Entropy and Higher Order Moment Analysis of Pixel DCE-MRI Parameters for Breast Cancer Diagnosis

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Introduction: With increasing evidence of intratumoral heterogeneity in tumor progression and resistance to therapy, biomedical imaging is perfectly poised to play an important role in future cancer detection and evaluation of therapy response by providing high resolution 3D *in vivo* assessment of heterogeneity in tumor function and microenvironment. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is one such imaging method which characterizes *in vivo* tissue microvasculature noninvasively. It has been shown that pharmacokinetic (PK) modeling of high temporal resolution breast DCE-MRI data improves accuracy in breast cancer diagnosis using parameters derived from the Standard (Tofts) Model (SM) and Shutter-Speed Model (SSM) PK analysis (1,2) – the latter takes into account the finite intercompartmental water exchange kinetics. The most promising diagnostic markers are K^{trans}(SM), K^{trans}(SSM), and ΔK^{trans} [=K^{trans}(SSM) - K^{trans}(SM)], with ΔK^{trans}, a measure of the exchange effects, being the most accurate (1,2). However, the parameter values used for discrimination of benign and malignant breast lesions were tumor ROI-averaged (1,2), lacking information in parameter heterogeneity. Analysis of pixel parameter values is required to quantify PK parameter heterogeneity, which remains a significant challenge. The conventional histogram evaluation of median, amplitude, and peak width through Gaussian fitting of pixel parameter values provides some insight into the nature of the tumor, but is not capable of in-depth assessment of the parameter heterogeneous distribution. In this study, using breast DCE-MRI data from a pre-biopsy population, we sought to explore the utility of entropy and higher order moment features of pixel K^{trans}(SM), K^{trans}(SSM), and ΔK^{trans} as imaging biomarkers of tumor heterogeneity for discrimination of malignant and benign breast lesions.

Theory: Entropy, the statistical measure of randomness of pixel PK parameter values within the whole tumor ROI can be estimated using Equation [1], where $f(p_i)$ is a probability density function representing the probability of the PK parameter of a pixel taking on the value p_i. The summation is performed for all pixels within the tumor ROI.

$$Entropy = -\sum_i f(p_i) \cdot \log_2 f(p_i) \qquad [1]$$

The variance (2nd moment; $n = 2$), skewness (3rd moment; $n = 3$), and kurtosis (4th moment; $n = 4$) of pixel PK parameter values can be determined by Equation [2], where $\overline{p}$ represents the mean of the PK parameter. Entropy and higher order moments reflect both the PK parameter value and its heterogeneous distribution within the tumor.

$$n^{th} \, moment = \sum_i (p_i - \overline{p})^n \cdot f(p_i) \qquad [2]$$

Fig.1a Mean; Fig.1b Variance; Fig.1c Skewness; Fig.1d Kurtosis; Fig.1e Entropy — Malignant / Benign

Methods: Seventy eight women with 82 mammography- and/or ultrasound-diagnosed suspicious breast lesions underwent research DCE-MRI exams prior to standard-of-care biopsies. The DCE-MRI study was IRB-approved, and informed consent was obtained from each patient. Axial bilateral DCE-MRI images with fat-saturation and full breast coverage were acquired with a 3T Siemens system using a 3D gradient echo-based TWIST sequence (2). Other acquisition parameters included 10^0 flip angle, 2.9/6.2 ms TE/TR, a parallel imaging acceleration factor of two, 30-34 cm FOV, 320x320 matrix size, and 1.4 mm slice thickness. The total DCE-MRI acquisition time was ~ 10 min for 32-34 image volume sets with 18-20 s temporal resolution. Gd contrast agent (Prohance®) IV injection (0.1 mmol/kg at 2 mL/s) was carried out following acquisitions of two baseline image volumes. Tumor ROIs were drawn by experienced radiologists based on post-contrast DCE images. The tumor ROI and pixel (within the ROI) DCE-MRI time-course data were subjected to both the SM and the SSM analyses to extract PK parameters. The whole tumor ROI mean parameter value was calculated by weighted (by pixel number) average of the slice ROI values from each of the image slices covering the entire tumor. Entropy, variance, and higher order moments (skewness and kurtosis) of K^{trans}(SM), K^{trans}(SSM), and ΔK^{trans} pixel values were computed with Eqs. [1] and [2] using all pixel values within the multi-slice ROIs encompassing the tumor.

