REVIEW ARTICLE

Computer-aided Diagnosis in Breast Ultrasound

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Cancer remains a leading cause of death in Taiwan, and the prevalence of breast cancer has increased in recent years. The early detection and diagnosis of breast cancer is the key to ensuring prompt treatment and a reduced death rate. Mammography and ultrasound (US) are the main imaging techniques used in the detection of breast cancer. The heterogeneity of breast cancers leads to an overlap in benign and malignant ultrasonography images, and US examinations are also operator dependent. Recently, computer-aided diagnosis (CAD) has become a major research topic in medical imaging and diagnosis. Technical advances such as tissue harmonic imaging, compound imaging, split screen imaging and extended field-of-view imaging, Doppler US, the use of intravenous contrast agents, elastography, and CAD systems have expanded the clinical application of breast US. Breast US CAD can be an efficient computerized model to provide a second opinion and avoid interobserver variation. Various breast US CAD systems have been developed using techniques which combine image texture extraction and a decision-making algorithm. However, the textural analysis is system dependent and can only be performed well using one specific US system. Recently, several researchers have demonstrated the use of such CAD systems with various US machines mainly for preprocessing techniques designed to homogenize textural features between systems. Morphology-based CAD systems used for the diagnosis of solid breast tumors have the advantage of being nearly independent of either the settings of US systems or different US machines. Future research on CAD systems should include pathologically specific tissue-related and hormone-related conjecture, which could be applied to picture archiving and communication systems or teleradiology.

KEY WORDS — breast, computer-aided diagnosis, ultrasound

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Introduction

Cancer remains a leading cause of death in Taiwan, and the prevalence of breast cancer has increased in recent years. The early detection and diagnosis of breast cancer is the key to ensuring prompt treatment and a reduced death rate. It is widely accepted that breast cancer is detected and diagnosed by a combination of physical examinations, imaging, and biopsy [1]. Mammography and ultrasound (US) are the main imaging techniques used in the detection of breast cancer. However, some patients with palpable breast cancers have normal or benign findings on both mammography and ultrasonography [2]. Physicians usually perform a biopsy to confirm breast lesions. However, biopsy is an invasive procedure and can result in both a physical and psychologic impact on the patient. Technical advances in breast imaging have been developed to avoid unnecessary biopsy and diminish the number of missed tumors.

Early attempts at computerization of medical images were made in the 1960s [3–5]. Recently, computer-aided diagnosis (CAD) has become a major research topic in medical imaging and diagnosis [6]. CAD is a diagnostic aid that takes into account equally the role of the physician and the benefits of computer systems. With the use of a CAD system in mammography, the physician can incorporate the quantitative analysis of mammograms into the diagnostic process. Doi et al [7] reviewed the detection programs used to analyze digitized mammograms and identify suspicious areas, and showed promising initial results with their database. A multi-institutional trial by Brem et al [8] claimed that the use of a computer-aided detection system significantly improved the detection of breast cancer by increasing radiologist sensitivity by 21.2%. Furthermore, a CAD system helped to reduce the false negative rate of screening mammography by 77% without increasing the recall rate [9]. In a prospective study, the use of a computer-aided detection system in screening mammography resulted in a 7.4% increase in cancer detection [10]. CAD of digitized screening mammograms is now routinely used in many medical centers, and the application of computer-aided detection in mammogram test sets was approved by the Food and Drug Administration in 1998. However, a recent study by Fenton et al [11] analyzing a total of 429,345 mammograms in 43 facilities showed that the use of computer-aided detection was associated with reduced accuracy in the interpretation of screening mammograms.

