

Original Article

# Discrimination of Benign and Malignant Suspicious Breast Tumors Based on Semi-Quantitative DCE-MRI Parameters Employing Support Vector Machine

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## ABSTRACT

**Purpose-** Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is an effective tool for detection and characterization of breast lesions. Qualitative assessment of suspicious breast DCE-MRI is problematic and operator dependent. The purpose of this study is to evaluate diagnostic efficacy of the representative characteristic parameters, extracted from kinetic curves of DCE-MRI, for discrimination between benign from malignant suspicious breast tumors.

**Methods-** Pre-operative DCE-MR images of twenty-six histopathological approved breast lesions were analyzed. The images were reviewed by an expert radiologist and the regions of interests (ROI)s were selected on the most solid part of the lesion. Semi-quantitative kinetic parameters, namely: maximum signal enhancement ( $SI_{max}$ ), initial area under the curve ( $IAUC_{60}$ ), time to peak (TTP), wash in rate (WIR), wash out rate (WOR) and signal enhancement ratio (SER), were calculated within each ROI. Mean values of the calculated features among benign and malignant groups were compared using student's t-test. Finally, a classification was performed employing support vector machines (SVM) using each of the parameters and their combinations in order to investigate the efficacy of the parameters in distinguishing between benign from malignant tumors.

**Results-** The performance of the classification procedure employing the combination of semi-quantitative features with ( $p$ -value < 0.001) was evaluated by means of several measures, including accuracy, sensitivity, specificity, positive predictive value and negative predictive value which returned amounts of 97.5%, 96.49%, 100%, 100% and 95.61% respectively.

**Conclusion-** In conclusion, semi-quantitative analysis of the characteristic kinetic curves of suspicious breast lesions derived from SVM classifier provides an effective lesion classification in breast DCE-MR images.

## 1. Introduction

Breast cancer is one of the leading causes of cancer death among women worldwide. Mammography is currently the proven standard of care for breast cancer screening, and has shown to decrease breast cancer mortality by

30% [1]. However, sensitivity of mammography is rather low in women of younger ages with dense breast tissue and those who carry BRCA1 or BRCA2 gene mutations. This has led the researchers of this field to search for alternative methods of screening in women at a high-risk of breast cancer [2-5]. MRI is increasingly being used in the clinical

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setting as an adjunct to x-ray mammography and sonography. Some suspicious breast lesions may only be observable on MRI [4]. This is in light of the fact that MRI is highly sensitive to invasive cancers and multifocal diseases. This high sensitivity is dependent upon neo-angiogenesis of malignant tumors. An overlap in the imaging appearance of benign and malignant tumors observed on dynamic contrast enhanced (DCE-) MRI can impose the requirement for further biopsies [6]. Qualitative assessment of breast enhancement in DCE-MRI is greatly operator dependent and is not considered an objective approach for diagnosis or therapy response assessment [7]. Breast lesions enhancement assessment by quantifying diagnostic features from time-intensity curves (TIC)s in DCE-MRI augments new elements such as internal enhancement characteristics and kinetic information to this assessment. This information can be helpful in the diagnosis between benignity from malignancy, and in the improvement of the overall sensitivity and specificity of the breast cancer diagnosis [8]. In time-intensity curve analysis, which is commonly used in clinical settings, malignant lesions typically show early enhancement with rapid wash-out, whereas benign lesions show a slow increase followed by persistent enhancement [9]. There is still a high rate of suspicious MR imaging lesions that yields a benign diagnosis at pathology. Recently, attempts have been made to automatically classify breast lesions employing different features derived from kinetic curves of DCE-MRI [10-13]. Nonetheless, there is still a debate in the literature regarding the interpretation strategies and the relative importance of different dynamic features in differentiation between benign from malignant lesions, especially in suspicious lesions. The improved sensitivity of MRI over conventional imaging and clinical examination allows more accurate delineation of tumor extent, but its low specificity in characterizing suspicious lesions would result in additional biopsy procedures: lesions with suspicious features on MR imaging should be confirmed with pathology results, which imposes additional costs and patient anxiety. It still remains a matter of investigation whether kinetic features would lead to decrease false-positive reading of suspicious breast lesions. The aim of our study is to evaluate the efficacy of semi-quantitative parameters for the classification of suspicious breast cancer lesions through an automated classification scheme.

