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Advances in CAD for diagnosis of breast cancer

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Abstract

Purpose of Review—Computer-Aided Diagnosis (CAD) is a technology used for detection and characterization of cancer. Although CAD is not limited to a single type of cancer, a large number of CAD systems to date have been designed and used for breast cancer. The aim of this review is to discuss the current state of the CAD systems for breast cancer diagnosis, their application as a second reader in clinical practice, and the studies that evaluated the effect of CAD on radiologists' performance.

Recent Findings—A large number of CAD applications are being developed for different imaging modalities. The main clinical use of CAD to date is for screen-film mammography due to the commercially available FDA approved systems. Many studies showed that CAD improves radiologists' performance. A large number of academic institutions have devoted substantial research effort to develop CAD methods.

Summary—CAD systems will play an increasingly important role in the clinic as a second reader. Clinical trials have shown that CAD can improve the accuracy of breast cancer detection. Preclinical studies have demonstrated the potential of CAD to improve classification of malignant and benign lesions. An increased number of CAD systems are being developed for different breast imaging modalities.

Keywords

Computer aided diagnosis; breast cancer; mammography; detection; characterization

Introduction

Mammography is currently the only recommended imaging method for breast cancer screening [1,2]. Mammography is especially valuable as an early detection tool because it can identify breast cancer at an early stage, before physical symptoms develop [3]. Early detection via mammographic screening and physical examination has demonstrated improved survival from breast cancer in randomized controlled trials [1,2]. However, the high sensitivity of mammography is accomplished at a cost of low specificity. In order to reduce false-negative diagnosis, lesions with greater than 2% chance of being malignant will be recommended for biopsy [4]. As a result, only 15–30% of patients referred to biopsy are found to have malignancy [4–6]. Unnecessary biopsies not only cause patient anxiety and morbidity but also increase health care costs. It is therefore important to improve the accuracy of interpreting mammographic lesions, thereby increasing the positive predictive value of mammography.

Computer-Aided Diagnosis (CAD) is becoming an increasingly important tool to assist radiologists in the mammographic interpretation process. Current CAD systems in clinical use

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serve as a second reader for breast cancer detection. CAD systems for classification of malignant and benign lesions are under development by a number of research groups.

For characterization of breast lesions detected either clinically or at screening, ultrasound and MR exams are frequently recommended. Encouraged by the promising results of CAD for mammographic interpretation, many research groups have started to investigate the use of CAD for the interpretation of ultrasound and MR breast images.

This literature review is mainly focused on publications published since 2004 that include CAD observer studies and CAD methods.

CAD for screen film mammography

The largest number of applications of CAD currently is for the lesion detection on screen film mammography.

Helvie et al. [7**] conducted a pilot prospective clinical trial of a noncommercial CAD system developed at the University of Michigan for screening mammography. A total of 2389 screening cases were read by 13 MQSA–qualified radiologists in two academic institutions. Of the 11 cancers detected at screening in this patient cohort, the CAD system detected 10, and the radiologists also detected 10. One of the cancers detected by the CAD system was not seen by the radiologist initially (10% increase in the detection rate). There was 10% increase in the call-back rate (from 14.4% to 15.8%) for the study cases with CAD. In one of the institutions where the call-back rate for non-study cases was available, this rate increased from 10.3% for non-study cases to 13.5% for study cases before the CAD marks were displayed.

In a medical center setting Birdwell et al. [8**] evaluated 8682 cases without and with CAD. They performed 165 interventions and found 29 cancers. Twenty one cancers were detected both by the CAD and the radiologists, six were detected only by radiologists and 2 were detected only by CAD. Radiologist reading with CAD resulted in 7.4% increase in the cancers detected. The increase of the recall rate because of CAD was 7.6%. A modest increase in the recall rate was observed for the study cases without CAD compared with that of the previous similar time period when radiologists interpreted the screening mammograms without having the CAD system present.

One interesting observation in the above two studies was that the radiologists' call-back rate for the study cases increased even before the CAD marks were displayed, indicating that they might become more vigilant when they were aware that their reading would be compared with a second reading.

