Angiogenic Progression of the Human Breast Tumor In Vivo: Is It Imaged?

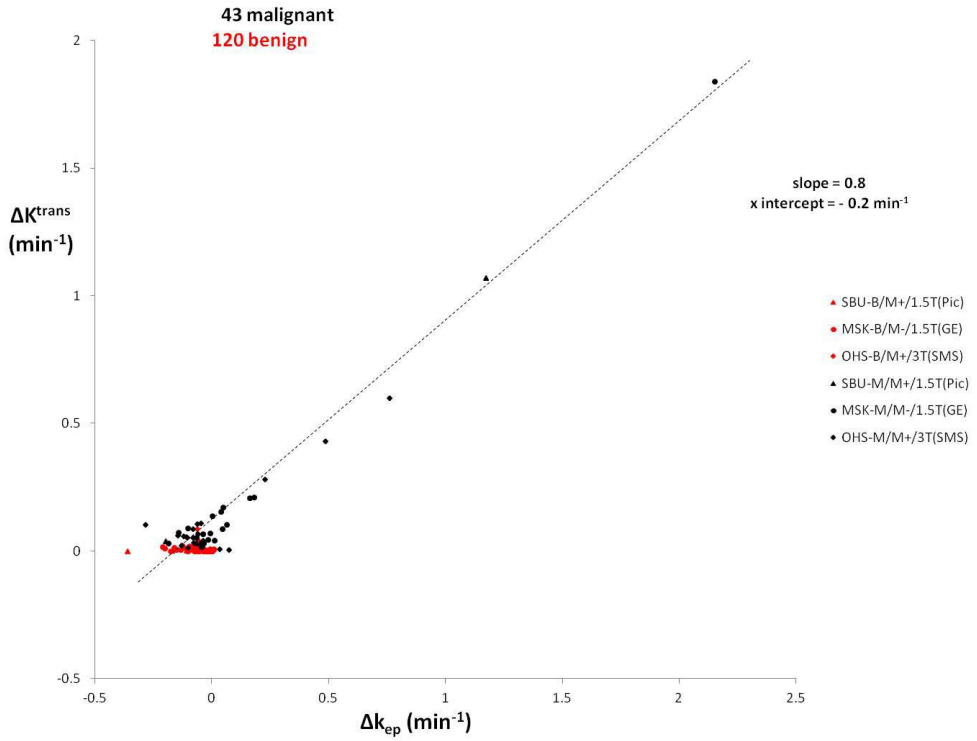
Charles S Springer[1,2], Ian J Tagge[1], Xin Li[1], Luminita A Tudorica[1,3], Sunitha B Thakur[4,5], Karen Y Oh[3], Elizabeth A Morris[5], Nicole Roy[3], Mark D Kettler[3], William D Rooney[1,6], Jason A Koutcher[4,5], and Wei Huang[1,2]

[1]Advanced Imaging Research Center, Oregon Health & Science University, Portland, Oregon, United States, [2]Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon, United States, [3]Diagnostic Radiology, Oregon Health & Science University, Portland, Oregon, United States, [4]Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York, United States, [5]Radiology, Memorial Sloan Kettering Cancer Center, New York, New York, United States, [6]Biomedical Engineering, Oregon Health & Science University, Portland, Oregon, United States

Introduction: In recent years, the efficacy of the ΔK^{trans} (Dynamic-Contrast-Enhanced) DCE-MRI biomarker for human breast cancer screening follow-up has been demonstrated (1-4). The K^{trans} parameter measures contrast reagent (CR) extravasation rate, and ΔK^{trans} is its difference when the same data are sequentially analyzed by the Standard [Tofts] pharmacokinetic Approximation (SA) and by the Shutter-Speed Approximation (SSA): $\Delta K^{trans} \equiv K^{trans}(SSA) - K^{trans}(SA)$. The only SSA / SA difference is that the latter assumes that equilibrium transcytolemmal water exchange is effectively infinitely fast. Thus, a nonzero (usually positive) ΔK^{trans} value for a region-of-interest (ROI) indicates that the interstitial CR concentration increased sufficiently to invalidate this assumption for at least some portion of the CR bolus passage. The ΔK^{trans} parameter is a sensitive measure of capillary wall permeability. Furthermore, since the SSA and SA analyses use the same arterial input function (AIF), ΔK^{trans} provides some immunity from AIF uncertainty systematic error (5). Here, we suggest that it might also monitor tumor progression. The independently determined permeation parameter, k_{ep} [the unidirectional passive CR intravasation rate constant (1-3)], was also ascertained.

