Tumor classification using perfusion volume fractions in breast DCE-MRI

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ABSTRACT

This study was designed to classify contrast enhancement curves using both three-time-points (3TP) method and clustering approach at full-time points, and to introduce a novel evaluation method using perfusion volume fractions for differentiation of malignant and benign lesions. DCE-MRI was applied to 24 lesions (12 malignant, 12 benign). After region growing segmentation for each lesion, hole-filling and 3D morphological erosion and dilation were performed for extracting final lesion volume. 3TP method and k-means clustering at full-time points were applied for classifying kinetic curves into six classes. Intratumoral volume fraction for each class was calculated. ROC and linear discriminant analyses were performed with distributions of the volume fractions for each class, pairwise and whole classes, respectively. The best performance in each class showed accuracy (ACC), 84.7% (sensitivity (SE), 100%; specificity (SP), 66.7% to a single class) to 3TP method, whereas ACC, 73.6% (SE, 41.7%; SP, 100% to a single class) to k-means clustering. The best performance in pairwise classes showed ACC, 75% (SE, 83.3%; SP, 66.7% to four class pairs and SE, 58.3%; SP, 91.7% to a single class pair) to 3TP method and ACC, 75% (SE, 75%; SP, 75% to a single class pair and SE, 66.7%; SP, 83.3% to three class pairs) to k-means clustering. The performance in whole classes showed ACC, 75% (SE, 83.3%; SP, 66.7%) to 3TP method and ACC, 75% (SE, 91.7%; 58.3%) to k-means clustering. The results indicate that tumor classification using perfusion volume fractions is helpful in selecting meaningful kinetic patterns for differentiation of malignant and benign lesions, and that two different classification methods are complementary to each other.

Keywords: Breast MRI, perfusion volume fraction, 3TP method, k-means clustering, tumor classification

1. INTRODUCTION

Dynamic contrast-enhanced (DCE) breast MRI is being used for detection, diagnosis, and staging of breast cancer, especially for women at high risk [1-4]. DCE-MRI is useful for determining the biological properties of a tumor because contrast enhancement features are representative of histological features of the tumor [5-7].

The advantages of DCE-MRI originate from the observation that the quantitative time courses of MR imaging signal intensity appear to be capable of enabling differentiation of malignant and benign lesions [8]. Thus, signal-intensity time course after injection of contrast agent was determined to evaluate the perfusion characteristics of enhancing breast lesions. Breast MR acquisitions consist of a pre-contrast baseline scan followed by several post-contrast series at multiple time points.

Computer-aided diagnosis (CAD) algorithms have focused the morphological information, but CAD for breast MR can use an entirely new class of temporal features. This study was attempted to examine a single temporal feature, a time versus percent enhancement curve.

Several studies have reported a marked difference between the slope of enhancement uptake of malignant and benign lesions: malignant lesions enhance earlier and greater than benign lesions [9]. Kuhl et al have showed that use of curve shape (washout, plateau, or persistent enhancement) based on three-time-points (3TP) method, which generates a colormap allowing pixel-by-pixel kinetic analysis from the intensity values measured at three judiciously chosen time points: the pre-contrast time plus two post-contrast times, can distinguish malignant lesions from benign [10], [11]. Curves that exhibited a washout type behavior after initial enhancement had an 87% probability of being malignant,
whereas curves that exhibited persistent only showed a 6% likelihood of being malignant. Washout behavior of lesions has also been shown to be correlated with tumor angiogenesis and vascular permeability [12]. However, other many investigators have found that there was a considerable overlap in the range of enhancement rates of malignant and benign lesions [13-17].

The 3TP method does not consider enhancement curves at full time points. In addition, the enhancement pattern varies according the imaging protocol and all of the first post contrast series of malignant tumors with wash-out behavior in late phase do not show the peak contrast enhancement. Thus, we additionally applied a clustering method as the model-free approach that use full time points of an enhancement curve.