Breast US plays an adjunctive role to mammography in aiding the classification of breast tumors; nevertheless, a breast US examination is more convenient and safer than mammography. Breast US has primarily been proven useful in differentiating cysts from solid tumors [12] and accurately classifying solid lesions as benign, allowing imaging follow-up rather than biopsy [13]. However, the sonographic technique demonstrated by Stavros et al [13] required an experienced interpreter for an extensive real-time evaluation. Breast US image interpretation is subjective and operator dependent. The presence of structure noise can camouflage the normal anatomical background and limit the physicians' ability to detect and diagnose disease during image interpretation. Significant progress has been made to overcome the shortcomings of US and improve physicians' confidence in image interpretation. Technical advances in breast US imaging, such as tissue harmonic imaging, compound imaging, split screen imaging and extended field of-view imaging, have made breast sonography an integral part of the breast imaging examination. Doppler US, the use of intravenous contrast agents, elastography, and CAD systems have expanded the clinical application of breast US. A breast US CAD system can be an efficient computerized model and can avoid interobserver variation. Various breast US CAD systems have been developed recently.

CAD Systems

A combination of image texture extraction and a decision-making algorithm have been proposed [14].

Texture provides cues on surface orientation, scenic depth, and color. Texture is an important component in image analysis [15]. Sonographic textural analysis is helpful in improving the distinction between benign and malignant lesions [16].

Neural networks can act as a decision-making algorithm. Neural networks are computational programs that make predictions, and the performance of the neural network can be estimated using a receiver operating characteristic (ROC) curve and the *k*-fold cross-validation method [17]. Neural network techniques have been applied in the analysis of mammograms and as a classifier used to differentiate benign from malignant breast masses [18], microcalcifications [19,20], and speculation [21] on digital mammographic images. Moreover, Naguib et al [22] proposed a neural model to predict nodal metastasis and prognosis in breast cancer. Baker et al [23] improved the interpretation of mammogram abnormalities using an artificial neural network that incorporated radiologists' descriptions of abnormal findings.

Chen et al have undertaken a series of studies on CAD applied to US of solid breast nodules using neural networks since 1999 [24–27]. The authors proposed a diagnostic scheme comprising a two-step approach [24] (Fig. 1). Firstly, textural information was extracted from the digitized US image. Secondly, the extracted information was fed into a multilayer perceptron (MLP) neural network, which was employed as a tool to distinguish benign from malignant solid breast nodules on digital sonographic images. The MLP neural network is an important class of neural networks, and the model can be used to extract high-order statistics by adding one or more hidden nodes (Fig. 2). Power error back-propagation has been proposed by Hirose et al [28] and Rumelhart et al [29] and is the most popular algorithm used in designing MLP neural networks. Because the diagnostic model is trainable, the authors claimed that the system differentiated solid breast nodules with an accuracy of 95.0%, a sensitivity of 98%, a specificity of 93%, a positive predictive value of 89%, and a negative predictive value of 99% [24].

Wavelet transform has been identified as a helpful technique in time frequency signals [30,31]. The wave transform can be employed to extract local textural features, to detect multiresolution characteristics, and can be applied in textural analysis. A CAD system with sonographic textural analyses using wavelet transform and neural networks has been described by Chen et al [26]. In this study, region-of-interest (ROI) images included the tumor region and the surrounding tissues, and an MLP neural network was programmed using an error

