Deconvolution-based dynamic contrast enhanced MR imaging of breast tumors: correlation of perfusion parameters with HER-2 gene amplification and hormonal receptor status

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Introduction Recent studies have shown that both angiogenesis and HER-2 gene amplification are independent prognostic factors in primary breast cancer [1]. Upregulation of angiogenesis increases both permeability and the number of microvessels in tumors [2]. Characterization of angiogenesis has been performed mostly by in-vitro immunohistochemical evaluation of angiogenic tumor markers. Non-invasive measurement of blood flow in tumors has potential for assessing changes in angiogenic vasculature because the blood flow in tumors is usually abnormal [3].
Previously we demonstrated that the T1-weighted dynamic contrast enhanced MR (DCE-MR), in which the uptake and washout of contrast in tissues is monitored with time and suitably quantified can assist in the diagnosis of breast tumors and can provide information on vascular permeability and perfusion [4]. The aim of our study was to test whether breast carcinomas possess characteristic values of tumor blood flow that depend on HER-2 gene amplification and hormonal receptor status.
Materials and Methods: 57 patients with carcinoma of the breast (age range 31–80 years; mean 51 years) who underwent mastectomy or wide excision after MR imaging at our institution were studied by in-vivo perfusion measurements on a 1.5 T scanner (Philips Intera). The routine MR mammography protocol was first applied, which included whole breast DCE MR and high-resolution fat suppressed gradient echo sequence. The slice in which the lesion enhanced maximally was located by visual inspection of the subtracted DCE MR images. A second bolus of 0.1 mmol/kg Gd-DTPA was injected and a dynamic single slice IR prepared FLASH acquisition (400 dynamics with a temporal resolution of 0.3s) was performed at that slice position. In this second bolus sequence, the AIF was selected manually in the aorta and the flow-induced signal fluctuations were removed by filtering of the arterial signal-time courses [5]. The relative enhancement time courses were deconvolved pixel-by-pixel, using standard-form Tikhonov regularization and an optimized minimization scheme for the L-curve criterion [6]. Finally, the parametric maps of tumor blood flow (TBF), tumor extracellular volume (TEV) and mean transit time (MTT) were generated from the Impulse Response Function (IRF) [4]. Quantitative values for each patient were derived as an average over a ROI covering the whole lesion.
The definitive diagnosis was obtained histologically after excisional biopsy or mastectomy. Formalin-fixed, paraffin-embedded slides were reviewed by senior pathologists to evaluate histological size, lymph node status and histological grade and Nottingham prognostic index. Tumor samples were stained for estrogen receptor (ER), progesterone receptor (PR) and HER-2 protein by immunohistochemistry (IHC). Tumors were considered hormone receptor positive if a nuclear staining was observed in at least 5% of the tumor cells. For the HER-2 protein, the slides were scored as 0, 1+, 2+, or 3+ according to DAKO guidelines. For an HER-2 protein DAKO score of 2+ and 3+, HER-2 gene status was assessed by fluorescence in-situ hybridization. For both hormone receptors and HER2 gene status, mean TBF was compared beween positive and negative groups.
Results: Mean TBF was lower in patients above 50 years, in tumors less than 2 cm in size, low-grade tumors (0-2) and in lymph node negative cases. TBF showed a statistically significant difference between the PR+ and the PR- groups (p value <0.05). At the same time, the mean TBF values were significantly higher in the HER-2 amplified (HER-2+) group (98 ± 37 ml/100ml/min) compared with the HER-2 non-amplified (HER-2-) group (71 ± 43 ml/100ml/min) (p value <0.05). Figure 1 illustrates an example of a hormone receptor negative malignant breast tumor where the HER-2 gene is amplified and has a TBF of 96ml/100ml/min as evident from the peak of IRF. In both the HER-2 amplified and the non-amplified group, the ER+&/PR+ had a lower mean TBF compared to the ER-&PR-and this difference in TBF was statistically significant in the HER-2 amplified group (p value <0.05) (Figure 2).
Conclusion: Our preliminary results show that a pixel wise deconvolution analysis of DCE MR data in malignant breast tumors can provide pre-operative information regarding the angiogenic status as assessed by the blood flow. Since accurate preoperative prediction regarding high-risk patients is required for neoadjuvant chemotherapy, this noninvasive MR based assessment of TBF and its pattern can provide prognostic and predictive information The trend of increased blood flow in poor prognostic (HER-2 amplified and hormone receptor negative) tumors support the literature findings [1]. Further validation of perfusion data against the biological markers of malignant breast tumors is needed [3]

References

[1]Blackwell KL et al. (2004) *MRM* **52**:420-429
[2]Miller JC et al. (2005) *J Natl Cancer Inst* **97**:172-187
[3]Pollitt MJK et al. (2005) Oncology reports **13**:931-936
[4]Makkat S (2005) *ISMRM* **13**:743
[5]Makkat S (2006) *ISMRM* **14**:1797
[6]Sourbron S et al. (2004) *MRM* **52**:209-213

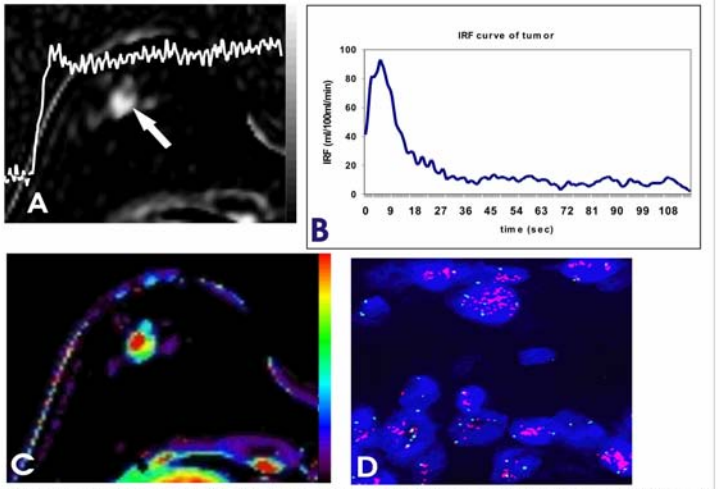

Figure.1: 55-year-old lady with a grade 1 invasive ductal carcinoma in the right breast (arrow) (A) subtracted image with the intensity-time curve (B) IRF curve from the tumor shows a peak corresponding to 96 ml/100ml/min (C) TBF map reveals the increased vascularity as well as the heterogeneity within the tumor (D) Amplification of the HER-2 gene is visualized by a high number of gene copies (red signal) in the tumor cells.

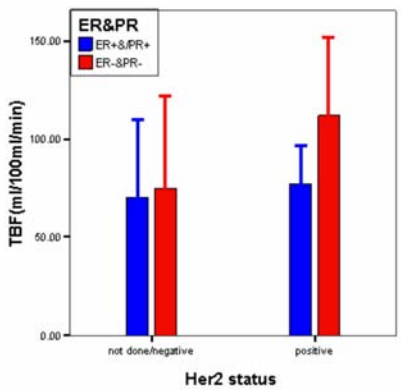

Figure.2:Clustered bar chart shows a higher mean TBF in HER-2 amplified group compared with the non-amplified group. In each group, the hormone receptor+ subgroup has a lower mean TBF than the hormone receptor- subgroup.