## 2. Materials and Methods

### 2.1. Patients

In this study, quantification and analysis of dynamic contrast-enhanced breast MRI were performed prospectively on 32 histopathologically confirmed breast lesions (17 malignant and 15 benign), from 26 patients with suspicious breast tumors (age range: 28-67, mean age: 52). Database was provided by the Breast-Diagnosis database of The Cancer Imaging Archive (TCIA) [14].

### 2.2. Data Acquisition

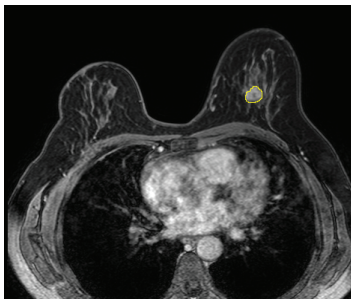
DCE-MR images of the patients diagnosed with breast cancer were acquired on a 1.5T MR scanner (Philips Medical Systems) using a 3D fast spoiled gradient-echo sequence with TE/TR= 3.5/7.1, flip angle= 12°, image matrix= 512×512, slice thickness= 4 mm without gap, field of view= 24×24 to 30×30 cm<sup>2</sup>, number of measurements= 8 at 100 sec/volume. The acquisition was performed before and immediately after the injection of 0.2 mL/kg of Gadolinium followed by the injection of 20 cc normal saline solution with 3 mL/min injection rate.

### 2.3. Preprocessing

Proper registration of dynamic images acquired at different time-points is essential for deriving accurate diagnostic information from semi-quantitative and quantitative analysis of DCE-MRI data. In DCE-MRI, breast motion artifacts are caused by the respiratory motion, relaxation of the muscles or involuntary patient motion during the imaging session [15], which invalidates the assumption of spatially-fixed region-of-interest during passage of the contrast agent [16]. DCE-MRI images registration is challenging due to a contrast change between post contrast and pre contrast images. Group-wise registration frameworks used to address this problem [17]. The proposed group-wise image registration framework consists of the following steps: [1] The first pre-contrast image in the sequence is used as the reference image and the average of the group of post-contrast images acquired after injection is aligned with the reference image; [2] The aligned image of the previous step is used as the reference image and consequent images are aligned with this image. Non-rigid registration is performed using MI similarity measure along with free-form deformation (FFD) B-spline transformation and gradient descent optimization technique.

## 2.4. ROI Segmentation

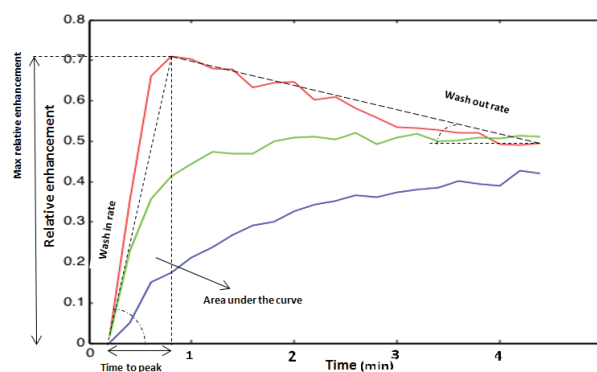
Morphological images (Turbo spin-echo T2- and T1-weighted) and functional fat-suppressed DCE-MR images were reviewed by an expert radiologist in a slice-by-slice fashion and regions of interest (ROI) s were manually placed within the breast lesions (Figure 1). For each patient, all the slices including the lesions were used in the analysis. Segmentation was performed using ImageJ software [18].