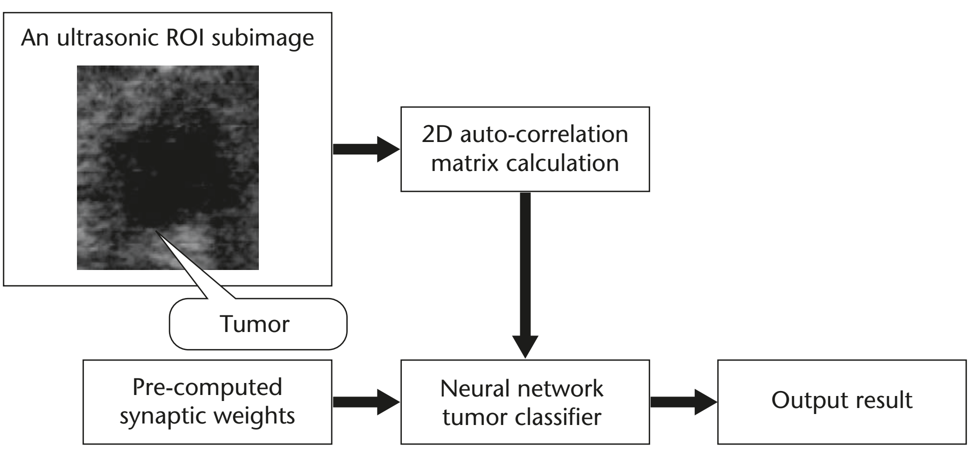

Fig. 1. *A proposed diagnostic scheme comprising a two-step approach. Firstly, the textural information was extracted from the digitized ultrasound image. Secondly, the extracted information was fed into a multilayer perceptron neural network that was employed as a tool to distinguish benign from malignant solid breast nodules on digital sonographic images. ROI = region-of-interest; 2D = two-dimensional. With permission from reference 24.*

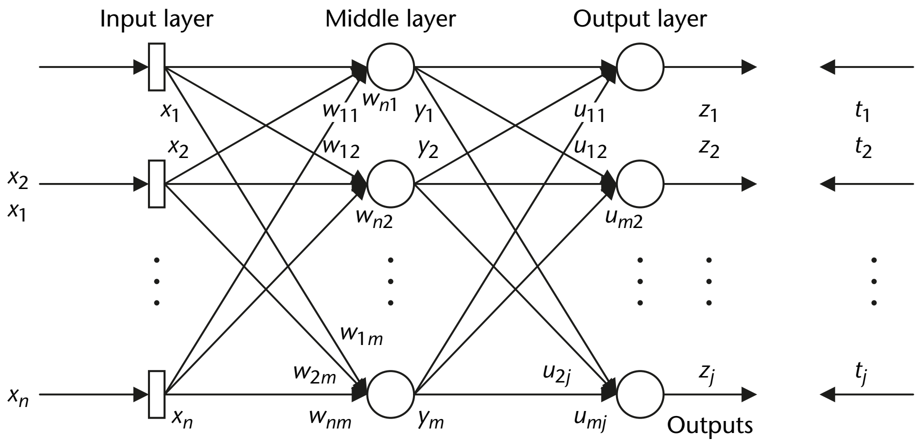

Fig. 2. *Model of a multilayer perceptron neural network. With permission from reference 26.*

back-propagation algorithm with momentum to classify breast tumors on sonogram. Wavelet transform has been identified as a useful technique for the representation of signals, especially in imaging processing application. The authors proposed three feasible features, which included variant contrast, autocorrelation contrast and distribution distortion of the wavelet coefficient, and showed that malignant tumors were distributed with higher variance contrast values, lower autocorrelation contrast values, and lower distribution distortion of wavelet coefficients. A ROC index of 0.9396 and a sensitivity of 98.77% were demonstrated in this study.

However, there is a disadvantage to the neural network methodology in that a large number of samples have to be collected to construct the CAD system. The bootstrap technique used as a diagnostic system requires only very few original samples to construct the model. The bootstrap method was introduced by Efron [32,33] as an approach to calculating confidence intervals for parameters when standard methods could not be applied. This method has been used to solve many problems that would otherwise be too complicated with the use of traditional statistical analysis [34]. The bootstrap technique is more cost-effective than traditional methods for the construction of diagnostic models, because fewer training cases are needed. Nevertheless, the use of a small sample has its limitations; the training samples need to include the variable characteristics of benign and malignant tumors to generate a good training set for the diagnostic system. Chen et al [35] proposed a diagnostic system using the bootstrap technique in which inter-pixel correlation on the US images was used to differentiate breast tumors. The authors showed that the diagnostic performance was improved by using the bootstrap technique. When the sample number was increased from 10 to 50, the diagnostic accuracy was much improved using the bootstrap technique (87.07% to 95.1%) than when the technique was omitted (87.07% to 88.97%).

