Update on the potential of computer-aided diagnosis for breast cancer

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Definition & rationale for computer-aided diagnosis: CADE & CADx

The role of radiological imaging in breast cancer diagnosis and treatment continues to expand, with advances in image quality regulations (e.g., the Mammography Quality Standards Act and Program [MQSA]), image acquisition systems (e.g., digital mammography and cross-sectional tomographic imaging) and computerized image analysis (e.g., computer-aided detection). The benefit of a medical imaging exam depends on both image quality and interpretation quality. Interpreting medical images is the main undertaking of radiologists. However, image interpretation by humans can be limited by incomplete visual search patterns, the potential for fatigue and distractions, the presence of structure noise (camouflaging normal anatomical background) in the image, the presentation of subtle and/or complex cancers that require integration of both image data and clinical information, the vast amount of image data in a screening program with low cancer prevalence and the physical quality of the image itself. Computer-aided diagnosis (CAD) is defined as a diagnosis made by a radiologist who uses a computer's output, obtained from an automated analysis of medical images, as a 'second opinion' (or second reader) in detecting lesions, assessing extent of disease, making diagnostic decisions and/or predicting response to therapy. In general, with CAD, the final diagnostic decision is made by the radiologist, using the computer output as an aid. Various CAD methods have been developed during the past 25 years to improve the interpretation stage of the medical imaging process [1–3].

Computer-aided detection (CADE) methods aim to provide a 'second opinion' to the radiologist in the task of locating suspicious regions within images, as in detecting regions on screening mammograms that may contain breast cancer, leaving characterization, diagnosis and patient management to the radiologist.

Today, the role of CAD is expanding beyond screening programs and towards applications in diagnosis, risk assessment and response to therapy. Computer-aided diagnosis (CADx) involves the characterization of a suspicious region or lesion, initially located by either a human or computer; in this situation, the computer output characterizes each suspicious region or lesion quantitatively and/or estimates its probability of malignancy (or other abnormality), again leaving the final diagnosis and patient management to the physician.

Thus, CADE is a localization task and CADx is a classification task for differential diagnosis.

CADe in screening mammography

Until now, the use of CAD in clinical practice has been confined largely to screening mammography. Here, the computer output 'points' to suspect lesions/regions that may contain a mass, clustered microcalcifications, architectural distortion or another sign of cancer. More advanced systems also indicate outlines of the lesions on which the computer performs analysis, correspondence between mammographic views (e.g., left vs right, prior vs current exam) and lesion characteristics.

In a screening mammography practice that employs CADE, the radiologists should first interpret the screening mammograms without use of the computer output, make their

interpretation and then view the computer output. If a re-assessment is made during the second interpretation, it is important that any potential lesion found initially by the radiologist be kept for additional consideration, even if the computer output does not note it. Deviation from this practice may be one of the reasons for the variation in performance levels in clinical studies/trials reported in the literature [4–14].

Another reason for the variation in reported performance levels for CAD in screening mammography is that two inherently different clinical study designs are commonly used to estimate the impact of CAD systems on diagnostic accuracy. One type of study employs a ‘sequential’ interpretation design in which each reader (i.e., radiologist) interprets a case without the computer aid, views the CAD output and then re-interprets the case [4–9]. The other design, which employs a ‘longitudinal’ (separate/historical) approach, compares the performance level of a radiology practice over a period of time in which CAD is not used to a performance level during another (usually subsequent) period in which computer output is employed in the practice [10–13]. Although both types of clinical studies compare the performances of radiologists without and with a computer aid, the study designs yield different conclusions, and such results will need to be interpreted and applied carefully [15].

Possible future forms of CAdE

As noted previously, the current proper use of CAdE is as a second reader, and thus, most clinical studies/trials have been performed comparing radiologists’ performance levels without and with the computer aid. However, if CAdE is to be used as a second reader, would it not be more realistic to compare CAdE with double reading, as was carried out in the study conducted by Gromet [14]? Because it is accepted that double reading – that is, having two radiologists read each case – improves the detection of breast cancer, one might argue that studies should be conducted to determine whether CAdE is as good or better than double reading – a statistical comparison (a noninferiority test) similar to those used in many pharmaceutical studies [16].

Also, as the stand-alone performance of the computer for the detection of cancer improves and its false-alarm rate continues to decrease, might we someday reach a time when breast image cases, which yield no computer-indicated

suspicious regions, would be allowed to bypass radiologist review, with the patient instead informed automatically that her mammogram was normal? Although this scenario may seem far-fetched at present, it might become reality in the future.