**Figure 1.** Manually segmented region of interest (ROI) on one of the patients.

## 2.5. Signal intensity-time curve analysis

The signal intensity values of the datasets at consequent time-steps were normalized to the pre-contrast signal intensity, and relative enhancement is calculated according to the following equation:  $(SI_{pre} - SI_{post}) / SI_{pre}$ , where  $SI_{pre}$  is the signal intensity in the pre-contrast image, while  $SI_{post}$  is the signal intensity in the post-contrast image [19, 20]. Based on relative enhancement signal intensity-time curves of the tumors, semi-quantitative features were extracted (Figure 2). Commonly-used kinetic parameters in DCE-MRI context, namely initial enhancement rate, maximal enhancement rate and amplitude, as well as enhancement rate at various time-points were calculated for each ROI [12]; as indicated in Table 1.



**Figure 2.** Typical relative time intensity curve of three different type of breast tumor.

**Table 1.** Description of semi-quantitative parameters.

Parameter	Description
$SI_{max}$	Total percentage intensity enhancement of tumor to that of normal tissue
$IAUC_{60}$	Initial area under the time-intensity curve during the first 60 seconds of the bolus passage
TTP	Time-to-Peak: the time to the maximum absolute enhancement
WIR	Wash-in-Rate
WOR	Wash-out-rate
SER	Signal enhancement ratio = $\frac{RE_1 - RE_0}{RE_8 - RE_0}$

## 2.6. Classification

The calculated semi-quantitative parameters were assessed individually and in the combined form for their potential in classifying benign and malignant tumors into the corresponding groups. To do so, an automated classification technique, namely support vector machine (SVM) was exploited. This classification method is among the most useful supervised pattern classification techniques due to its flexibility in tuning to the data by varying few parameters [21]. The basic idea is to find a hyper-plane which perfectly separates  $d$ -dimensional data into its two classes and to orient it in such a way to keep it at the maximum distance from the nearest data-points. These data-points which appear closest to the hyper-plane are known as “support vectors”. Since the example data are often not linearly separable, SVMs introduce the notion of a “kernel induced feature space” which casts the data into a higher-dimensional space where the data is separable. In this study, the SVM classifier is used to automatically recognize malignant from benign tumors. The classification algorithm was implemented using MATLAB v.13.0; MathWorks, Inc. The performance of the designed classifier was assessed using leave-one-out cross-validation method.

## 2.7. Statistical Analysis

An unpaired student's t-test was used to analyze the parameters associated with benign from malignant lesions. A  $p$ -value of less than 0.001 was considered

to be statistically significant. The extracted parameters from the time-intensity curve analysis were individually tested by one-sample Kolmogorov–Smirnov test. Several evaluation measures, such as accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used to evaluate diagnostic performance of the classification schemes.