Fractal analysis has been used in several medical imaging investigations both in US [15] and mammography [36–39]. Garra et al [16] designed a CAD algorithm using fractal analysis and statistical textural analysis methods to markedly reduce the number of biopsies for benign lesions without missing existing cancers. Chen et al [40] established a CAD algorithm of a *k*-means classification method based on fractal analyses with US preprocessed by morphology operation and histogram equalization (Fig. 3). The diagnostic performance of an A_Z value of 0.9218 was shown in the study.

Support vector machines (SVMs) have been proposed as a very effective method for pattern recognition between two point classes by finding a decision surface determined by certain points in the training set and a CAD algorithm based on SVM.

SVMs can be used by physicians as a second opinion in US image interpretation [41,42]. Several breast US CAD systems using SVM algorithms have

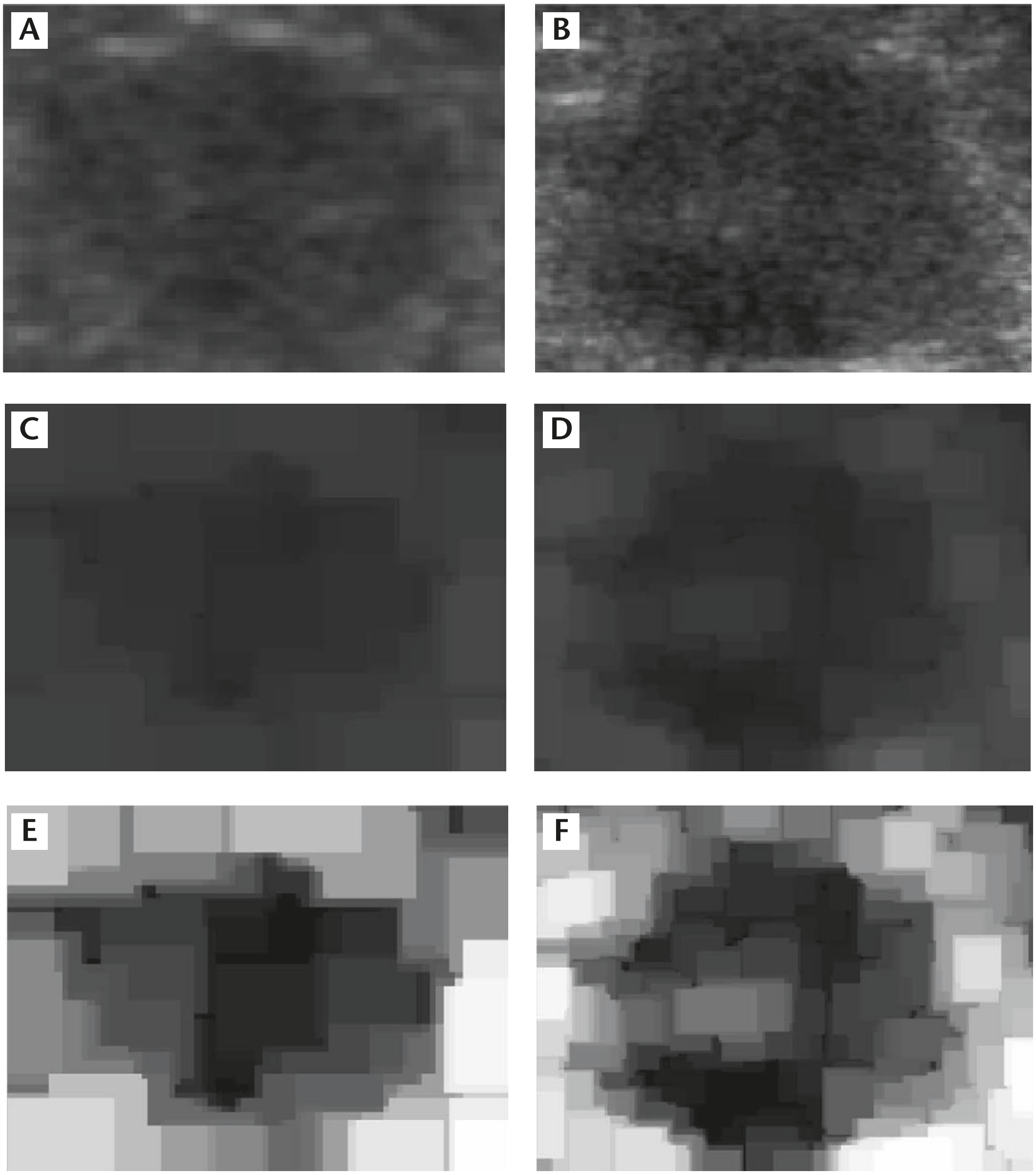

Fig. 3. *A computer-aided diagnosis algorithm of a k-means classification method based on fractal analyses with ultrasound pre-processed by morphology operation and histogram equalization. Original tumor images: (A) benign; (B) malignant. Morphologic operation: (C) benign; (D) malignant. Histogram equalization after morphologic operation: (E) benign; (F) malignant. With permission from reference 40.*

been proposed [43–45]. Chang et al tested an advanced SVM and compared its performance with that of an MLP neural network [43]. The authors concluded that SVM was helpful in the image diagnosis of breast cancer, and the classification ability of the SVM was nearly equal to that of the neural network model. The SVM has a much shorter training time than the neural network model. The advantage of SVM in reducing the training and diagnostic time was also demonstrated [44].

Speckle is a special characteristic of sonography; it can be produced by the superposition of numerous waves scattered on the various surface elements of the object. In a published study, Chang et al combined speckle information with autocovariance as features of sonography to classify breast tumors