Correlating with pathology results, receiver operating characteristics (ROC) curve analysis was conducted to assess diagnostic accuracy of each metric of the PK parameters using area under the curve (AUC).

Results: The biopsy pathology analyses revealed 29 malignant and 53 benign lesions, indicating a 35% positive predictive value (PPV) for the clinical imaging protocol. **Fig. 1** shows box plots of the tumor mean (1a), variance (1b), skewness (1c), kurtosis (1d), and entropy (1e) of K^{trans}(SSM), K^{trans}(SM), and ΔK^{trans} for the malignant (light blue) and benign (dark blue) lesion groups. For all three PK parameters, the malignant lesions generally had greater values of the five metrics than the benign ones, allowing improved diagnostic accuracy compared to clinical imaging. **Table 1** summarizes the ROC AUC values of the 5 metrics for each PK parameter as diagnostic markers. Except for K^{trans}(SM) skewness, each metric had a ROC AUC value greater than 0.8, indicating good to excellent capability of discriminating benign and malignant breast lesions. The ΔK^{trans} mean, variance, and entropy were excellent diagnostic markers with ROC AUC ≥ 0.9, while its skewness and kurtosis had ROC AUC values near 0.9.

Discussion and Conclusion: The ROC AUC analysis confirmed that the DCE-MRI PK parameter ΔK^{trans} is the best diagnostic marker for breast cancer in this cohort of

Table 1. ROC AUC for Breast Cancer Diagnostic Accuracy

	Mean	Variance	Skewness	Kurtosis	Entropy
K^{trans}(SSM)	0.898	0.883	0.828	0.874	0.873
K^{trans}(SM)	0.845	0.813	0.730	0.807	0.813
ΔK^{trans}	0.931	0.900	0.892	0.892	0.915

suspicious lesions. This is consistent with the previous findings from a mammography-occult lesion population (1). Though not better, the variance, skewness, kurtosis, and entropy of all three PK parameters provided comparable diagnostic accuracies as the mean metric (Table 1), suggesting that increased heterogeneity of perfusion properties in malignant tumors can be used to differentiate them from the benign tumors (Figs. 1b-1e). Additionally, by incorporating the water exchange effects, the SSM analysis corrects K^{trans} underestimation by the SM analysis, and thus provides increased dynamic range of the K^{trans} parameter and possibly more accurate depiction of perfusion heterogeneity in malignant tumors. It is reasonable to expect that measures of tumor K^{trans} heterogeneity may be more effective imaging biomarkers for evaluation of therapeutic response when utility of the mean K^{trans} parameter is lessened due to partial-volume-averaging effects caused by therapy-induced tumor necrosis. The spatial heterogeneity of the PK parameters was not investigated in this study. A method proposed by Rose et al. (3) will be explored in future studies to generate imaging metrics that are sensitive to both values and geometric information of the PK parameters.

References: 1. Huang *et al. Radiology* 2011;261:394-403. 2. Tudorica *et al. Magn Reson Imaging* 2012;30:1257-67. 3. Rose *et al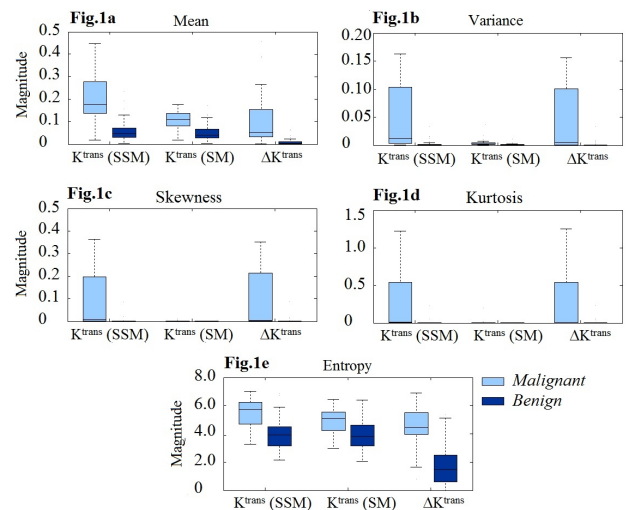. Magn Reson Med* 2009;62:488-99.