### 3. Results

Our experiments were conducted using a database of 38 pathologically proven breast tumors (15 benign and 23 malignant). Mean value, standard deviation and  $p$ -values of student's  $t$ -test for semi-quantitative parameters were calculated. Benign tumors showed lower values in maximum relative signal intensity ( $SI_{max}$ ) in comparison with malignant tumors ( $0.23 \pm 0.12$  vs.  $0.74 \pm 0.11$ ) ( $p < 0.001$ ) and lower in the area under the curve ( $IAUC_{60}$ ) ( $0.06 \pm 0.11$  vs.  $0.82 \pm 0.87$ ) ( $p < 0.001$ ). For benign tumors, longer time elapses to reach the peak of relative time intensity curve (TTP) ( $605.85(s)$  vs.  $496(s)$ ) ( $p = 0.03$ ). Malignant tumors showed faster wash-in-rate (WIR) ( $0.4 \pm 0.3$  vs.  $0.22 \pm 0.31$ ) ( $p = 0.01$ ), faster wash-out-rate (WOR) ( $0.03 \pm 0.03$  vs.  $0.002 \pm 0.003$ ) ( $p < 0.001$ ) and higher signal enhancement ratio (SER) ( $0.02 \pm 0.02$  vs.  $0.003 \pm 0.002$ ) ( $p < 0.001$ ), in comparison with benign tumors. Figure 3 illustrates box and whisker plots of these different features. Evidently,  $SI_{max}$  and  $IAUC_{60}$  show no overlaps among benign and malignant groups. Benign and malignant tumors indicated a little overlap in WOR and SER features. The combined features with  $p$ -value  $< 0.001$  were considered for the classification of benign and malignant tumors. We assigned 70% of the data as the training group and the remaining 30% was used to train the SVM classifier. A non-linear SVM with a polynomial kernel was exploited as the classifier. The performance of the classification capability of each parameter set in diagnosing between benign from malignant breast cancers was evaluated by several objective indices; the results are summarized in Table 2. Our results suggest that a combination of all parametric features with low  $p$ -values could act as an accurate classifier to discriminate malignancy from benignity in suspicious breast lesions. Using a combination of  $SI_{max}$ , AUC, WOR and SER, evaluation of the SVM for classifying malignancies results in an accuracy of 97.5%; sensitivity of 96.49%;

specificity of 100%; positive predictive value of 100%; and negative predictive value of 95.61%.

### 4. Discussions

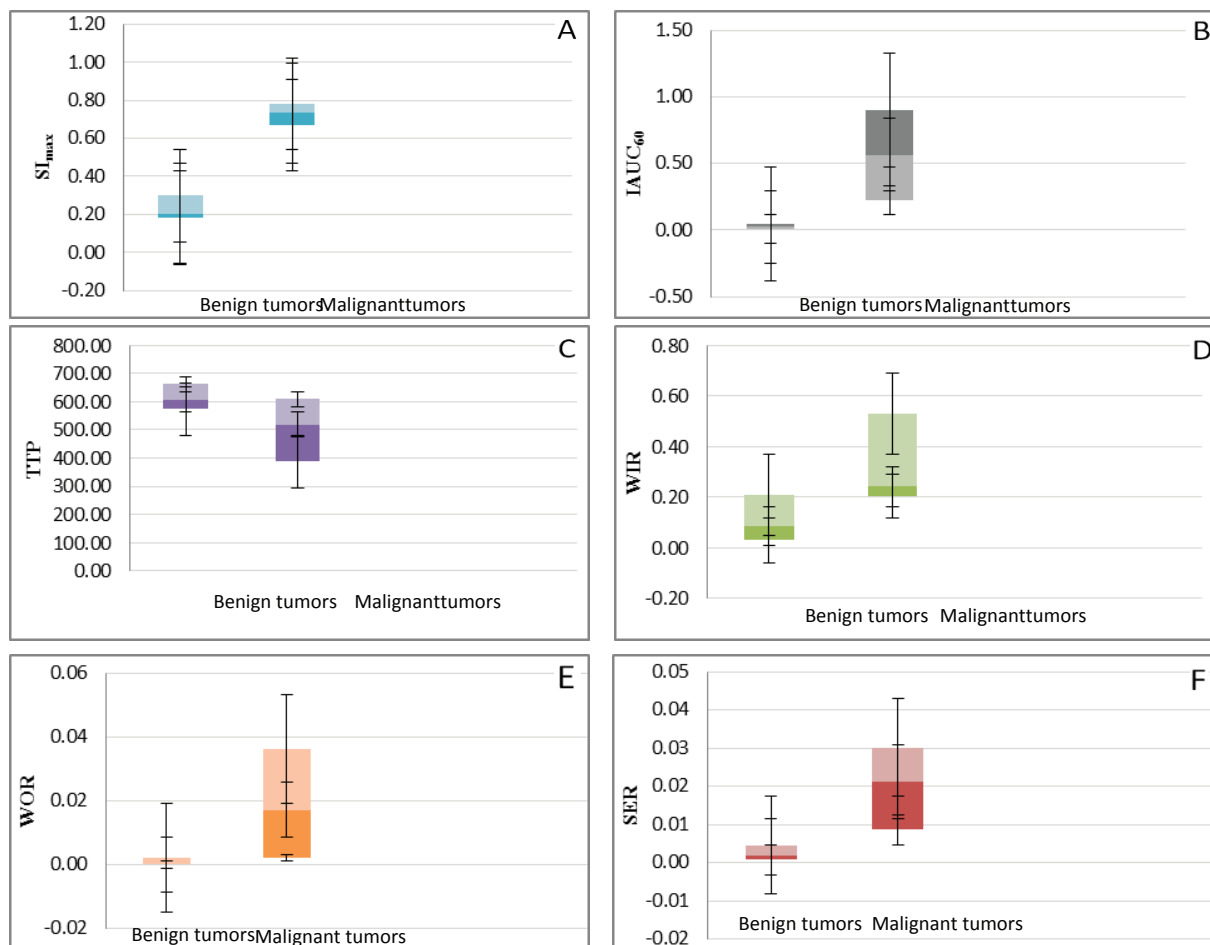
Dynamic contrast enhanced (DCE-) MRI is a relatively new technique in clinical applications, with high sensitivity for detecting breast lesions that appear with suspicious features on mammography, sonography, and clinical breast examination [22]. DCE-MRI provides kinetic information about the contrast enhancement behavior, related to the changes of signal intensity of MR images over time due to the propagation of contrast agent throughout vasculature of the tumor [23]. According to former studies, attempts have been made to automatically classify breast lesions in terms of dynamic contrast enhancement features [13]. Nonetheless, few investigations have been made to explore the role of semi-quantitative parameters in the discrimination of suspicious breast lesions [24].