Until now, many investigators have reported mostly the findings on kinetics with existence of washout behavior within a lesion for differentiation of malignant and benign lesions, depending on the user-specific ROIs. This study introduces a novel approach of semi-automatic segmentation procedure and tumor classification using perfusion volume fractions of curve types assigned by the 3TP method and k-means clustering in order to characterize the vascularity of a lesion volume. This trial is based on hypothesis that there are some critical perfusion volume fractions for differentiation of malignant and benign lesions. The purpose of this study is to classify contrast enhancement curves of a lesion using the 3TP method and the k-means clustering and to comparatively examine meaningful enhancement patterns having improved accuracy in differentiation of malignant and benign lesions using perfusion volume fractions.

2. MATERIALS AND METHODS

2.1 Materials and protocol

DCE-MRI was applied to surgically proven 24 lesions (12 malignant, 12 benign) using 1.5 T Sonata (Siemens, Erlangen, Germany). First, the pre-contrast T1 weighted 3D fast low angle shot (FLASH) sagittal image (TR 4.9 ms, TE 1.83 ms, FA 12°, FOV 170 mm, matrix 448×448, acquisition time 84 sec, slice thickness 1-1.4 mm without gap) was obtained with fat suppression and next four consecutive post-contrast images using the same condition after an injection of 0.1 mmol/kg Gd-DTPA (Magnevist, Schering, Berlin, Germany). The contrast material was administered manually at a flow rate of 2 ml/s for 5 s and imaging was performed within 15 sec after injecting the contrast agent.

2.2 Image registration and segmentation

Before selection of enhancement curves, all image series were aligned using 3D rigid registration algorithm based on open source Insight segmentation and Registration Toolkit (ITK). The reference dataset was set to pre-contrast series. A maximum intensity volume image among all registered time series was made in order to use as the reference image for segmentation of lesion volume. After connected threshold region growing segmentation for each lesion, hole-filling and 3D morphological erosion and dilation were performed for extracting final lesion volume. The segmentation volumes were not significantly different from the radiologist’s tumor VOIs.

2.3 3TP method

The enhancement rate was defined by the intensity difference in the first two time points (the wash-in phase) and by the change in enhancement between the second and third time points (the wash-out phase). Suspicious areas were based on the enhancement properties of the tissue. The percent enhancement (PE),

\[ PE = \frac{s1 - pre}{pre} \]  

was calculated for each voxel of the segmented lesion volumes. The voxel passing an uptake threshold PE, 50% was included for further analysis. The first post contrast series was selected s1. The signal enhancement ratio (SER),

\[ SER = \frac{s1 - pre}{s2 - pre} \]  

was for all voxels that pass both the uptake and the difference threshold. The fourth post contrast series was selected s2. The SER measures the temporal kinetics at the end of dynamic series; voxels can be classified into washout, plateau or persistent enhancement curve types (Figure 1).
2.4 K-means clustering

The k-means clustering algorithm is a popular method used to divide \( n \) patterns \( X=\{x_1, \ldots, x_n\} \) in \( d \) dimensional space into \( k \) clusters. The result is a set of \( k \) centers, each of which is located at the centroid of the partitioned dataset. In this study, enhancement patterns at full time points were classified into 6 classes by \( k \)-means clustering and cluster validation technique using within-class scatter and between-class scatter indices was applied for optimal separation at a given number of clusters and iterations. This algorithm was performed in the following steps (Figure 2) and notations used in this algorithm are given at Table 1.

1) The numbers of cluster \( k \) (\( k=6 \)) and iteration (=100) were chosen and contrast enhancement curves of PE\( \geq 50\% \) from the dynamic dataset of all patients was inputted. The initial candidates for the \( k \) cluster centers were randomly selected from the dataset.
2) Each pattern was assigned to the nearest cluster using a vector distance measure. For each pattern, the membership function was calculated in each cluster. The membership function defined the proportion of a pattern that belongs to a cluster. The \( k \)-means algorithm used a hard membership function which assigns each kinetic curve to a single cluster. 

