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Computer-aided prediction model for axillary lymph node metastasis in breast cancer using tumor morphological and textural features on ultrasound

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ABSTRACT

Background and objectives: Axillary lymph node (ALN) status is a key indicator in assessing and determining the treatment strategy for patients with newly diagnosed breast cancer. Previous studies suggest that sonographic features of a primary tumor have the potential to predict ALN status in the preoperative staging of breast cancer. In this study, a computer-aided prediction (CAP) model as well as the tumor features for ALN metastasis in breast cancers were developed using breast ultrasound (US) images.

Methods: A total of 249 malignant tumors were acquired from 247 female patients (ages 20–84 years; mean 55 ± 11 years) to test the differences between the non-metastatic (130) and metastatic (119) groups based on various features. After applying semi-automatic tumor segmentation, 69 quantitative features were extracted. The features included morphology and texture of tumors inside a ROI of breast US image. By the backward feature selection and linear logistic regression, the prediction model was constructed and established to estimate the likelihood of ALN metastasis for each sample collected.

Results: In the experiments, the texture features showed higher performance for predicting ALN metastasis compared to morphology (*Az*, 0.730 vs 0.667). The difference, however, was not statistically significant (p-values > 0.05). Combining the textural and morphological features, the accuracy, sensitivity, specificity, and *Az* value achieved 75.1% (187/249), 79.0% (94/119), 71.5% (93/130), and 0.757, respectively.

Conclusions: The proposed CAP model, which combines textural and morphological features of primary tumor, may be a useful method to determine the ALN status in patients with breast cancer.

1. Introduction

Axillary lymph node (ALN) status is a key indicator in assessing and determining the treatment strategy for patients with newly diagnosed breast cancer [1–3]. The use of less invasive sentinel lymph node (LN) biopsy or non-invasive methods to predict ALN status is increasing since conventional axillary surgery is associated with complication and morbidity such as lymph edema, range-of-motion restriction, and arm paresthesia and pain [4,5]. Combining several nomograms to predict the probability of ALN metastases before or after sentinel LN biopsy have been developed and are widely used to assist in the choice of the optimal patient treatment [6,7].

The axillary ultrasound (US) has also been utilized to detect and guide a biopsy of suspicious ALN [8]. The results could be applied to determine whether to execute the sentinel LN biopsy or perform LN dissection for axillary staging in some patients [9]. However, the accuracy of axillary US examination for determining ALN metastases is not enough to obviate an axillary surgery in breast cancer. The ranges of sensitivity were 48.8% to 87.1% and 26.4% to 75.9% when the LN size and morphology were considered bases of decision models, respectively [8]. The prognostic variable in patients with early stage breast cancer may be sourced from tumor characteristics such as tumor size, grade, micro-vessel density, and lymphovascular invasion [10]. Indeed, previous studies suggest that sonographic features of a primary tumor have the potential to predict ALN status in the preoperative staging of breast cancer [11,12].

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Algorithm 1
Pseudocode of finding the tumor contour.

Input: 2D ultrasound image $\boldsymbol{I}$, initial point x inside the tumor
Output: tumor contour
{Step 1}//Perform first sigmoid filter on gray scale image I
$I = (255-0)\cdot(1+\exp(-\frac{I-5}{9}))^{-1}+0$
{Step 2}// Perform gradient magnitude filter
for each adjacent pixels n, m in I **do**
$\nabla I(n,m) = \sqrt{(\partial I/\partial_n)^2+(\partial I/\partial_m)^2}$
{Step 3}// Perform second sigmoid filter
$I = (255-0)\cdot(1+\exp(-\frac{\nabla I-0.2}{0.015}))^{-1}+0$
{Step 4}// Perform level-set segmentation on processed image I
Search $\Gamma=\{(\boldsymbol{x}, t)|\phi(\boldsymbol{x}=0)\}$ **from** initial point x to the outer region.
{Step 5}// Perform morphological operations
smoothed-Γ = Use *closing* to smooth contour with a disk-shaped structuring element of radius 20 pixels.
completed-Γ = Use *hole-filling* to remove small holes inside the segmented area.
return *completed*-Γ

Moreover, a computer-aided prediction (CAP) system was proposed by using features from abnormal tissue around the tumor [11].

