Monitoring micro-vasculature damage induced by radiotherapy on mouse breast carcinomas using DCE-MRI

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Introduction: Microscopic changes in the tumor tissue following radiotherapy occur before variations in shape and volume can be observed. Those changes include the effect of radiation on the microvasculature, which can be monitored using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Radiosensitivity of a tissue usually depends on the local oxygen concentration, which is itself related to tissue perfusion and vascular permeability. By quantifying the exchange process between blood vessels and tissue interstitium before radiotherapy, DCE-MRI has the potential to become a predictive tool of the outcome of a treatment. In this study DCE-MRI was used to analyze changes in the microvasculature following the irradiation of mouse breast carcinomas.

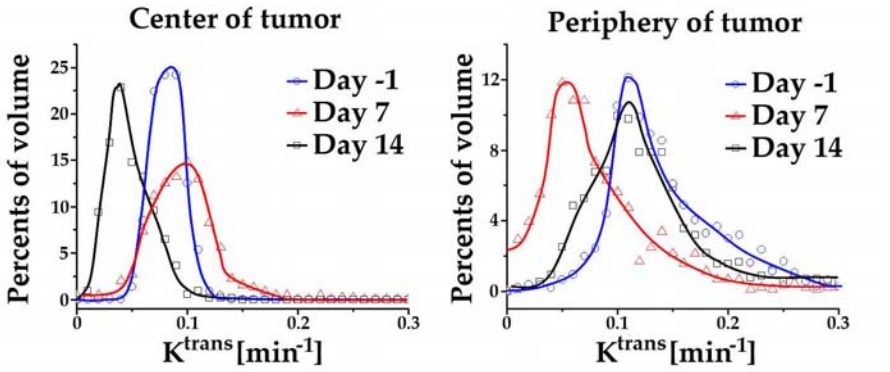

Figure 1 : Normalized distribution of pixels of the center and periphery for the irradiated (MC4-L2) tumor (right tumor on Fig. 2). Solid lines are guides to the eye.

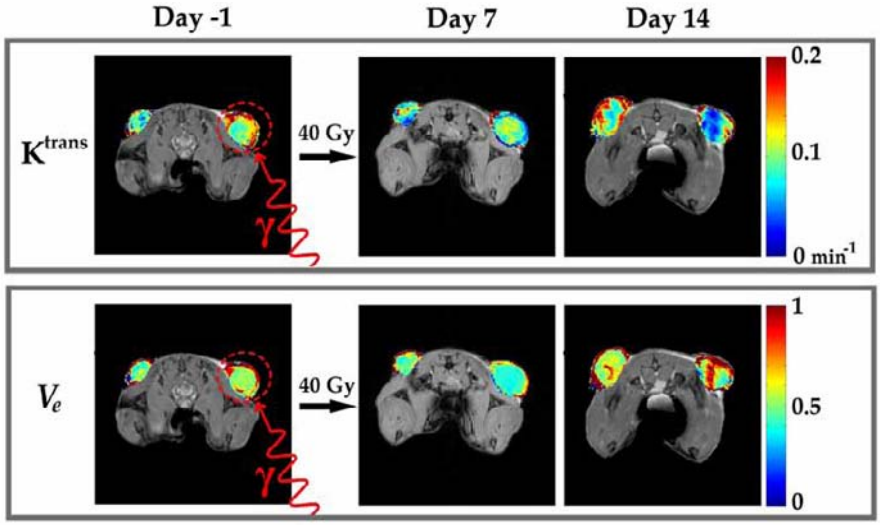

Figure 2 : Axial images of a mouse which has received 40 Gy of gamma rays on its right side tumor. Top row shows changes in the transcapillary transfer rate (K^{trans}). Bottom row shows changes in the extracellular-extravascular volume fraction (v_e).

Experimental Protocol: Ten mice have received a subcutaneous injection of 10^7 Balb/c mouse mammary carcinoma, clone MC7-L1 (left hind limb) and clone MC4-L2 cells (right hind limb).[1] After 4 to 5 weeks, the MC4-L2 tumor was irradiated (day 0) to 40 Gy from a concentric array of 201 ^{60}Co sources of a Leskell Gamma Knife. DCE-MRI was performed at days -1, 1, 7 and 14. A 7T magnet (Varian) using a gradient coil insert and a 40 mm millipede™ probe were used. Sixty consecutive sets of gradient-echo images were acquired with the following parameters : TR/TE = 100/2.5 ms, matrix size 128x128, FOV 30x30 mm^2, 8 slices of 1.5 mm, α=30°, NA = 4. Multi-flip angle pre-contrast T_1 map was produced using α=10, 20, 25, 30, 35, 50°. A bolus of Gd-DTPA (180 µl, 2.5:1) was injected i.v. after the second set. During imaging, animals were anesthetized with ~1.5% isoflurane and body temperature was maintained by blowing warm air on the animals.

Data were analyzed using the reference region model proposed by Yankeelov et al.[2] The model returns two parameters, the transcapillary transfer rate, K^{trans} in min^{-1} and the extracellular-extravascular volume fraction, v_e.

Results and Discussions: No modification in the microcirculation of tumor tissue is observed at day 1. At day 7, a drastic decrease of K^{trans} is seen at the periphery of the irradiated tumors, where this parameter had the highest initial value (Fig. 1). This phenomenon is explained by the radiosensitizing effect of oxygen. With time, an increasing proportion of the irradiated tumor core displays very low values of K^{trans} (Figs. 1 and 2). The interpretation of v_e is less straightforward. The very high values of this parameter ($v_e >\approx 1$) are related to a limitation of the model but are associated to necrotic areas. Diffusion from the tumor periphery rather than perfusion is responsible for the accumulation of contrast agent in the necrotic tumor core. This uptake by diffusion leads to low values of K^{trans} and artificially high values of v_e. Regression of the irradiated tumor volume was not observed 14 days after treatment. However, very low K^{trans} values expanding to most of the tissue announce the onset of global necrosis and eventually regression. The volume of control tumors was such at day 14 that animals had to be euthanized.

Conclusion: DCE-MRI can monitor the changes in tumor microvasculature induced by radiotherapy. The transcapillary transfer rate shows a degradation of tissue perfusion that precedes the onset of necrosis and eventually, tumor regression. The potential of DCE-MRI for predicting tumor response requires further investigations but the current findings support this potential usefulness.

References : 1 - C. Lanari et al. Cancer Res. 61, 293-302 (2001); **2 -** Yankeelov et al., Magn. Reson. Imaging 23, 519-529 (2005).