CADx & beyond

Once a lesion is detected on a mammogram, the next step is a diagnostic decision on patient management. Should the patient have a biopsy? Return in a few months? Have additional mammographic views? Have a sonogram and/or a MRI? The role of computers in diagnostic breast imaging workup has been mainly as a visual aid in assessing the kinetic characteristics in dynamic contrast-enhanced (DCE)-MRI [17]. However, various investigators are developing computer methods that ‘mimic’ the human eye–brain system – that is, segment lesions from the parenchymal background, extract mathematical descriptors of lesion characteristics, merge these features into an estimate of the probability of malignancy, and present the computer findings in a variety of output formats to the user for mammography, breast ultrasound and/or breast MRI [18,19].

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Some have expressed concern with CADx in that the characteristic features and the corresponding estimate of the probability of malignancy go beyond indicating the location of a suspect lesion, but contribute directly to the diagnostic decision-making task of asserting that the lesion is cancerous. However, with thorough validation and robustness studies, such an output should be similarly viewed as other medical diagnostic tests.

In CAD, various mathematical descriptors – that is, features – are developed to characterize a lesion of interest. However, not all of these features may contribute to the overall decision-making task – for example, on whether or not the lesion is likely to be cancerous. It is noteworthy that the various feature selection techniques used in CAD development are analogous to gene selection in DNA

microarray experiments. Algorithms from these two research fields should be shared to expedite the development in each.

Also, it is interesting to note that use of computerized image analysis in the workup of breast lesions on multimodality images may improve the accuracy of the exam, as well as the efficiency of the interpretation process. For example, the analysis of 4D breast DCE-MRI data requires analyses of 3D image data over multiple acquisition times. Current investigative systems can perform such analyses within seconds after a lesion location has been indicated to the computer [19].

Various observer studies of breast CADx have yielded performance results demonstrating that the performance of the computer alone is similar to or exceeds the performance level of the radiologists in the task of distinguishing between cancerous and noncancerous lesions [18,20]. This implies that CADx might be better used as a concurrent reader than as a second reader. An analogy may be made to the incorporation of blood tests and electrocardiogram (ECG) analyses into a physician's assessment of a patient's condition. Perhaps in multimodality breast imaging, the computer assessment of the image data might be employed as just another 'modality', just another diagnostic test result.

Future role as an image-based biomarker in assessing prognosis, staging & predicting response to therapy

In the future, research efforts from scientists working in CAD should be combined with efforts from those working on quantitative imaging systems to yield information on morphology, function, molecular structure and more. The potential goal here is twofold – output from the quantitative analysis of an image might be used as an image-based biomarker, and such output might be used as a means with which to validate biomarkers in pharmaceutical discovery studies.

In quantitative imaging, an image acquisition system is developed to yield images that represent quantitative information regarding an underlying biological phenomenon, such as actual tumor size in CT or the dynamic-uptake rate in DCE-MRI [21]. However, segmentation and feature extraction techniques from CAD may benefit quantitative imaging in terms of delineating the tumor more objectively, in merging multiple quantitative values for a composite biomarker, or in yielding a relative value (e.g., relative to a known population with

similar tumor characteristics and/or response) that might be more robust than absolute values from the overall image acquisition system, which might require careful calibration [3].

The CAD approach and its algorithms are being extended from the diagnostic discrimination task for malignant and benign lesions to prognostic tasks, for example, in distinguishing between noninvasive and invasive lesions and between lymph-node-positive and lymph-node-negative lesions, thereby yielding MRI-based prognostic markers [22]. In this role, the computer-extracted features of the tumor can potentially be used to assess the aggressiveness of the tumor. Here again, the computer output could potentially be used along with clinical indicators to yield noninvasive methods – that is, 'virtual biopsies', that will help to determine the next steps in patient management.

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If the imaging and subsequent image analyses are successful in indicating the underlying biology of the cancer, then computerized image analyses of the types used in CAD may play a role in triaging patients for appropriate therapy regimens (such as neoadjuvant therapy in the treatment of breast cancer), or in terminating or modifying a regimen if image-based analyses indicate a lack of response. Moreover, association studies between breast cancer phenotypes from image-based biomarkers and genomic studies may yield new non-invasive means to localize and/or characterize the cancer.

In summary, the current goals of CAD are to reduce search errors, reduce interpretation errors, reduce variation between and within observers and/or improve the efficiency of the breast imaging interpretation process. These goals can be achieved if the computer's output is presented in an effective and efficient manner, and if the computer output is used appropriately by the radiologist. However, the potential of various developments in CAD goes beyond the radiologist's interpretation process, to future roles as image-based biomarkers for assessing prognosis and estimating response to therapy.

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