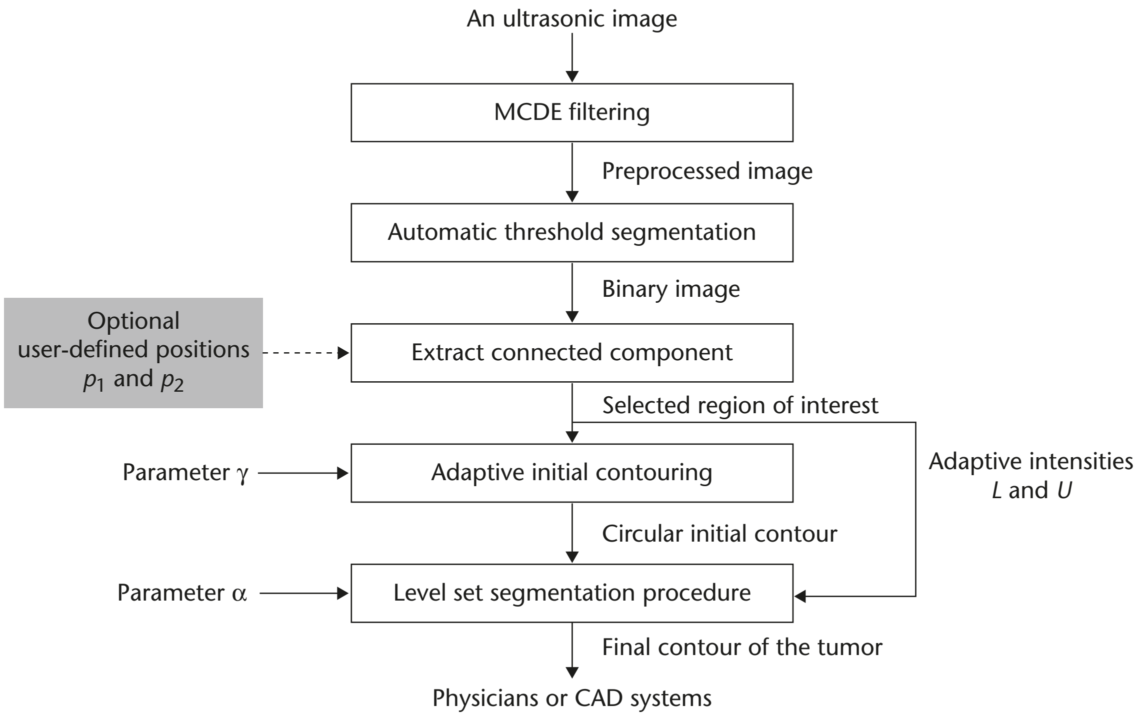

Fig. 4. *A proposed computer-aided diagnosis (CAD) system comprising a three-step approach. Firstly, the original ultrasound images were processed using modified curvature diffusion equation (MCDE) filtering. Secondly, a closed circle contour was obtained as the initial contour function. Finally, the level set method was employed to segment the tumors in the ultrasound images. With permission from reference 46.*

[45]. Performance among three different textural features, including speckle emphasis, conventional all pixels and non-speckle emphasis, were compared. The study demonstrated that speckle information may be used as an alternative in CAD research of breast ultrasound.

The level set method is a numerical technique for calculating and analyzing the curve propagations. It can offer an accurate model for tracking interfaces with complex motions. In a recent study, Huang et al [46] proposed a CAD system based on level set contouring for breast tumors in sonography. This system used a three-step approach (Fig. 4). Firstly, the original US images were processed using modified curvature diffusion equation (MCDE) filtering. Secondly, a closed circle contour was obtained as the