In this paper, we presented a classification scheme based on support vector machine (SVM) using semi-quantitative features extracted from signal intensity-time curves, and for classifying suspicious breast lesions in DCE-MR images. Results showed distinct differences between extracted kinetic features of malignant versus benign lesions. There were significantly higher values of maximum relative signal intensity ( $SI_{max}$ ), area under the curve ( $IAUC_{60}$ ), wash-out-rate (WOR) and signal enhancement ratio (SER) in malignant tumors. This suggests that the proposed parameters can be used as potential indicators for differentiating between benign from malignant suspicious breast tumors. Our classification method showed an acceptable performance in classifying suspicious lesions in DCE-MRI of the breast with accuracy of 97.5%; sensitivity of 96.49%; and specificity of 100%.

There were some limitations in this study as follows: first, the technique requires an operator to select the tumorous areas, which makes the method semi-automatic. Second, the sample size was small; therefore, it included patients with different breast tumor subtypes when such low number of patient population was not sufficient to perform further analysis on the tumor type within each subgroup.

Our study shows that an effective combination of semi-quantitative DCE-MRI parameters in an SVM classification scheme could improve the diagnostic performance of suspicious breast lesions with acceptable accuracy.





**Figure 3.** Box-plots-and-whisker diagrams of semi-quantitative parameters after the injection of the contrast agent, for malignant and benign suspicious breast cancers. The box represents the values from lower to upper quartile and the central line is representative of the median. The whiskers are expanded from lower to upper values. (A) Maximum signal enhancement, (B) Initial area under the curve, (C) Time to peak, (D) Wash in rate, (E) Wash out rate and (F) Signal enhancement ratio.

**Table 2.** The amounts of objective indices, namely sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) for evaluating the capability of each parameter in classifying benign from malignant suspicious breast cancers.

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
$SI_{max}$	84	85	86	68	82
$IAUC_{60}$	86	79	83	61	86
WOR	87	85	87	84	91
SER	72	83	84	67	79
Combination of four feature	96.49	100	97.5	100	95.61

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