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

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Introduction: In recent years, the efficacy of the ΔKtrans (Dynamic-Contrast-Enhanced) DCE-MRI biomarker for human breast cancer screening follow-up has been demonstrated (1-4). The Ktrans parameter measures concentration change (ΔC) due to extravasation (ΔV) of the contrast reagent (CR) at each pixel. Ktrans is its difference when the same data are sequentially analyzed by the Standard [Tofts] pharmacokinetic approximation (SA) and by the Shutter-Speed approximation (SSA): Ktrans,SSA = Ktrans,SA - ktrans,SA. The only SSA / SA difference is that the latter assumes that capillary transcytologial water exchange is effectively infinitesimally fast. Thus, a nonzero (usually positive) ΔKtrans value for a region-of-interest (ROI) indicates that the intravascular CR concentration increased sufficiently to invalidate this assumption for at least some portion of the CR bolus passage. The ΔKtrans is a sensitive measure of capillary permeability. Furthermore, since the SSA and SA analyses use the same arterial input function (AIF), ΔKtrans provides some immunity from AIF uncertainty systematic error (5). Here, we suggest that it might also monitor tumor progression. The independently determined permeation parameter, ktrans [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] (1,2,3,6), 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 ΔKtrans vs. Δktrans ≡ ktrans,SA - ktrans,SSA 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 ΔKtrans and Δktrans, CR permeability parameters, which climb to over 2 min⁻¹. Though Ktrans = vek, where vek is the extracellular extravascular volume fraction (1,2), ΔKtrans ≠ ΔvekΔktrans. Secondly, all 120 benign lesion points are very tightly clustered in the lower left sector – below ΔKtrans = 0.2 min⁻¹ and Δktrans = 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, Magnetovist 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 [mammographically positive (M+) at SBU and OHS, MRI negative (M-) at MSK].

Discussion: All 120 benign lesion points are clustered near the bottom left of the plot - with small ΔKtrans and (even negative) Δktrans values. However, the malignant lesion parameters are strongly correlated, and rise to large ΔKtrans and Δktrans magnitudes. Though each subject is independent, and underwent DCE-MRI at a certain point in her disease progression, the plot might provide a view of breast tumor progression. There might be a temporal microvessel permeability increase that occurs before each subject is independent, and underwent DCE-MRI at a certain point in her disease progression, the plot might provide a view of breast tumor progression. The plot is suggestive of some kind of "threshold" behavior independent of lesion type: after the tumor ΔKtrans and Δktrans 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 ΔKtrans and Δktrans 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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