Pharmacokinetic parameter of DCE-MRI and US-localized optical imaging in Breast cancer: According to Pathologic Biomarker

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Background and Purpose

Diffuse optical tomography (DOT) utilizes near infrared light to probe tissue optical properties. It can measure hemoglobin concentration and oxygen saturation percentage, which are related to angiogenesis known to be critical for autonomous growth and spread of breast cancer. However, the low spatial resolution of DOT has limited its clinical application. Recently, the availability of US-localized DOT (US-DOT) provides a useful complementary imaging modality for breast imaging. Dynamic contrast-enhanced magnetic resonance (DCE-MRI) is a very useful clinical imaging modality, which in addition to providing high quality breast images without limitation of breast density, can also be used to measure vascular information. DCE-MRI and US-DOT can be applied to measure tumor angiogenesis, but there were few studies for comparison between DCE-MRI and optical imaging data, as well as for their correlation with histological/molecular biomarkers. These tumor biomarkers are important for prediction of prognosis, the choice of neoadjuvant chemotherapy regimen, and the interpretation of response to chemotherapy. The correlation of imaging features with histopathologic marker will provide very helpful information for interpreting the response to therapy as well as predicting prognosis. In this study we investigated the correlation between pharmacokinetic features of DCE-MRI and parameters of US-DOT, and their association with pathologic makers of breast cancer.

Materials and Methods

Among consecutive 63 breast cancer patients who underwent US-DOT between June 2009 and August 2009, thirty-seven patients (with 38 histologically-confirmed lesions) also received diagnostic breast MRI, and they were included in this study. Using US-DOT, the total hemoglobin concentration (THC) and oxygen saturation percentage (SO_2) for each breast cancer were measured. The value of THC reflected the maximal hemoglobin concentration in a given region of interest (Fig.1 a,b). Using DCE-MRI (22 cases with 3T and 15 cases with 1.5T), contrast enhancement kinetics was measured from the manfully placed ROI encompassing the entire enhanced tumor based on color-coded enhancement map (Fig.1c). The standard Tofts model was applied to obtain K_{trans}, and k_{ep}. Histopathological results and molecular biomarkers, including tumor size, nuclear grade, histologic grade, estrogen receptor (ER), progesterone receptor (PR), HER-2, androgen receptor (AR), Ki-67 , lymphvascular invasion and axillary lymph node metastasis (LN mets), were evaluated on surgical specimen. The tumor size was determined as the maximal diameter of invasive component at the surgical pathology. The presence of systemic metastasis was assessed. Pearson correlation was employed to determine whether the optical (THC and SO2) and DCE-MRI parameters (K_{trans} and k_{ep}) were correlated each other. The lesions were separated into two dichotomized groups based on each pathologic biomarker, and the difference between the mean values of each imaging marker in the two groups was tested using the student t-tests.

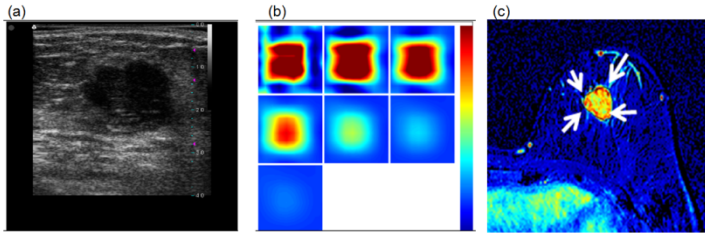
Results

The MRI parameters (K_{trans} and k_{ep}) and the optical imaging parameter (THC, SO_2) had a wide variation, possibly due to the heterogonous nature of breast cancer, and there were no consistent correlations between them (p>0.05). The mean value of these imaging parameters in the two groups with different pathologic and molecular biomarkers are listed in Table 1. For SO2, the cases with smaller tumor size and negative PR showed higher SO2 than those with larger tumor size and positive PR (p=0.03 and 0.025, respectively). THC was significantly higher in the Ki-67 positive and high histologic-grade groups than those in the Ki-67 negative and non-high histologic-grade groups (p=0.023 and 0.03, respectively). The k_{ep} was higher in ER negative than ER positive cases (p=0.01). A higher kep value indicates a higher vascular permeability, or a higher angiogenesis.