Gur et al. [9**] reported the results of a prospective study of CAD in their academic setting. Their study design compared the changes in breast cancer detection rate and recall rates between two periods of time, before and after the CAD system was introduced into their screening mammography practice. They found no statistically significant changes in the average recall and breast cancer detection rates between the 56432 cases read by 24 radiologists before the introduction of the CAD system and the 59139 cases read after its introduction. These findings therefore appeared to differ from those of the previous studies. The outcome of a study for evaluating the effects of CAD is expected to depend on a number of factors, such as the expertise of the radiologists using the system, the radiologists' vigilance in interpreting the CAD masks, and the study design. The study design used by Gur et al. [9**] was different from the sequential reading design of the above studies in that the statistics without and with CAD were obtained from different periods of time. The change, if any, in a radiologist's decision caused by CAD was not recorded for individual cases or individual readers. This design thus yields a global average of the effects from many factors that may influence the

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cancer detection rate. For example, Gur et al. [9**] reported that the proportion of patients who were screened for the first time decreased from about 40% to 30% during the entire study period. Potential differences in the demographics of the two patient cohorts recruited in the two periods might also contribute variances to the breast cancer detection and recall rates. It is not known whether any differences between the two patient cohorts might have masked the potential change in the breast cancer detection rate due to CAD.

Hadjiiski et al. [10**] evaluated the effects of CAD on radiologists' characterization of masses on serial mammograms using 253 temporal image pairs (138 malignant and 115 benign) obtained from 96 patients who had masses on serial mammograms. Eight radiologists and 2 breast imaging fellows assessed the temporal pairs with and without computer aid. Receiver operating characteristic (ROC) methodology was used for analysis of classification performance. The average area under the ROC curve, *Az* for radiologists' estimates of the likelihood of malignancy was 0.79 without CAD and improved to 0.84 with CAD. The improvement was statistically significant (P =0 .005). On the basis of BI-RADS assessments, it was estimated that with CAD, each radiologist reduced 0.7% of unnecessary biopsies on average and correctly recommended 5.7% additional biopsies.

Destounis et al. [11**] retrospectively evaluated the role of CAD in reducing the rate of false negative findings on screening mammograms considered normal at initial double reading. The CAD correctly marked 71% of the 52 actionable findings read as negative in previous screening year. This shows the potential of CAD to reduce FN rate at double reading.

The effect of CAD on the detection of clinically unsuspected breast cancers was studied by Butler et al. [12**]. Breast cancers occurred at location other than the site of the presenting clinical finding in 15 % (30/197) of the patients in whom cancer was detected. CAD identified 87% of these incidentally detected cancers and may be useful as an aid to the radiologists.

In an observer experiment with 5 radiologists and 185 patients, Marx et al. [13**] recorded an increase in short term call back rates ranging between 5% and 7% when the cases were evaluated with CAD. With CAD they also observed a reduced number of recommended unnecessary biopsies (range from 12% to 34%).

Baker et al. [14*] studied the consistency of a commercial CAD system by scanning 10 times the mammograms and evaluating the prompts from the CAD system. He concluded that there was an inconsistency in the CAD analysis for the breast cancers detected at screening; however, the CAD system was reasonably consistent in the overall number of cancers identified at different runs. Greater variability was observed for the false-positive marks compared to true-positive marks.

Two commercial and a in-house CAD schemes were compared by Gur et al. [15*] on 219 patients. The mass detection rate for the systems varied between 67% and 72%, and the differences were not statistically significant. The differences in the FP rate were statistically significant, however, ranging from 1.08 to 1.68 per four view examinations.

CAD for full field digital mammography

Full field digital mammography (FFDM) is becoming important imaging modality. Wei et al. [16**] proposed a multistage CAD for detection of masses on FFDM. They reported a case-based sensitivity of 70%, 80%, and 90% at 0.85, 1.31, and 2.14 FP marks/image. McLoughlin et al. [17**] developed a method for noise equalization in FFDM images and showed that the proposed square root noise model improved the performance of their CAD algorithm for detection of microcalcification clusters on FFDM images.

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CAD for breast Ultrasound

A number of CAD schemes were proposed for characterization of malignant and benign breast lesions on ultrasound scans.

Sahiner et al. [18**] designed a CAD system for characterization of breast masses as malignant and benign on three-dimensional (3-D) ultrasound scans using 102 biopsied masses. Four radiologists evaluated the 3-D ultrasound volumes in an observer study. The CAD system based on 3-D segmentation method achieved an area under ROC curve, *Az*, of 0.92 for testing. The *Az* values of the four radiologists ranged from 0.84 to 0.92. The accuracy of the classifier designed for differentiating malignant and benign breast masses on 3-D US volumes in this study was similar to that of experienced breast radiologists.

