Improved Differential Diagnosis of Breast Masses on Ultrasonographic Images with a Computer-Aided Diagnosis Scheme for Determining Histological Classifications

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Objectives: A computer-aided diagnosis (CAD) scheme for determining histological classifications of breast masses is expected to be useful for clinicians in making a differential diagnosis. The purpose of this study was to evaluate the usefulness of using the CAD scheme on ultrasonographic images.

Methods: The database consisted of 390 breast ultrasonographic images with masses. Three experienced clinicians independently provided subjective ratings on the likelihood of malignancy for each of the 390 masses. Fifty benign masses (25 cysts and 25 fibroadenomas) and 50 malignant masses (25 noninvasive ductal carcinomas and 25 invasive ductal carcinomas) were selected as unknown cases for an observer study based on a stratified randomization method with the ratings. The likelihood of the histological classification in each unknown case was evaluated by the CAD scheme with image features that clinicians commonly use for describing masses. In the observer study, seven observers provided their confidence levels regarding the malignancy of the unknown case before and after viewing the likelihood of the histological classification. The usefulness of the CAD scheme was evaluated with a multireader multicase receiver operating characteristic (ROC) analysis.

Results: The areas under the ROC curves (AUCs) for all observers were improved by use of the CAD scheme. The average AUC increased from 0.716 without to 0.864 with the CAD scheme ($P = .006$).

Conclusion: The presentation of the likelihood of the histological classification evaluated by the CAD scheme improved the clinicians' performance and therefore would be useful in making a differential diagnosis of masses on ultrasonographic images.

Key Words: Computer-aided diagnosis; breast mass; ultrasonographic image.

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Breast ultrasonography is thought to be more useful than mammography for detecting small breast cancers in dense breasts (1). However, introducing ultrasonography to breast cancer screening might result in a lower specificity and thereby increase the false positive rate (2–4). Tohno et al showed the rate of positive findings by ultrasonography to be 24%, and that it would decrease to 10% if simple cysts would be excluded from the positive findings (5). Therefore, ultrasonography may be able to achieve more effective breast cancer screening than mammography if clinicians can more accurately make a differential diagnosis on ultrasonographic images.

Computer-aided diagnosis (CAD) is one of the solutions for improving clinicians' performance (6). CAD is a diagnostic method in which clinicians use the results analyzed by a computer as a "second opinion." The usefulness of CAD at mammography has been shown on many studies. Jiang et al conducted observer studies for distinguishing between benign and malignant clustered microcalcifications with and without the computer output indicating the likelihood of malignancy. The average area under the receiver operating characteristic (ROC) curve (AUC) was thus found to increase from 0.61 to 0.75 by the computer aid ($P < .0001$) (7). Timps et al showed the radiologists' performances to improve significantly ($P < .05$) when they used the computer output for the characterization of benign and malignant masses on mammograms using a temporal change analysis (8). Nakayama et al

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investigated the effect of presenting similar images on radiologists' differential diagnosis of clustered microcalcifications on mammograms (9). The observer study found that the radiologists' performance significantly increased with the use of similar images ($P = .0009$).

The use of CAD with not only mammography but also breast ultrasonography would therefore help clinicians make a correct diagnosis. In differential diagnosis on ultrasonographic images, clinicians usually take into account the histopathological images associated with a lesion. Therefore, we have developed a CAD scheme for determining the histological classification of masses based on the approach employed for clinical diagnosis (see Appendix) (10,11). The CAD scheme can evaluate the likelihood of cyst, fibroadenoma, noninvasive ductal carcinoma, and invasive ductal carcinoma when analyzing solid masses. In this study, the potential usefulness of presenting the likelihood of histological classification estimated by the CAD scheme was evaluated in distinguishing between benign and malignant masses on ultrasonographic images.

MATERIALS AND METHODS

Institutional review board approval was obtained for this study.

Case Selection

A database first consisted of 793 ultrasonographic images including a 4- to 25-mm mass. These images were obtained from 793 patients using an ultrasound diagnostic system (APLIO XG SSA-790A, Toshiba Medical Systems Corp.) with a 12-MHz linear-array transducer (PLT-1204AT) at Mie University Hospital in 2010. All cases had already been pathologically proven. The diagnosis of benign cases was confirmed by fine needle aspiration, and then the patients were again examined at 6 to 12 months after the initial diagnosis. A total of 403 that underwent vacuum assisted needle biopsy, excisional biopsy, or medication were excluded in order to avoid the influence of artifact.

It was necessary to obtain the clinicians' subjective ratings on the likelihood of malignancy for all of the remaining 390 ultrasonographic images (225 benign masses: 138 fibroadenomas and 87 cysts; 165 malignant masses: 116 invasive ductal carcinomas and 49 noninvasive ductal carcinomas) in order to use moderately difficult cases in an observer study for evaluating the usefulness of the CAD scheme (9). Therefore, three experienced clinicians (with more than 5 years of experience devoted in breast image diagnosis) provided their confidence level regarding malignancy (or benignity) on a continuous rating scale from 0 to 1 corresponding to "definitely benign" and "definitely malignant," respectively, for each of the 390 masses.

We finally selected 100 images of 50 benign masses (25 cysts and 25 fibroadenomas) and 50 malignant masses (25 noninvasive ductal carcinomas and 25 invasive ductal carcinomas) with the stratified randomization method based on the average confidence levels of malignancy. Fifty malignant lesions were selected as unknown cases such that the average confidence levels of malignancy for the unknown malignant lesions would be distributed approximately normally in the range from 0.20 to 0.90, as shown in Figure 1, whereas 50 benign lesions were also selected as unknown cases so that those for unknown benign lesions would be distributed approximately normally in the range from 0.10 to 0.80.

Observer Study

In the observer study for evaluating the potential usefulness of the CAD scheme, an unknown image was first displayed on a laptop computer. The observer was then asked to mark his or her confidence level regarding the malignancy of the unknown case on a continuous rating scale from 0 to 1 corresponding "definitely benign" and "definitely malignant," respectively. The likelihood of the histological classification for the unknown case evaluated by the CAD scheme was then displayed after the observer marked the initial confidence level. The observer was asked again to mark his or her confidence level.

Seven clinicians, including three experienced clinicians (more than 5 years of experience devoted in breast image diagnosis; expert group) and four clinicians who sometimes diagnose breast images in local hospitals (5 to 30 years of experience; general group), participated in the observer study. We did not provide the participants with any information regarding possible histological classifications. We also did not give them any information about the performance (sensitivity, specificity, positive predictive value, negative predictive value, and AUC) of the CAD scheme.

The observers were instructed that: 1) the purpose of this study is to evaluate the usefulness of the presentation of the likelihood of histological classification estimated by the CAD scheme in distinguishing between benign and malignant masses on breast ultrasonography; 2) they were being asked to provide a confidence level regarding the malignancy (or benignity) of a mass on a bar using a mouse first, and then the system shows the evaluated likelihood of the histological classification, they would be asked to provide a confidence level again after viewing the estimated likelihood of the histological classification; 3) a training session with two cases is provided at the beginning of the study; 4) 100 unknown cases are included in this study; and 5) there is no time limit.

Statistical Analysis

A ROC analysis with a sequential-test method was used to evaluate the usefulness of the presentation of the likelihood of histological classification in distinguishing between benign and malignant masses (12–14). The AUCs were obtained by using the DBM MRMC software package (version 2.2) that was developed by researchers at the University of Iowa and the University of Chicago. The significance of the

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