Since cancer spreading extent is uncertain and susceptible to stage of cancer variability, the region of the tumor surrounding tissue analysis for pattern recognition on images was subjectively and empirically determined by expert observers. Instead of performing image matting [13] on the surrounding tissue segmentations in the CAP of ALN status study [11], this work simplifies the pre-processing of feature extraction and quantifies the substitute features by analyzing the segmented tumor. In order to develop the discriminative features and to predict the probability of ALN metastases from primary tumor characteristics, an automatic segmentation method with feature selection skills were used along with classifier on breast US images. All quantitative features, which have been employed in computer-aided diagnosis (CAD) systems to identify malignant tumors in early stage [14], were collected and further applied to propose a novel CAP system for ALN metastasis in this study.

2. Materials and methods

2.1. Patients and data acquisition

This study was approved by the institution review board, and informed consent was waived for retrospective analysis. The collected US database included 249 consecutive biopsy-verified breast cancers (tumor size 0.37–2.93 cm; mean 1.38 ± 0.47 cm) obtained from 247 female patients (ages 20–84 years; mean 55 ± 11 years) between June 2009 and May 2012. Each 2D image, captured with whole ultrasonic screen (760×574 pixels, 0.08 mm/pixel image resolution) and stored in 8-bit pixel depth with DICOM format, was acquired using the scanners from EUB-8500 (Hitachi Medical, Tokyo, Japan) or Aixplorer (Supersonic Imagine, Aix-en-Provence, France) with linear transducers of 5–12 MHz frequency.

All patients underwent breast cancer surgery and the ALN status was confirmed by the sentinel LN biopsy or the LN dissection. There were 130 non-metastatic and 119 metastatic ALN cases (metastases 1–10 nodes; mean 2.61 ± 2.60 nodes) including 230 invasive ductal carcinomas, 11 invasive lobular carcinomas, 2 mucinous carcinomas, 2 metaplastic carcinomas, 2 invasive papillary carcinomas, 1 apocrine carcinoma, and 1 medullary carcinoma. Further, various US characteristics were extracted and typed as morphology and texture feature sets to explore the performance of the CAP system.

2.2. Tumor segmentation

For extracting metastasis characteristics in breast cancer, a semi-automatic segmentation method verified by previous studies [14,15] for distinguishing tumor from background tissues in breast US image was used in this study. Through Algorithm 1, the tumor boundary was obtained automatically from a human-defined seed point on the whole US image. Based on the fast-marching level set method [16], a few image processing techniques were employed to improve image quality and obtaining a well-segmented tumor contour. The processes of sequential segmentation are shown in Fig. 1 and are described in details below.

First, the contrast enhancement was performed on the gray scale image I by the sigmoid filter [17]:

$$I_S = (\max-\min)\cdot\left(1+\exp\left(-\frac{I-\beta}{\alpha}\right)\right)^{-1}+\min \tag{1}$$

where α and β denote the width and center of the intensity range, respectively. The intensity of the target image is assigned to the interval [min, max].

Next, the pixel intensity was transformed to edge strength by the gradient magnitude filter [18]:

$$I_G(\nabla I_S) = \sqrt{g_x^2+g_y^2} \tag{2}$$

where the gradient between adjacent pixels x and y calculated on the image I_s is

$$\nabla I_S(x,y) = \begin{bmatrix} g_x \\ g_y \end{bmatrix} = \begin{bmatrix} \partial I/\partial_x \\ \partial I/\partial_y \end{bmatrix} \tag{3}$$

Finally, the level-set segmentation [16] was performed on the enhanced image after using the sigmoid filter again to enlarge the edge strength in I_G.

Given the user-defined seed as the zero level set, $\Gamma(\boldsymbol{x}, t)=\{\varphi(\boldsymbol{x}, t=0)\}$, the initial contour $\gamma(t=0)$ is evolved to obtain automated tumor contour by the level set function defined as

$$\varphi(\boldsymbol{x}, t=0) = \pm d \tag{4}$$

where $\mathbf{x}\in\Re^N$ is a point in image, d represents the distance from $\boldsymbol{x}$ to $\gamma(t=0)$, and the negative or positive sign indicate whether the place of x is inside or outside the initial contour, respectively. The partial differential equation for φ is

$$\varphi + s|\nabla\varphi| = 0 \tag{5}$$

where s influences the progression step in the outward direction from the initial contour.

Following our previous study [14] about CAD system for breast cancer in US, the parameters related to segmentation were set