A two stage CAD system which first detected the lesions on US images and then classified the lesion by distinguishing the cancer from all other lesions was developed by Drukker et al. [19**]. Four hundred cases were used for training and 485 cases were used for testing. The *Az* for the task of distinguishing the true lesions and false-positives was 0.94 and 0.91 for the training and testing data sets, respectively. For the task of classifying cancer from all other detections, the Az was 0.87 and 0.81 for the training and testing data sets, respectively.

Sahiner et al. [20**] designed a combined 3-D US and mammographic CAD system using 67 patients and performed an observer study with 5 radiologists. The *Az* of the combined CAD system was 0.91. The radiologists improved significantly (p=0.03) their average performance to an *Az* of 0.95 when using combined CAD.

Drukker et al. [21**] also designed a CAD system combining an ultrasound and mammographic information. The system was evaluated on a data set of 100 lesions from 97 patients having available mammograms and US images. The Az for the combined system was 0.92, which represented a statistically significant improvement compared to the mammography system alone (Az=0.77) and the ultrasound system alone (Az=0.88).

Additional CAD systems for classification of breast masses as malignant or benign on US images were reported by Joo et al. [22*], Chang et al. [23], Moon et al. [24*], and Song et al. [25]. The CAD systems were based on artificial intelligence techniques (support vector machines (SVM) and artificial neural networks (ANN)) and developed with data sets of different sizes (from 54 cases to 584 cases). The classification accuracy Az obtained with these CAD systems ranged from 0.86 to 0.95.

CAD for breast MRI

Recently MRI is used more frequently for diagnosis of breast cancer. A number of studies have been reported which explored the feasibility of CAD use for characterization of breast lesions as malignant and benign using contrast enhanced MRI.

Deurloo et al. [26**] designed a computer system to estimate the likelihood of malignancy of lesions on contrast enhanced MR images. They used 100 lesions (in 78 patients) to train the computer system. In addition they had the descriptive rating (benign, probably benign, indeterminate, suspicious, or highly suggestive of malignancy) of the lesions on MR images by an experienced radiologists. The scores from the computer system and the radiologist were merged by using the logistic regression analysis in a combined model. The model was tested on an independent set of 72 clinically and mammographically occult lesions in 60 patients. The A_z values for the radiologist's readings, the computer system and the combined model were 0.86, 0.85 and 0.91, respectively. The study demonstrated that the complementary

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information from a radiologist and a computer system has the potential to increase the overall performance for clinically and mammographically occult lesions.

Malignant and benign classification on T1-weighted 3D spoiled gradient echo sequence without and with intravenously injected contrast was performed by Chen et al. [27**]. A data set of 121 cases (77 malignant and 44 benign) was used. Features related to morphology, enhancement kinetics, and time course of enhancement-variation over the lesion were extracted from both the hand outlined and automatic computer segmented lesion contours. The classification accuracy in terms of Az using a linear classifier was 0.80 and 0.86 for hand and computer segmented contours, respectively.

Nattkemper et al. [28*] developed a classifier to distinguish between malignant and benign breast masses using MRI data from 74 cases (49 malignant and 25 benign). They extracted contour and wash-out type features determined by radiologists from dynamic contrast enhanced magnetic resonance imaging time-course data. Using Support Vector Machines (SVM) classifier they obtained an A_z of 0.88.

DeMarini et al. [29*] evaluated 15 patients with 16 newly diagnosed locally advanced breast cancers using MRI before and after neoadjuvant chemotherapy. CAD assessments, including presence or absence of significant enhancement, enhancement profiles, and maximum sizes, were recorded. Prior to chemotherapy, all tumors demonstrated CAD-assessed significant enhancement. Following chemotherapy, the results showed a decrease in washout enhancement in patients with minimal residual malignancy at pathology. However, 7 of 16 tumors showed no residual significant enhancement after chemotherapy, but all had residual disease at pathology. In this patient population CAD for breast MRI may complement but should not replace the careful assessment of tumors by the radiologist.

CAD for new modalities - breast tomosynthesis

Digital breast tomosynthesis (DBT) is a promising new modality allowing 3D imaging of the breast.

Chan et al. [30*,31**] have developed a CAD system for breast masses on DBT mammograms. Twenty-six cases obtained with a prototype DBT system were used. The CAD system first screened the 3D volume for mass candidates by gradient field analysis. Each candidate was segmented from the structured background. Morphological and texture features were extracted. A feature classifier was designed to differentiate true masses from normal tissues. The CAD system was trained and tested using a leave-one-case-out method. The classifier obtained an area under the test ROC curve of 0.91±0.03. The CAD system achieved a sensitivity of 85% at 2.2 false positives/case. The results demonstrate the feasibility of this approach to the development of a CAD system for DBT mammograms.