Discussion

The SO_2 in smaller tumors was higher than that in larger tumors, which could result from the more heterogeneous nature of larger tumors (Kim et al.). High Ki-67, which is a marker of high cell proliferation, is a sign of more aggressiveness and a poor prognosis; also associated with a good chance of clinical response to chemotherapy (Kumaki et al.). Histologic grade is one of three strongest prognostic determinants (LN mets, tumor size and histologic grade)(Rakha et al.). Therefore, our results suggest that breast cancers showing a high THC have poorer prognosis than those with a low THC. The more aggressive ER negative cases had a significantly higher k_{ep} than ER positive cases. Our results did not show any significant association between the MRI parameters and almost every biological factor, in consistent with Fernández-Guinea et al's study. There is no difference between THC values in HER-2 positive and HER-2 negative groups (p>0.05), in contrast to previous study by Brown et al. It could be because we used maximal total hemoglobin concentration value in the analysis, while they used the mean THC value. The lack of correlation between MRI and US-DOT was also likely coming from the sampling differences; while DCE-MRI analyzed the entire tumor, the maximal THC value was used in the statistical analysis. In conclusion, although the pharmacokinetic parameter of DCE-MRI and the US-localized optical tomography was lack of association, k_{ep} among the pharmacokinetics of DCE-MRI and the THC of US-DOT were associated with parameters indicatives of tumor aggressiveness in breast cancer.

Figure 1. DCE-MRI kinetic parameter vs. US-DOT parameter



A 56-year-old woman with invasive ductal carcinoma (a) Gray-scale ultrasound image shows a hypoechoic mass with microlobulated margins, measuring 1.8 cm in diameter (high HG, LVI (-), ER(-), PR(-), HER-2 (+), AR (+), Ki-67 (+)). (b) A reconstructed optical absorption map shows a distinct mass with high maximum THC of 293.4μmol/L. The first section (slice 1, top left) is 6×6 cm spatial x-y image (coronal plane of the body) obtained at a depth of 0.5 cm, as measured from the skin surface. The last section (slice 7, bottom left) is a 6×6 cm spatial x-y image (coronal plane of the body) obtained at a depth of 3.5 cm, as measured from the skin surface. Spacing between sections is 0.5 cm in the direction of propagation. (c) A enhancement map showed the mass marked with thin line (arrows) on the 1 min color-coded enhancement map from one of slices of DCE-MRI.

Table 1. US-DOT vs. MRI parameter : pathologic biomarkers

		SO_2		THC (ng/mL)		K trans (A.U./min)		Kep (1/min)	
		Mean	*p*	Mean	*p*	Mean	*p*	Mean	*p*
Tumor size	<2cm (n=21)	0.9991	0.026	175.46	0.513	4.4932	0.645	0.2900	0.711
	≥2cm (n=17)	0.9655		192.06		69.3718		0.2750	
LN mets	Neg (n=25)	0.9891	0.368	182.33	0.951	82.3006	0.897	0.2824	0.952
	Pos (n=13)	0.9744		183.97		4.4932		0.2849	
NG	Low (n=23)	0.9831	0.877	169.18	0.175	69.3718	0.374	0.2897	0.694
	High (n=15)	0.9855		203.90		82.3006		0.2735	
HG	Low (n=17)	0.9843	0.971	153.50	0.030	4.4932	0.606	0.2757	0.727
	High (n=21)	0.9839		206.68		69.3718		0.2894	
LVI	Neg (n=24)	0.9923	0.363	178.22	0.554	82.3006	0.535	0.2629	0.437
	Pos (n=3)	0.9655		146.14		4.4932		0.2140	
ER	Neg (n=16)	0.9886	0.616	210.23	0.059	69.3718	0.300	0.3489	0.002
	Pos (n=22)	0.9807		163.00		82.3006		0.2355	
PR	Neg (n=15)	1.0050	0.025	202.22	0.213	4.4932	0.239	0.2730	0.680
	Pos (n=23)	0.9704		170.29		69.3718		0.2900	
HER-2	Neg (n=32)	0.9895	0.095	181.57	0.810	82.3006	0.678	0.2886	0.528
	Pos (n=6)	0.9546		189.91		4.4932		0.2547	
Ki-67	Neg (n=17)	0.9833	0.794	148.50	0.023	4.4932	0.055	0.2690	0.756
	Pos (n=18)	0.9876		207.20		69.3718		0.2803	
AR	Neg (n=11)	1.0033	0.148	191.05	0.557	82.3006	0.067	0.3244	0.201
	Pos (n=25)	0.9783		174.39		16.8118		0.2677	
mets	Neg (n=37)	0.9845	0.702	182.02	0.677	36.9817	0.714	0.2756	0.012
	Pos (n=1)	0.9660		214.97		0.3676		0.5722	

Reference 1.Agrawal G, Annals of oncology 2007;18(11):1903-1904. 2.Brown JQ, Cancer research 2009;69(7):2919-2926. 3.Kim MJ, European radiology 2011;21(7):1353-1363. 4.Kumaki N, Breast cancer 2011;18(2):98-102. 5.Millar EK, British journal of cancer 2011;105(2):272-280. 6.Rakha EA, Journal of clinical oncology 2008;26(19):3153-3158. 7.Su MY, Technology in cancer research & treatment 2005;4(3):255-263. 8.Tozaki M. MRMS 2004;3(4):189-197. 9.Zhu Q, Radiology 2010;256(2):367-378. 10.Fernández-Guinea BMC cancer 2010 10(8)