initial contour function. Finally, the level set method was employed to segment the tumors in the US images. Automatic segmentation can save much of the time required to sketch a precise contour with very high stability. The potential role of this approach is to provide robust and fast automatic contouring for breast images.

The potential of textural analyses in ultrasonographic CAD systems could provide an accurate and reliable second opinion for physicians to distinguish benign breast tumors from malignant lesions.

One- and Two-view Analyses

In clinical practice, two perpendicular views of a tumor are necessary in breast US interpretation. However, in most breast US CAD studies, only one view (image) is used. Chen et al [25] proposed a multi-view hierarchical neural network (HNN) diagnostic system in 2000. Briefly, the authors analyzed 1,020 sonograms of ROIs from 255 patients. Each case contained four ROI images, and these four images were captured in two orthogonal imaging planes (i.e. longitudinal and transverse) for each tumor. MLP neural networks were designed as

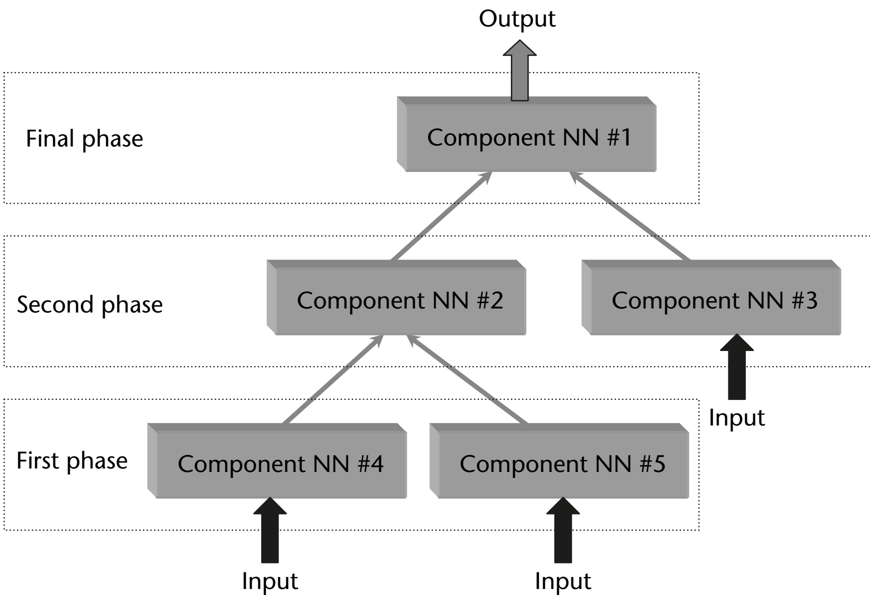

Fig. 5. *A HNN model composed of five component neural networks (NNs). With permission from reference 25.*

