A tracer kinetic model with optimal compartments for assessing intravoxel tumor heterogeneity in papillary thyroid carcinoma

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Target audience: Researchers who develop tracer kinetic models to investigate quantitative imaging biomarkers in cancers.

Purpose: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has shown potential in characterizing tumor microvasculature [1]. In DCE-MRI, tracer kinetic models are currently used for quantifying tumor vascular characteristics. The Tofts' model, a simplified two compartment model that is commonly used, regards the tumor tissue as the combination of single intravascular and extravascular space with negligible plasma transit time [1]. However, at intravoxel level, tumors have complex microvascular kinetics which is heterogeneous in nature, not effectively characterized by the Tofts' model with two compartments. In this study, a tracer capillary-tissue exchange model with optimal multiple compartments (oCXM) is proposed to address the intravoxel tumor heterogeneity. The model is evaluated in papillary thyroid carcinoma (PTC).

Methods: *DCE-MRI data acquisition:* Our institutional review board approved this retrospective study. Seven patients (age: 28-66 years, M/F: 3/4) with biopsy proven PTC underwent DCE-MRI examinations before surgery. A 3D-SPGR pulse sequence with multiple flip angles (2°, 8°, 16°, 20°) was used for native T1 mapping, followed by dynamic imaging with contrast agent administration (flip angle=16°). The contrast of Gd-DTPA was delivered by antecubital vein catheters at a bolus of 0.1 mmol/kg and 2 cc/s, followed by saline flush. Other acquisition parameters were: TR = 5.3 ms, TE = 1.9 ms, phases = 50, NEX = 1, slices = 4-8, slice thickness = 4-8 mm. *Tracer kinetic modeling:* A multiple compartment exchange model which consists of a single vascular compartment (denoted by i=1) and n-1 interstitial compartments (i=2, 3, …, n) with tracer exchange between vascular and interstitial compartments was proposed (Figure 1). A partial differential equation (PDE) was used to model the exchange behavior [3]. Metrics such as $k_{1i}(k_{i1})$ (rate constants of tracer exchange), F(flow rate), and τ (transit time) were quantified by solving an inverse PDE problem. For optimal compartment determination, Bayesian Information Criterion was employed and the model with the lowest value of BIC was determined to be the optimal model ($BIC=N_b\times\ln(\chi^2/N_b)+ N_p\times\ln(N_b)$, where χ^2 is the sum of squared error (SSE) between observed and expected data, N_b is the sample size and N_p is the number of free parameters to be estimated (N_p = 2n, where n is the number of compartments, for example, N_p =6 for 3 compartments) [3]. In this study, a maximum of four compartments was used. ROIs (regions of interest) were placed on the thyroid tumor tissue in each patient. Voxel-wise analysis was performed and parametric maps were generated. *Statistical analysis:* Paired t test and Spearman correlation analysis were used to compare the parametric differences and correlation between the Toft's model and the oCXM model.

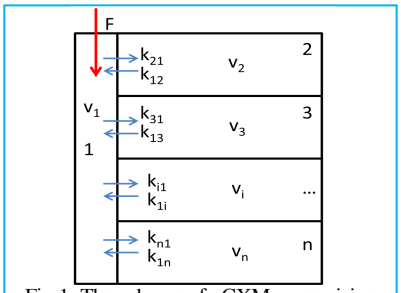

Fig.1. The schema of oCXM, comprising of a single vascular compartment (denoted by i=1) with n-1 interstitial compartments (i=2, 3, …, n); v_i denotes the volume fraction of i[th] compartment. The rate constant $k_{1i}(k_{i1})$ denotes the tracer exchange from the compartment i to the compartment 1 (vice versa). The direction of blood flow rate F is along the length of capillary.

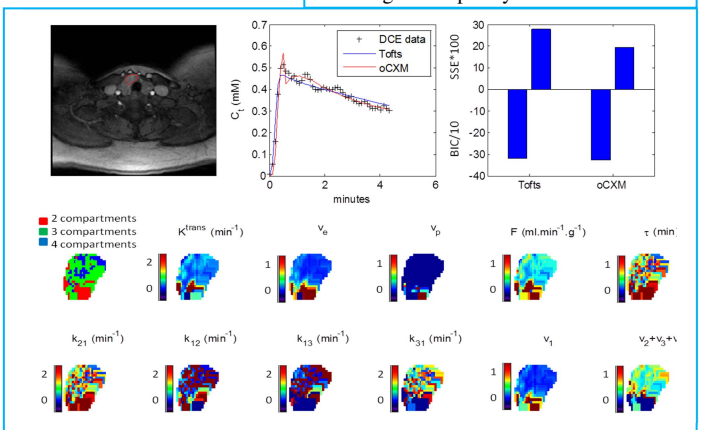

Fig.2. Model comparison of the Tofts and oCXM models with data from a representative PTC patient. Top row: from left to right, the ROI (red contour) placed on a DCE-MRI image, curve fittings based on the ROI, SSE and BIC; middle and bottom row: compartment distribution map (middle row, first on the left side) and parametric maps.