Reiser et al. [32**] presented initial results for a computerized mass lesion detection scheme for DBT images. The algorithm used a radial gradient index feature for the initial lesion detection and for segmentation of lesion candidates. A set of features was extracted for each segmented partition. Performance of two- and three dimensional features was compared. For gradient features, the additional dimension provided no improvement in classification performance. For shape features, classification using 3D features was improved compared to the 2D equivalent features. The system was designed using a leave-one-case-out method on 21 DBT cases. The preliminary overall performance was 76% sensitivity at 11 false positives per case.

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CAD development – new methods and approaches for breast CAD

Automated interval change analysis of breast lesions is an important direction of CAD development. Filev et al. [33*], Marias et al. [34*] and Timp et al. [35*] proposed automatic methods for registration of corresponding masses on temporal pairs of mammograms that will assist a CAD system in interval change analysis.

Breast density is a risk factor for developing breast cancer. Wei et al. [36**] used an automated CAD system for estimation of the breast density on mammograms. The system estimated breast density using histogram analysis [37]. They evaluated the correlation between the percent mammographic dense area and the percent glandular tissue volume as estimated from MR images. The correlation was high, which indicated that changes in mammographic density may be a useful indicator of changes in fibroglandular tissue volume in the breast.

Li et al. [38**] developed computerized texture analysis of mammograms that provided radiographic descriptors of mammographic parenchymal patterns, which may be useful for identifying women at high risk for breast cancer and for monitoring the treatment of breast cancer patients.

Brem et al. [39**] studied the effect of breast density on CAD performance. They found no statistically significant difference in breast cancer detection in dense and nondense breasts. However the false-positive rate was lower in nondense breasts than in dense breasts for mass detection. The authors suggested that CAD may be particularly advantageous in patients with dense breasts, in which mammography is most challenging.

Brem et al. [40*,41*] also studied the effect of cancer size and tumor histopathology on CAD detection performance. They found that CAD detection performance does not strongly depend on cancer size and tumor histopathology, and that the CAD system correctly marked a large majority of the biopsy-proven breast cancers.

An area of active CAD research is the improvement of breast mass detection algorithms. Catarious et al. [42*] and Timp et al. [43*] developed methods to improve the segmentation of the breast masses using iterative linear segmentation and segmentation based on dynamic programming, respectively. Wei et al. proposed a dual CAD system approach to detection of subtle masses [44*]. An improvement in detection sensitivity by 2 % to 10 % without an increase in FP marks was achieved.

Soo et al. [45*] used a commercial system to detect amorphous calcifications, which usually are difficult to detect for the radiologists. The case sensitivity of CAD was found to be relatively low at 51% with 2 FP per case.

Breast lesion characterization is also an important topic of CAD research. Bilska-Wolak et al. [46*] designed a likelihood ratio classifier for classification of masses as malignant and benign and tested its performance on an independent set. A test Az of 0.90 was obtained. Lim et al. [47] developed a classifier using generalized dynamic fuzzy neural networks and texture features. They obtained an Az of 0.87 for classification of malignant and benign masses.

Paquerault et al. [48*], Kallergi et al. [49*], Leichter et al. [50*], Wei et al. [51*], Papadopoulos et al. [52] presented methods for classification of microcalcifications on malignant and benign. The classification methods used included LDA, ANN, SVM, and Bayesian ANN. The classification accuracy ranged from an Az of 0.80 to 0.98. Nakayama et al. [53*] performed computer classification of microcalcification clusters on five different histological types. The classification accuracy ranged from 75% to 100%.

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To facilitate automated analysis of mammograms for CAD system, a number of breast segmentation methods have been developed. Zhou et al. [54*] reported a new automated method for breast nipple detection. Ferrari et al. [55*] and Kwok et al. [56*] reported computerized methods for pectoral muscle segmentation.

Conclusions

CAD is an active area of research and development in medical imaging and diagnostic radiology. Recently, there are an increased number of CAD applications. To date the largest number of CAD systems have been developed for screening mammography. However, an increasing number of applications for US and MRI breast imaging are being evaluated. Although most clinical applications are devoted to breast cancer detection at present, it can be expected that CAD characterization will be an important component of the next-generation CAD systems.

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