a classifier. The features of the four images were extracted to represent the textural information, and a HNN was employed to classify the tumor using the autocorrelation features. The proposed multi-view HNN diagnostic system consisted of functionally similar or different neural network models called component networks (Fig. 5). There were four diagnostic subsystems, and the A_Z values were 0.9495, 0.8605, 0.9237, and 0.7348. The multi-view HNN diagnostic system had a higher A_Z value (0.9840) than any of the subsystems. The authors also compared the diagnostic results with the findings of three experienced radiologists. The radiologists had a higher negative predictive value compared with the neural network system, and the authors claimed that experienced radiologists using the proposed neural network system should be able to diagnose breast cancers with fewer benign biopsies.

How to Apply Textural Analysis to Different US System

A limitation of textural analysis in CAD is that it can usually only be applied to one US system. Several studies have investigated whether the CAD system can satisfactorily be applied to different US machines.

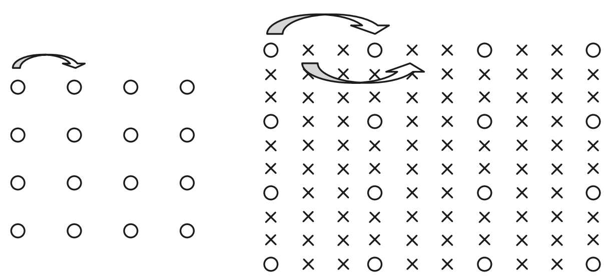

Fig. 6. *A computer-aided diagnostic system in one ultrasound unit can be applied to another after the adjustment of certain parameters. With permission from reference 47.*

Kuo et al [47] showed that a CAD system in one US unit can be applied to another, following the adjustment of certain parameters (Fig. 6). The authors designed a CAD system using textural analysis and data mining with a decision algorithm to classify breast tumors using different US systems and compared the results. Initially, they collected a database of training and test cases using different US systems in different countries; they then proposed adjustment schemes for the different US systems. The results of their study showed that diagnostic performance was improved by using the adjustment schemes, and the accuracy was improved from 82.2% to 89.9%. The authors claimed that different resolutions and different machine settings are not obstacles in the application of such a CAD system.