Results: The results from a representative PTC patient (female, 41 years old) are shown in Figure 2. With the averaged data from the whole tumor as an ROI, the oCXM with 3 compartments has a better fit with lower value of SSE (0.0195 vs 0.0281) and BIC (-325.6731 vs -320.6885) than the Tofts model, showing its improved characterization of the tumor tissue. The map of the compartment distribution of oCXM (Fig.2) demonstrated that based on the BIC analysis, 11% of voxels were assigned 2 compartments, 48% of voxels were assigned 3 compartments, and 41% of voxels were assigned 4 compartments. For voxel-wise modeling from 7 patients with a total of 750 voxels, 24% of the voxels (180 voxels) were assigned 2 compartments, 45% (337 voxels) were assigned 3 compartments, and 31% (232 voxels) were assigned 4 compartments. Table 1 shows the comparison of metrics between the oCXM and Tofts model in the seven PTCs. The k_{12} (k_{ep}), v_1 (v_p), and v_e (v_{2+} v_{3+} v_4) were significantly different between the two models. Correlation analysis indicated that there was a strong positive relationship between K^{trans} and F (correlation coefficient r=0.89, p<0.01).

Discussion: By using the oCXM with 7 PTC patient data, we found that most voxels (76%) exhibited multi-compartment microvascular kinetics and the contrast kinetics can be best described by regarding tumor interstitium as non-uniform space with more than one compartment, revealing tumor heterogeneity at intravoxel level in PTCs. Different values of $k_{1i}(k_{i1})$, and v_i provided by the oCXM revealed the underlying heterogenous tumor kinetics and provided a more comprehensive and potentially more realistic characterization of tumor tissues than the Tofts's model. The strong correlation between K^{trans} and F indicated that K^{trans} was mostly influenced by the flow rate in PTCs, which is consistent with findings from other investigators [4][5]. For example, Donaldson SB et al in a study of 30 patients with carcinoma of the cervix [4] found that the 2CXM provided superior fits to the data for all 30 patients (p values < 0.005), and a strong correlation (r = 0.944; P = 0.01) was found between K^{trans} and F. In this report we present results from 7 PTC patients, with a larger cohort of PTC patients currently being enrolled for assessing tumor aggressiveness in PTCs.

Conclusion: We have presented a model to characterize tumor kinetics with intravoxel heterogeneity in PTCs. Once validated, this model could provide additional imaging biomarkers for assessing tumor characteristics including tumor aggressiveness in PTCs.

References: [1] Padhani, AR et al., JMRI 2002;16(4): 407-22. [2] Koh TS, et al., IEEE on Biomedical Engineering, 2003; 50(2):159-167. [3] Lu Y et al., JMRI 2012;36(5):1088-96. [4] Donaldson SB et al Magn Reson Med. 2010;63(3):691-700. [5] Kallehauge JF et al, Acta Oncologica, 2014; 53: 1064–1072.

Table 1. Values (mean ±SD) of metrics derived from the Tofts and oCXM models in 7 PTCs.

Metrics	Tofts	oCXM	P value
F ($ml.min^{-1}.g^{-1}$)		0.44±0.24	
τ (min)		0.51±0.14	
k_{12} (k_{ep}) (min^{-1})	3.24±1.72	1.03±0.11	<0.05
k_{21} (K^{trans}) (min^{-1})	0.65±0.50	1.06±0.29	
k_{13} (min^{-1})		0.72±0.35	
k_{31} (min^{-1})		0.61±0.23	
k_{14} (min^{-1})		0.33±0.19	
k_{41} (min^{-1})		0.22±0.14	
v_1 (v_p)	0.01±0.01	0.20±0.09	<0.05
v_2		0.23±0.08	
v_3		0.14±0.07	
v_4		0.03±0.02	
v_e (v_{2+} v_{3+} v_4)	0.21±0.10	0.41±0.15	<0.05