3) The centroids (centers) of these \( k \) clusters were recalculated to find new cluster centers and the sum of the square errors between a centroid and its membership kinetic curves in each cluster was calculated. 

\[
\nu_j = \frac{\sum_{i=1}^{n} m(C_j | x_i) x_i}{\sum_{i=1}^{n} m(C_j | x_i)} \quad \text{for } j = 1, \ldots, k 
\]

\[
E = \sum_{j=1}^{k} \sum_{x_i \in C_j} || x_i - \nu_j ||^2 
\]

4) If a centroid had no membership pattern, the candidate of the center from the dataset until all centroids included more than a single membership pattern. Step 2 and 3 were repeated until it converged. In this study, the convergence criterion was where there was no more reassignment of patterns to new clusters when the change of the sum of square errors \( (E) \) fell under a threshold. 

5) Cluster validation index (CVI) was calculated in order to obtain optimal partitions of clusters as the ratio of inter-class scatter to intra-class scatter as the following our proposed expressions. 

\[
S_b = \sum_{j=1}^{k} P_j \sqrt{|| x_{NN}^{(j)} - x_{NN}^{(r \neq j)} ||^2} 
\]

\[
S_w = \sum_{j=1}^{k} P_j \sum_{x_i \in C_j} \sqrt{|| x_i - \nu_j ||^2} 
\]

\[
CVI = \frac{S_b}{S_w} 
\]
2.5 Volume measurement
Each lesion volume was calculated by voxel counting of the segmentation outcome. Intratumoral perfusion volume fractions of the classes assigned by the 3TP method and k-means clustering were computed in lesion volume, respectively.

2.6 Receiver operating characteristic (ROC) and linear discriminant analysis
ROC analysis was performed using perfusion volume fractions for each class in MedCalc statistical software version 8.2.1.0 (Belgium) in order to evaluate the performance for differentiation of malignant and benign lesions. Linear discriminant analysis was performed with the multi-dimensional distributions of perfusion volume fractions for pairwise and whole classes, respectively. The best performances to each class and pairwise classes were determined. The performances to two different classification methods and three different analyses were compared with one another.

2.7 Color map visualization
The voxels corresponding to the position of contrast enhancement curves assigned by each classification criterion were highlighted with different colors, which were assigned by classification scheme of 3TP method and by the magnitude of the initial enhancement in k-means cluster centroids.

3. RESULTS
The result from k-means clustering classified diverse enhancement curves into six reference patterns (or centroids), which reflect the cluster centers of real world enhancement curves within malignant and benign lesions (Figure 3).

![Fig. 3. (a) Part of the enhancement curves from our dataset (100 curves) and (b) k-means cluster centroids (k=6)](image)

The volume crop map of classification results was shown within a lesion volume by different colors reflecting each reference pattern. Homogeneity or heterogeneity of the contrast enhancement patterns within the lesion volume were able to be visually identified, and anatomic lesion volume and perfusion volume fraction for each color confirmed (Figure 4). The color maps by the 3TP method reflected well the diagnostic criteria in which malignant lesions have relatively more distinct rim enhancement with washout behavior and more heterogeneous textures than benign lesions. On the other hand, the color maps by k-means clustering did not perfectly reflect the existing diagnostic criteria on lesion kinetics, because k-means clustering in this study can classify the reference patterns of enhancement curves at full-time points in the real world but the reference patterns may converge to plateau patterns in some cases by average effect between washout curves and persistently increasing curves assigned into their same reference pattern by similar distance if the number of clusters is small compared with diversity of input patterns. However, in terms of the discrimination of malignant and benign lesions, it cannot be concluded that the k-means clustering using perfusion volume fractions is inferior to the 3TP method, because the k-means clustering does not adopt the pre-defined threshold of curves unlike the 3TP method for each lesion and may extract unknown meaningful reference patterns in diverse enhancement curves by
model-free method without prior knowledge and assumption about the underlying physiological process. In addition, in this study, the disadvantage of the \( k \)-means clustering sensitive to initial centroids was able to be reduced by applying the optimal separation criterion of the cluster validation index which is calculated with the ratio of inter-class scatter to intra-class scatter in the given number of clusters.

Fig. 4. Crop maps of tumor volumes, and anatomic lesion volume and perfusion volume fractions of colors assigned by 3TP method and \( k \)-means clustering within (a) malignant and (b) benign lesions.