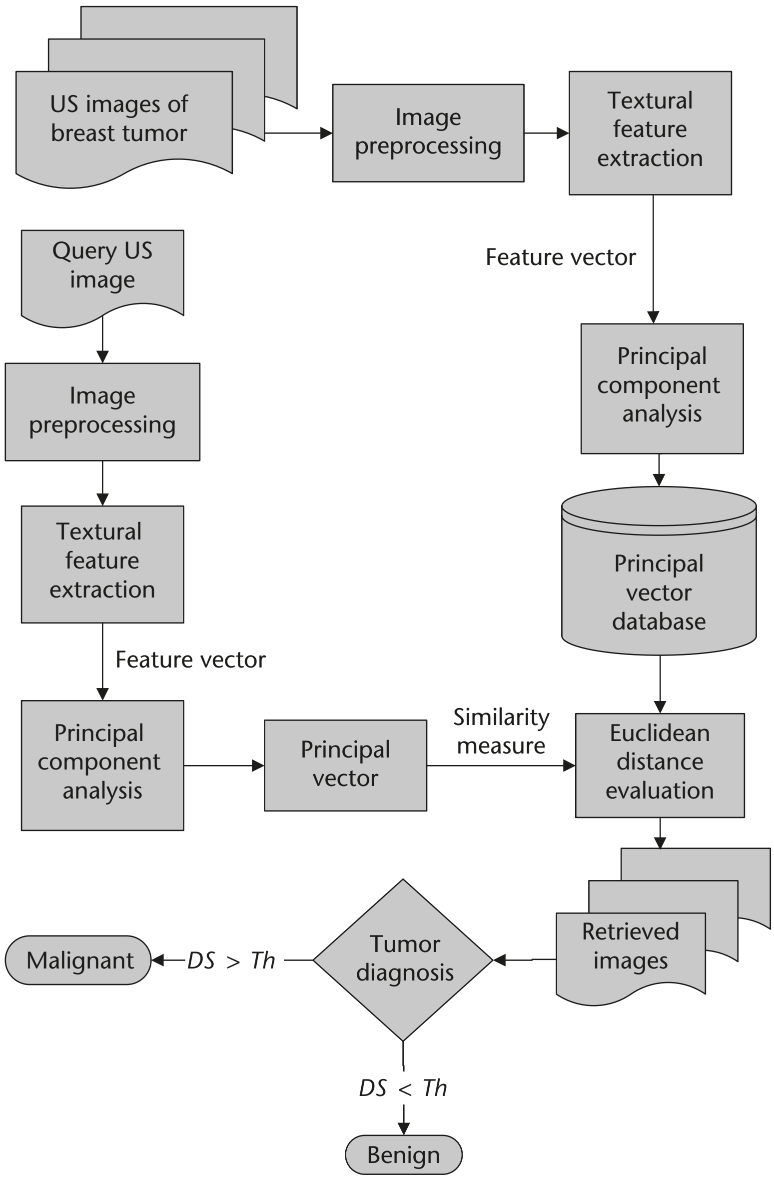

Fig. 7. *Flow chart of a proposed CAD system. DS = difference score; Th = cutoff threshold. With permission from reference 48.*

Another study on CAD systems applied to various US systems was reported by Huang et al [48]. The authors acquired 600 US images of solid breast nodules from four quite distinct commercial US systems. Original textural features were extracted from suspected tumor areas on US images (Fig. 7). The original textural features used as a high-dimensional vector was unsatisfactory at differentiating breast tumors. The authors proposed a principal component analysis to summarize the original feature information by projecting the original features into lower dimensional vectors; by using this technique, the training and diagnostic time can be reduced. The image retrieval technique with principal component analysis was satisfactory in classifying breast tumors as benign or malignant. The authors demonstrated that such a CAD system could be used with various US machines, mainly for the preprocessing techniques in homogenizing textural features between systems. Therefore, a CAD system for textural analysis can be applied to different US machines using adjustment schemes for the various US systems.

Textural Analysis *vs.* Morphology Analysis

Textural analysis is system dependent, and can be performed well in one specific US system unless adjustment schemes for various US systems are used as described previously. Morphology-based diagnosis of solid breast tumors has the advantage of being nearly independent of either the settings of US systems or different US machines. Chang et al used SVM and shape information to classify breast tumors [49]. In their study, tumors in ultrasonic images were segmented automatically by a level set method, and six morphologic features including form factor, roundness, aspect ratio, convexity, solidity and extent were used. The results showed that the accuracy of such a classification using a SVM model was satisfactory. Another study in breast US CAD with nearly setting-independent features was proposed by Chen et al [50]. The authors developed five new morphologic features, including the number of substantial protuberances and depressions, lobulation index, elliptic-normalized circumference, elliptic-normalized skeleton, and long axis to short axis ratio. The following three steps were performed. Firstly, tumors in ultrasonic images were segmented manually by four physicians. Secondly, seven morphologic features (the number of substantial protuberances and depressions, lobulation index, elliptic-normalized circumference, elliptic-normalized skeleton, long axis to short axis ratio, depth-to-width ratio, size of the lesion) were used. Finally, a multilayer feed-forward neural network was employed as the classifier to differentiate benign lesions from malignant breast tumors. According to this study, the A_Z value was 0.95 for all 271 lesions.

Future Research

In the past decade, many researchers have developed novel approaches for CAD systems based on textural or morphologic features. Most CAD analyses are focused on differentiating between benign lesions and malignant tumors. Breast cancer is heterogeneous, and features of benign and malignant lesions do overlap. In addition, the US examination is very operator dependent, especially in conventional US. Future research of CAD systems should include pathologically specific tissue-related and hormone-related conjecture, which could be applied to picture archiving and communication systems or teleradiology.

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