SELF-ORGANIZING MAP KINETIC FEATURES AS PROGNOSTIC MARKERS FOR CLASSIFYING GENE EXPRESSION RISK FOR BREAST CANCER RECURRENCE

Majid Mahrooghy[1], Ahmed B. Ashraf[1], Dania Daye[1], Carolyn Mies[2], Mark Rosen[1], Michael Feldman[2], and Despina Kontos[1]

[1]*Department of Radiology, University of Pennsylvania, Philadelphia, PA, United States,* [2]*Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, United States*

Target Audience: Imaging scientists and clinicians interested in the value of quantitative breast DCE-MRI features in prognostic assessment.

Purpose: Breast dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is an effective modality for diagnosis, prognosis, and predictive characterization of breast tumors. Various methodologies and techniques have been developed based on DCE-MRI to provide quantitative markers for characterizing lesions[1,2,3,4]. Several studies have evaluated such biomarkers extracted from DCE-MRI for characterizing breast tumors in terms of being benign, malignant, invasive ductal carcinoma (IDC), or ductal carcinoma in situ (DCIS), having lymph node involvement, and evaluating tumor grade, and other histopathologic markers[1,2]. The most commonly used features extracted from DCE-MRI include standard kinetic, morphological, and textural descriptors[1]. Most current standard kinetic features are typically based on selected regions of the tumor (i.e., "hot-spots", etc.), which cannot fully capture the spatiotemporal patterns of the contrast agent uptake, a potential marker of intra-tumor heterogeneity [1,2]. Because each pixel of tumors has different kinetic features, we propose to cluster pixels based on pixel-wise kinetic features by using SOM, to identify tumor regions (i.e.,clusters) with high intra-tumor heterogeneity. SOM can represent multidimensional data into lower dimensional spaces (two dimensions) and using a neighborhood function, can also preserve the topological properties of the input data (i.e., here the individual pixel-wise kinetics) [5].

Methods (Fig. 1): The most representative slice of each tumor is manually segmented from the background by an expert radiologist. We then extract kinetic features such as peak enhancement (PE), Time-to-Peak (TTP), Wash-in-Slope (WIS), Washout Rate (WOS), Curve Shape Index (CSI) from each pixel[1]. We use the SOM to cluster these features (Fig. 2 shows examples of the WIS values of the clusters (left) and the number of cluster members. Fig. 3 also shows clustering examples of a high (left) and low (right) recurrence risk tumor). We then compute the entropy and variance of the cluster member numbers, the variance of the cluster kinetic features, mean and variance of weighted cluster kinetic features (obtained by multiplying the cluster member numbers with the kinetic features and normalizing to the total cluster members, from which the mean and variance are estimated), and the kinetic features of the cluster with maximum peak enhancement, extracting a total of N=26 SOM kinetic heterogeneity features. Sequential feature selection is applied to these features, and the selected features are fed to a logistic regression model for classifying tumors at low versus high risk for breast cancer recurrence as determined by the validated Oncotype DX (Genomic Health Inc.) gene expression assay[6]. ROC analysis with leave-one-out cross validation is performed to evaluate classifier performance based on different kinetic features as inputs.

Fig. 1 Block diagram of feature extraction and classification.

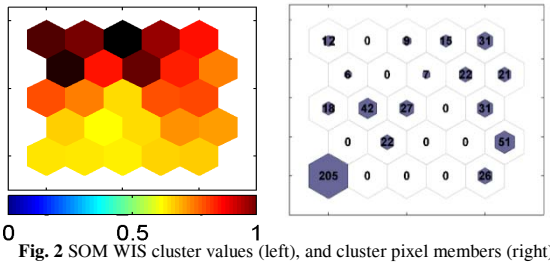

Fig. 2 SOM WIS cluster values (left), and cluster pixel members (right).

Bilateral breast DCE-MRI sagittal scans of 56 women diagnosed with primary invasive breast cancer were retrospectively analyzed. The women were imaged prone in a 1.5T scanner (GE LX echo, GE Healthcare, or Siemens Sonata, Siemens); matrix size: 512 × 512; slice thickness: 2.4-4.4 mm; flip angle: 25° or 30°. The images were collected before and after the administration of gadodiamide Omniscan) or gadobenate dimeglumine (MultiHance) contrast agents. DCE-MR images were acquired at 90 second intervals for 3 post contrast time points. All women had estrogen receptor positive (ER+) tumors, which were analyzed with the Oncotype DX gene expression assay. This assay calculates the risk of cancer recurrence by measuring the expression of 21 genes in RNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue samples[6]. The output is a continuous recurrence score that predicts the likelihood of recurrence 10 years after treatment. Here we tested our features for predicting the Oncotype DX recurrence risk categories, where we consider women with score greater than 30 as high-risk, and with less than or equal to 30 as low-risk for recurrence[6].

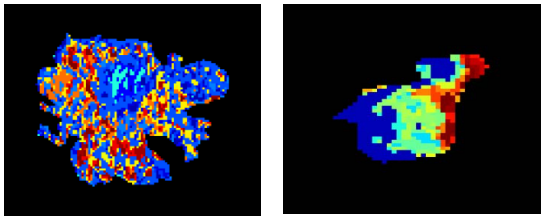

Fig. 3 SOM pixel clustering for a high-(right) and low-risk tumors.

Results and Discussion: ROC comparison of our SOM kinetic features to other previously published standard kinetic features[1] shows that our SOM features substantially outperform these standard kinetic features for recurrence risk classification (Fig. 4). The ROC AUC of the SOM kinetic features and standard features are 0.80 and 0.65, respectively. Our results also show that the feature selection technique more frequently selects WIS and the CSI kinetic features of maximum peak enhancement cluster, mean and variance of weighted WIS and CSI cluster features, and the variance of the cluster size (i.e., cluster member number) among the SOM kinetic features. This shows that capturing heterogeneity patterns based on variance of the cluster size, the mean and variance of the weighted cluster kinetic features provides valuable information for recurrence risk classification. In addition, the kinetic features of the cluster with maximum peak enhancement provide discriminatory information. The feature selection method also selects more frequently PE, WOS, and CSI for standard kinetic features.

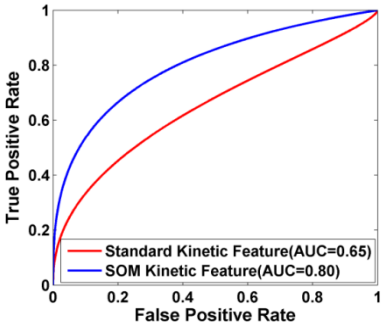

Fig.4 ROC comparison of SOM vs standard kinetices

Conclusions: DCE-MRI features based on SOM clustering of pixel-wise kinetic features can capture spatial patterns of tumor heterogeneity, providing valuable prognostic information for classifying breast cancer recurrence risk as determined by a validated gene expression assay.

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