Table 2 shows the results of ROC analysis for lesion classification in each class of 3TP method and \( k \)-means clustering. The class 1 (moderate uptake and washout; \( 50\% \leq \text{PE} < 100\% \) and \( \text{SER} > 1.1 \)) showed the best performance (ACC, 84.7%; sensitivity (SE), 100%; specificity (SP), 66.7%) to 3TP method based on accuracy (ACC) and class 4.
(ACC, 73.6%; SE, 41.7%; SP, 100%) to k-means clustering. Table 3 shows the results of linear discriminant analysis in pairwise classes of the 3TP method and the k-means clustering. The multiple class pairs of class 1 and 5 (ACC, 75%; SE, 83.3%; SP, 66.7%), class 2 and 5 (ACC, 75%; SE, 83.3%; SP, 66.7%), class 3 and 6 (ACC, 75%; SE, 83.3%; SP, 66.7%), class 4 and 5 (ACC, 75%; SE, 83.3%; SP, 66.7%) and class 4 and 6 (ACC, 75%; SE, 58.3%; SP, 91.7%) showed the best performance to the 3TP method, and class 1 and 3 (ACC, 75%; SE, 66.7%; SP, 83.3%), class 3 and 4 (ACC, 75%; SE, 75%; SP, 75%), class 3 and 5 (ACC, 75%; SE, 66.7%; SP, 83.3%) and class 3 and 6 (ACC, 75%; SE, 66.7%; SP, 83.3%) to the k-means clustering. Figure 5 shows the matrix scatter plots with distributions of perfusion volume fractions within malignant and benign lesions for each class pair. Table 4 shows the results of linear discriminant analysis in whole classes of the 3TP method and the k-means clustering. The performances were similar each other in the two different methods (ACC, 75%; SE, 83.3%; SP, 66.7% to the 3TP method and ACC, 75%; SE, 91.7%; SP, 58.3% to the k-means clustering).

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Fig. 5. The matrix scatter plots with distributions of perfusion volume fractions between malignant and benign lesions for each class pair; (a) 3TP method and (b) k-means clustering
This study provides new insight which is able to examine volumetric distributions of contrast enhancement curves within a lesion. Many investigators have reported the diagnostic efficacy of pattern evaluation of signal intensity time curves, but they only analyzed distribution of curve types based on user-specific ROIs [11], [18], [19]. On the other hand, our study uses the volume fraction of each curve type on a voxel-by-voxel basis. In addition, current commercial softwares do not still give an acceptable solution for lesion segmentation on breast DCE-MRI and they are designed to perform only simple curve thresholding or ROI decision by user for extraction of suspicious regions. The appropriate selection of initial lesion segmentation method is important for obtaining accurate perfusion volume fractions because the perfusion volume fraction of each reference pattern can be over- or underestimated, depending on segmentation method. In this study, the selection of threshold value in the process of connected threshold region segmentation is an essential factor for obtaining appropriate lesion volume because final lesion volume depends on initial suspicious regions extracted by the selection of the threshold value. Now we are developing the automatic thresholding method of the suspicious regions without user selection of threshold value.

The performances on tumor classification using perfusion volume fractions in this study were not high compared to other studies, but a radiologist’s diagnosis with CAD were not additionally performed. Probably our classification scheme using perfusion volume fractions may have the possibility to surpass existing experimental results and improve the efficacy of radiologists’ diagnosis. In addition, our results suggest that the performance for tumor classification can be different according to the selection of perfusion volume fractions. It is necessary to demonstrate the usefulness of perfusion volume fractions after collecting more patient data with appropriate scheme of lesion segmentation in order to extract and select meaningful enhancement curve patterns. On the other hand, the overall performances between the 3TP method and the \( k \)-means clustering were mainly similar each other, and ACC, SE and SP of individual curve types were divers. This implies that \( k \)-means clustering can provide supplementary information with 3TP method for tumor classification.

### 4. CONCLUSION

The results in this study indicate that tumor classification using perfusion volume fractions is helpful in selecting meaningful contrast enhancement patterns for differentiation of malignant and benign lesions, and that the performances of 3TP method and \( k \)-means clustering are complementary to each other.

### REFERENCES


