LONGITUDINAL FUNCTIONAL IMAGING OF THE HER-2/NEU TRANSGENIC MOUSE MODEL OF HUMAN BREAST CANCER BY DCE-MRI AND DIFFUSION WEIGHTED IMAGING

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PURPOSE: Breast cancer is the most frequent malignancy of woman worldwide. Features characterizing the progression of preinvasive ductal carcinoma to invasive breast cancer remain elusive, thus *in vivo* imaging methods are required to assess the longitudinal progression of mammary carcinogenesis exploiting the important framework provided by transgenic mouse model in preclinical settings [1]. DCE-MRI is an important non invasive tool which allows to asses changes in vessel permeability and perfusion with an increased sensitivity when done by using blood-pool contrast agents on a 1T MRI scanner [2]. Diffusion weighted imaging (DWI) is a MRI technique that reports on tissue cellularity. Both the techniques have been employed to study functional changes during the multistage process of mammary cancer progression in the HER-2/Neu transgenic mouse model.

METHODS: BALB-neuT female mice develop spontaneous orthotopic mammary cancers through atypical ductal hyperplasia (7-14 weeks of age – stage I), ductal carcinoma in situ (14-21 weeks of age – stage II) and invasive lobular carcinoma (21-28 weeks of age – stage III). For each stage a total of 14 BALB-neuT mice and 6 BALB/c mice were selected for *in vivo* MR imaging looking at the left and right IV mammary glands. All procedures were done in accordance with the EU guidelines and with the approval of the university animal care use committee. MR images were acquired with an Aspect M2 1T MRI scanner (Aspect Magnet Technologies,Israel).After the scout image acquisition, T2w anatomical images were acquired with a Fast Spin Echo sequence. Baseline tumour T1 map was acquired by using a variable flip-angle Gradient-Echo (VFA-GRE) sequence (7 flip angles 15°-160°). DCE MRI dynamic protocol was carried out by using an axial T1w 3D spoiled Gradient Echo sequence with three initial pre-contrast images and 47 dynamic post-contrast images with the following parameters: TR/TE = 40/1.8 ms, flip angle = 60°, number of slices = 10, slice thickness = 1.5 mm, FOV = 40 mm, matrix = 128x128. The Gd-containing, Serum albumin binding contrast agent (Phenoquant, Cage Chemicals, Italy), was injected into the tail vein through a 27-gauge needle at a dose of 0.05 mmol/kg. The acquired raw DCE-MRI data were analyzed by a quantitative method implementing a two-compartment Tofts model by an in-house C++ developed software, yielding the relevant parametric maps (Ktrans, Kep, Vp). DWI images were acquired with a Spin-Echo sequence with seven b-values between 0 and 600 sec/mm^2 with the same geometrical setting for DCE images. A Student t-test was used to compare mean parametric maps between BALB-neuT and BALB/c mice. Mice were euthanized and mammary glands excised, fixed in formalin and H&E stained.

RESULTS AND DISCUSSION: In BALB/c mice a slight overlap of Ktrans values was found in lymphnode and normal mammary gland area (Fig.1a-b). In BALB-neuT mice Ktrans values show higher values at stage II and III in lymphnodes and mammary glands. In both the healthy and transgenic mice Ktrans values of back muscle were similar (Fig. 1c). Analogous trends were observed for Vp maps (Fig. 1d-e-f). BALB-neuT mice showed a significant increase of Ktrans values in mammary glands during Stage II and III, in comparison to Balb/c mice which showed a reduction (Ktrans = 7.0±1.1E-4 and 4.7±1.5E-4 for BALB-neuT mice at stage II and III; Ktrans = 4.3±0.2E-4 and 1.2±0.1E-4 for BALB/c mice at stage II and III). Vp values were significantly higher for BALB-neuT mice in comparison to BALB/c mice at Stage II and III. Therefore an increase of permeability/perfusion was found with the progression of mammary carcinogenesis, as well as an increase of heterogeneity of mammary glands tissues as depicted by the corresponding higher standard deviations values for BALB-neuT mice. Diffusion values were similar along the three stages for lymphnode and back muscle areas, for both the BALB/c an BALB-neuT mice (ADC =0.5±0.1E-3 and 1.4±0.2E-3 mm^2/s for lymphnode and back muscle). In BALB-neuT mice a slight increase of diffusion was found at stage III (ADC = 0.4±0.1E-3 and 0.6±0.1E-3 mm^2/s at stage II and stage III). Such changes may be related to the underlying morphological changes involved in the transition between pre-invasive and invasive lobular carcinoma.

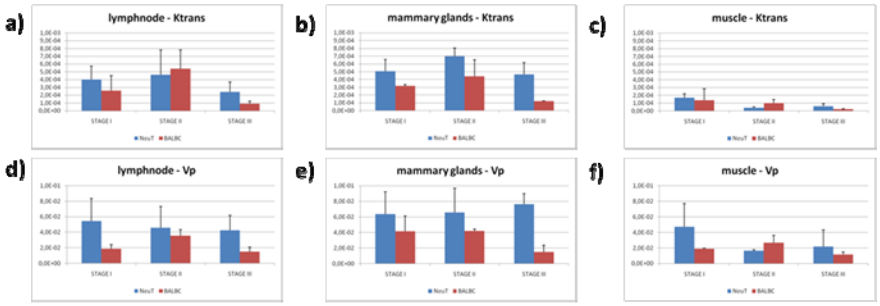

Fig.1 Mean Ktrans and Vp values obtained from the Tofts' model

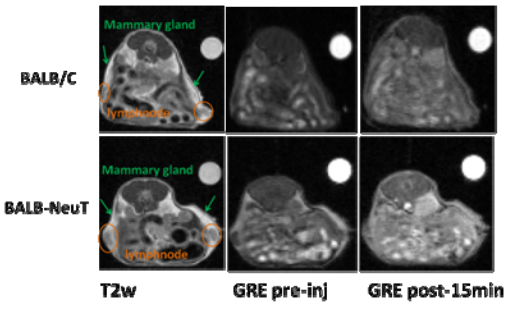

Fig. 2 representative DCE images at Stage II

CONCLUSIONS: There results provide new insights into the permeability/vascular/cellularity functional changes associated to the progression of early stage mammary cancer disease.

REFERENCES:

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