key element in the pathophysiology of tumor growth and metastasis¹. Traditionally dynamic gadolinium contrast enhancement was used to estimate tumor blood flow and vascular permeability; however, quantification of these imaging endpoints has been challenging, and the results could depend on the data analysis model used. Alternatively, arterial spin labeling (ASL) is a noninvasive and quantitative technique that measures perfusion by magnetically labeling water as a freely diffusible endogenous tracer. Application of ASL to measure perfusion in tumor is a challenge due to the low perfusion and artifacts caused by animal movement, susceptibility, and fat in the abdomen (the region where tumors in experimental models are typically transplanted). Previously, we successfully demonstrated and quantified mouse renal perfusion using Flow-sensitive Alternating Inversion Recovery (FAIR) ASL². We also optimized the technique to measure low blood flow³. In this study, using a mouse xenograph model we applied this optimized FAIR ASL method to quantify tumor perfusion before and after acute and chronic treatment of an anti-angiogenic agent (Avastin®).

Methods

All animal studies were approved by the local Institutional Animal Care and Use Committee (BMSI, A*STAR, Singapore).

Tumor model: Tumors were induced in 8 week old female nude mice by intradermally inoculating 1.25 million renal carcinoma cells (A498 cell line; suspended in 0.1 ml of 50% matrigel) at the right flank of each animal. Two treatment schemes were studied: chronic and acute. For the chronic treatment study, once the tumor volume reached around 100 mm³, the animals were randomly divided into 2 groups (n = 9) and then treated either with Bevacizumab (Avastin®, Roche, 5 mg/kg ip, twice per week), or an equal amount of isotype control (The Binding Site, UK). The animals were imaged 43 days after the start of treatment. In the acute treatment study, Avastin or isotype was given only once when the tumors volume reached 400 mm³. The animals were imaged before and 24h after the treatment.

Imaging and Analysis: The MRI was carried out on a 7T Bruker ClinScan scanner. A 10 mm surface receive coil was placed on top of the tumor. FAIR ASL was acquired using single-shot spin-echo EPI (TR/TE = 6s/18ms). Water excitation and 3D shim were used to minimize artifacts. An axial slice of 2 mm thickness crossing the center of the tumor was acquired with an in-plane resolution of 0.218 mm x 0.218 mm. 6 TIs were varied from 0.1 s to 4 s for flow quantification. T1 measurement was performed with inversion recovery SE-EPI with TI changing from 0.2 s to 8 s. Using Matlab, the perfusion was calculated based on the pair-wise subtracted FAIR images and the T1 map.

Results

Figure 1 shows the reduction of both volume and overall blood flow in tumor at 43-days post-treatment. The tumors exhibit heterogeneous perfusion with values ranging between 10-280 ml/100g/min: high perfusion (170 ± 20 ml/100g/min) near the periphery and low perfusion (31 ± 5 ml/100g/min) in the core, which is consistent with a previous report⁴. However, the difference in tumor perfusion between the control (61 ± 10 ml/100g/min) and treatment (39 ± 4 ml/100g/min) groups was not significant ($p=0.069$). On the contrary, acute Avastin administration effectively lowered tumor perfusion from 110 ± 10 to 80 ± 10 ml/100g/min ($p < 0.05$, $n=9$) with no reduction found in the isotype control group (baseline: 121 ± 17 ml/100g/min and post-drug: 117 ± 21 ml/100g/min, $n=6$) (Figure 2).

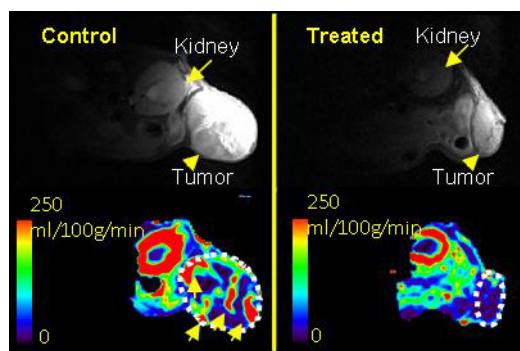


Figure 1: T2 weighted images (above) and ASL flow maps (below) after chronic isotype (left) and Avastin (right) treatment.

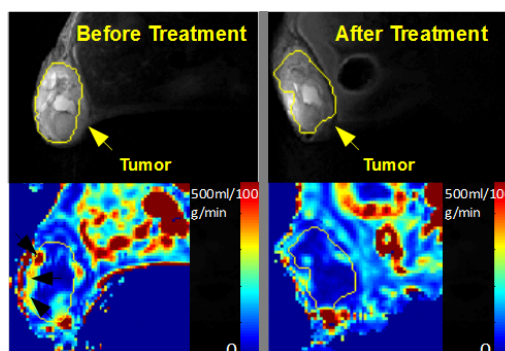


Figure 2: T2 weighted images (above) and ASL flow maps (below) before (left) and 24h after (right) Avastin treatment.

Discussion: We have shown robust, but heterogeneous reductions in tumor perfusion and peripheral flow in mice treated with Avastin. Notably, in the acute treatment study reduction of tumor perfusion occurred prior to volumetric changes, which supports the notion that FAIR ASL could be used for early detection of drug response. However, we found that tumor perfusion and size varied significantly across animals in the chronic treatment study. These observations allow us to further investigate the value of acute response for the prognosis of respondents and non-respondents observed in the chronic study. In summary, we have demonstrated that FAIR ASL can be applied to evaluate treatment effect in mouse tumor models, and ultimately, translated to the clinic.

References

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