Methods: We combine three sub-populations of women screened positive for potential breast cancer. DCE-MRI data were obtained before the subjects underwent biopsy procedures. Six were studied at Stony Brook University [SBU] (1,2,4,6); ninety-five tumors (92 subjects) at Memorial Sloan Kettering [MSK] (1-4); and sixty-two lesions at Oregon Health & Science [OHS] (4). The DCE-MRI acquisition details are given in (6), (1-3), and (4), respectively. The DCE-MRI ROIs for pharmacokinetic analyses were selected by six different investigators at the three institutions. Since they were blinded from each other, the pharmacokinetic analyses were independent of the pathology analyses subsequent to the biopsies. Of the 163 tumors studied, pathology found 43 (26%) malignant. Thus, in this sense, over 120 biopsy procedures (several patients underwent more than one) were unnecessary.

Results: The **Figure** plots the ROI ΔK^{trans} *vs.* Δk_{ep} [$\equiv k_{ep}(SSA) - k_{ep}(SA)$] values for all 163 lesions. The SBU, MSK, and OHS points are given as triangles, circles, and diamonds, respectively. Those found benign are colored red while those malignant black. There were 16 types of benign and 5 types of malignant tumors. Detailed pathology findings are given in (3,4,6). There are several features of this plot that seem remarkable. Most obvious is the strong correlation (essentially linear) between the independent ΔK^{trans} and Δk_{ep} CR permeability parameters, which climb to over 2 min^{-1}. Though $K^{trans} = v_e k_{ep}$, where v_e is the extracellular extravascular volume fraction (1,2), $\Delta K^{trans} \neq \Delta v_e \Delta k_{ep}$. Secondly, all 120 benign lesion points are very tightly clustered in the lower left sector – below $\Delta K^{trans} = 0.2$ min^{-1} and $\Delta k_{ep} = 0.1$ min^{-1}. The correlation is independent of quite a number of factors that might have been anticipated influential. These include: **1)** magnetic field strength [1.5T and 3T], **2)** instrument vendor and software platform [Picker, GE, SMS], **3)** slight acquisition sequence variation, **4)** CR [Omniscan at SBU, Magnevist at MSK, Prohance at OHS], **5)** tumor size, **6)** the exact lesion type, **7)** ROIs chosen by different investigators, **8)** ROI thickness (from 1.4 to 3 mm), and **9)** initial positive screening modality [mammographically positive (M+) at SBU and OHS, mammographically negative (M-) at MSK (this high-risk population was screened positive by clinical MRI)].



Discussion: All 120 benign lesion points are clustered near the bottom left of the plot - with small ΔK^{trans} and (even negative) Δk_{ep} values. However, the malignant lesion parameters are strongly correlated, and rise to large ΔK^{trans} and Δk_{ep} magnitudes. Though each subject is independent, and underwent DCE-MRI at a certain point in her disease progress, the plot might provide a view of breast tumor progression. There might be a temporal microvessel permeability increase that occurs before a tumor size increase is evident. The plot is suggestive of some kind of "threshold" behavior independent of lesion type: after the tumor ΔK^{trans} and Δk_{ep} reach ~0.2 and ~0.1 min^{-1}, respectively, it "takes off." A "discrete step in tumor progression" is known - "the angiogenic switch" (7). If this is what we are observing, it would represent an important minimally invasive imaging assessment of tumor metabolic stage. We are preparing pixel-by-pixel ΔK^{trans} and Δk_{ep} parametric maps and histograms. An obvious test of this hypothesis is to monitor the progress of an animal breast tumor model under experimental control. Parametric maps and histograms can be compared with histological staining specific for angiogenesis. We are initiating such a study.

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