

Effect of vascular targeting on tumor vessel volume and size distribution

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Introduction: The tubulin binding agent combretastatin A-4 disodium phosphate (CA4DP) (OXiGENE Inc., Waltham, MA, USA) is a leading vascular disrupting agent in clinical trials¹⁻³. It has cytotoxic and antiproliferative effects against dividing endothelial cells and thereby induces vascular damage in various tumor types. As CA4DP acts on dividing endothelial cells, we hypothesize that CA4DP affects vessels of particular sizes. The aim of this study was to evaluate the effect of CA4DP by the magnetic resonance imaging method vessel size imaging (VSI)⁴⁻⁶.

Materials and Methods: The C3H mammary carcinoma was grown to 200 mm³ in the right rear foot of CDF₁ mice. A control group of mice (n = 13) received no treatment, and a treatment group (n = 16) had CA4DP administered intraperitoneally at a dose of 250 mg/kg. VSI was performed on a 3 Tesla system (Signa Excite HD, General Electric Medical Systems, Milwaukee, WI, USA) using the intravascular contrast agent Sinerem (Laboratoires Guerbet, Aulnay-sous-Bois, France). From estimates of the tissue relaxation rates R_2 and R_2^* before and after administration of the contrast agent, estimates of blood volume (ζ_0) and mean vessel radius (R) were calculated.

Results: The maps of ζ_0 and R showed heterogeneity and indicated different spatial distributions of the two parameters. Tumor median and quartile values of ζ_0 were all significantly reduced by about 35% in the CA4DP treated group compared to the control group, and the median and upper quartile of R were significantly increased. Histograms of ζ_0 and R showed a general decrease in ζ_0 following treatment, and values of R in a certain range (~20-30 μ m) were decreased in the treatment group. The drug induced change in ζ_0 was in agreement with our DCE-MRI results on the same tumor model⁷.

Conclusions: The estimates of blood fraction and mean vessel size showed a clear response of the tumor model to CA4DP, and the change in distribution of mean vessel size supports our hypothesis that CA4DP acts on certain vessel calibers as a consequence of its action on mitotic endothelial cells only. VSI may on sight be valuable in estimation of tumor angiogenic status and prediction of response to vascular disrupting agents.

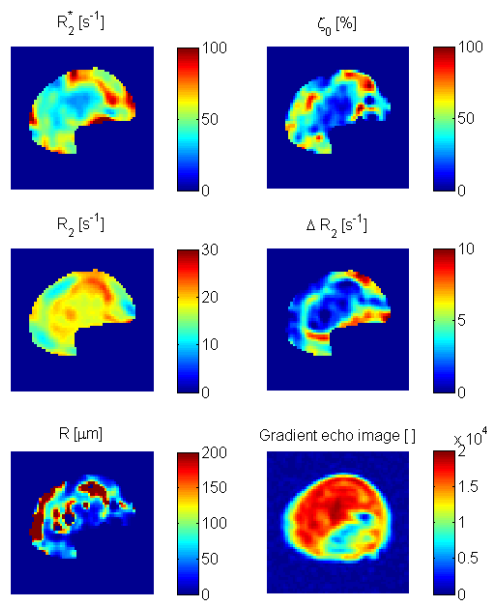


Figure 1: Parametric maps for an untreated tumor showing heterogeneity in all parameters, and a gradient echo image showing the foot containing the tumor.

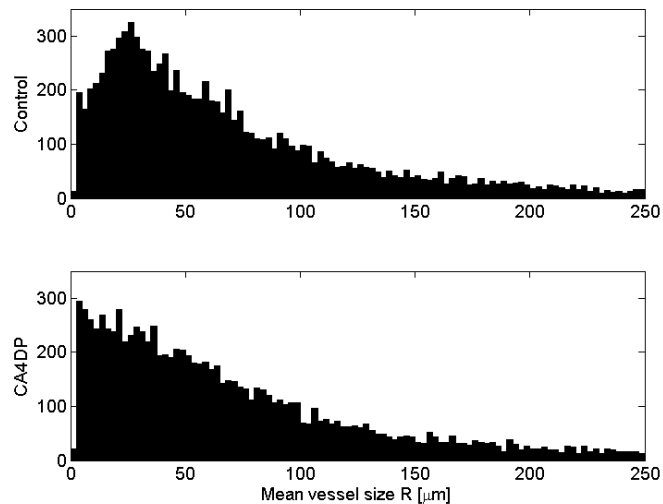


Figure 2: Histograms showing the distribution of pooled R voxel values for the two treatment groups. CA4DP changed the distribution mainly for the lower vessel radii, which shifted towards even lower values.

References:

- ¹ Dowlati, A. et al. Cancer Res, 62: 3408-3416, 2002.
- ² Galbraith, S. M. et al. J Clin Oncol, 21: 2831-2842, 2003.
- ³ Rustin, G. J. et al. J Clin Oncol, 21: 2815-2822, 2003.
- ⁴ Dennie J. et al. Magn Reson Med, 40 : 793-799, 1998.
- ⁵ Tropès I. et al. Magn Reson Med, 45 : 397-408, 2001.
- ⁶ Robinson et al. J Magn Reson Imaging, 17 : 445-454.
- ⁷ Nielsen et al. Int J Radiat Oncol Biol Phys, 70 : 859-866, 2008.

This study was financially supported by the Danish Cancer Society, the Danish Research Agency, the Danish National Research Foundation, and The Danish Council for Strategic Research.