Pharmacokinetic Parameters Analyzed from MR Contrast Enhancement Kinetics of Multiple Malignant and Benign Breast Lesions Detected in Same Patients

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Purpose

Incidental lesions were commonly found in pre-operative breast MRI, which might correctly impact on surgical planning but could also result in unnecessary biopsy or over-treatment [1-3]. A better characterization of these lesions is very important. In this study, contrast enhancement kinetics were measured from patients who had two confirmed malignant lesions of identical pathology (Group-1), and also from patients who had one malignant lesion and a second benign lesion (Group-2). By analyzing lesions from same patients, the differences in whole body hemodynamics thus the blood kinetics could be controlled. The enhancement kinetics measured from each lesion was analyzed using 3 different models, Tofts model with or without the vascular component and a 3-parameter heuristic model, to obtain fitting parameters. Two questions were addressed, 1) What is the association between pharmacokinetic parameters analyzed from multiple cancers of identical pathology in same patients?, and 2) What is the difference between secondary malignant lesions and secondary benign lesions with reference to the primary cancer?

Methods

Nineteen cases with histological confirmed multiple malignant lesions in the same breast of same patient (Group-1), which were greater than 6 mm each and could be distinctly identified on MRI, were identified. Eight patients with malignant lesions and one histological-proven benign lesion (Group-2) were selected.

The dynamic contrast enhanced study was performed using a 3D SPGR (RF-FAST) pulse sequence with 16 repetitions, 32 axial slices with 4 mm thickness to cover bilateral breasts. Enhancement % time course was measured from each lesion.Three different models were used to fit the enhancement kinetics. Model-1: modified Tofts model, the 2-compartmental pharmacokinetic model with the vascular component (3 parameters: Vp K^{trans} and k_{ep}); Model-2: standard Tofts model (2 parameters: K^{trans} and k_{ep}); and Model-3: the 3-parameter heuristic model based on the shape of the curve, SE (t) = A [1 – exp (-t / Tc)] – C t, (3 parameters: A, Tc, and C). All 8 parameters were obtained for each malignant and each benign lesion in every patient. Linear regression analysis was performed to investigate the association of fitting parameters obtained from the primary and secondary cancers in Group-1 patients. The second test compared the differences between regression equations of Group-1 (primary cancer vs. secondary cancer) and Group-2 (primary cancer vs. secondary benign lesion).

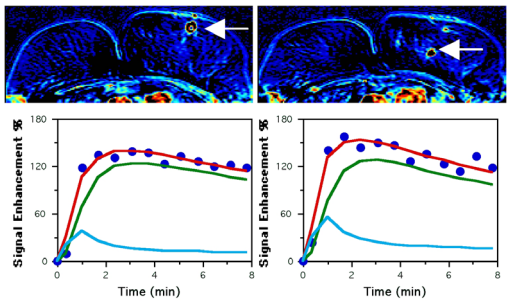

Fig. 1: Enhancement kinetics measured from the primary (left) and the secondary l cancer (right), fitted with Model-1, vascular (blue) and extravascular (green) components.

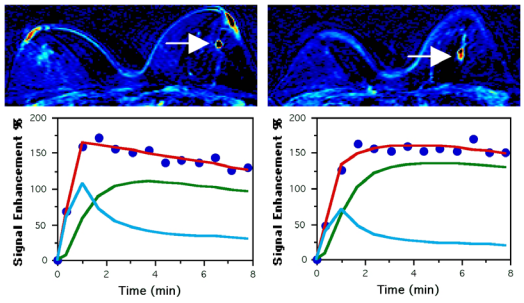

Fig. 2: One ductal cancer (left) and one benign lesion (right).

Results

Fig. 1 shows one case with two ductal cancers (1.0 and 0.8 cm), and Fig. 2 shows one case with one ductal cancer and one benign lesion (sclerosing adenosis). The fitting results using Model-1 are shown. It can be seen that in case-1 the smaller lesion had a faster up-slope, higher enhancement %, and a faster washout compared to the larger lesion. In case-2 the malignant lesion had a faster up-slope and a faster washout but with a similar enhancement % compared to the benign lesion. Fig. 3 shows the scattered plot between K^{trans}(a) and k_{ep} (b) of the secondary lesion vs. that of the primary lesion using Model-2. The blue regression line shows the correlation between 2 malignant lesions in Group-1. All 3 models could satisfactorily fit the enhancement kinetics. The slopes are close to 1, and p values < 0.0001, indicating that the primary and secondary cancers are significantly associated with each other. Since the blood kinetics were the same for each patient, the deviation from the unity line gave the range of tumor heterogeneity effects, and that was used to compare to Group-2 cases with benign lesions. The significance level (p values) in separating Group-1 and Group-2 for all 8 parameters obtained using 3 models are summarized in Table 1. In Fig.3a, a substantial overlap between K^{trans} of secondary malignant and secondary benign lesions (p = 0.19) was seen, but k_{ep} of benign lesions in Group-2 were smaller than that of malignant lesions, which was significantly different from Group-1 (p=.0001).

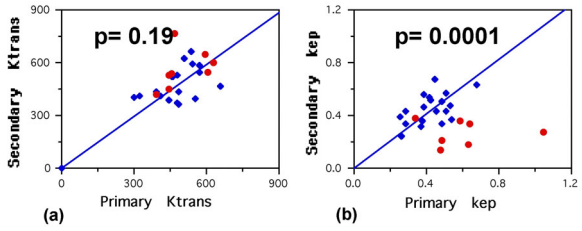

Figure 3: K^{trans}(a) and k_{ep} (b) of the secondary lesion vs. that of the primary lesion usingModel-2. Group-1with 2 malignant lesions are shown by blue, and Group-2 with one malignant and one benign lesion are shown by red. The benign lesions had a lower k_{ep}, which could be differentiated from malignant lesions, but not K^{trans}.

Table 1: Significance level in comparison between Group-1 with secondary malignant and Group-2 with secondary benign lesions

	Parameter	p
Model-1 Pharmacokinetic with Vp	Vp (A.U.)	.002*
	K^{trans} (A.U./min)	.007*
	kep (1/min)	< .0001*
Model-2 Pharmacokinetic without Vp	K^{trans} (A.U./min)	0.19
	kep (1/min)	.0001*
Model-3 3-parameter Heuristic	A (A.U.)	0.22
	Tc (min)	.005*
	C (A.U./min)	.001*

Discussion

We presented a novel analysis method to investigate the association of multiple malignant lesions under controlled hemodynamic conditions, then further to demonstrate that it may be applied to study the power of different pharmacokinetic parameters in making differential diagnosis. In comparison between Group-1 and Group-2 subjects, the washout parameter k ep in Models-1 and 2 could differentiate benign from malignant lesions with high significance, but not the magnitude parameter K^{trans} in Model-2 and the amplitude parameter A in Model-3. If analyzed appropriately the early up-slope Vp in Model-1 and Tc in Model-3 might be able to distinguish between benign and malignant lesions. When more data are available it may be possible to establish a reference database with the method described in this study, and from which to determine the likelihood of malignancy for each incidental lesion found in preoperative MRI, with reference to the primary cancer.

References [1] Bedrosian et al. *Cancer* 2003 98:468-473. [2] Rieber el al. *Br. J. Radiol.* 2002 75:789-798. [3] Schelfout et al. *Eur. J Surg. Oncol.*2004 30:501-507.

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