Computer-aided visualization and analysis (CAVA) research system for breast cancer detection and diagnosis

G. Newstead
Department of Radiology, The University of Chicago, Chicago IL, USA.

L. Arbash Meinel
Clinical Site Research Program, Philips Research North America, Briarcliff NY, USA.
Visiting Scientist, University of Chicago, Chicago IL, USA.

Breast cancer is the most common cancer diagnosed among women, excluding non-melanoma skin cancers, and accounts for 26% of all female cancers in the United States of America (USA). It is the second leading cause of cancer death in women today (after lung cancer) and is estimated to cause 15% of cancer deaths. Approximately 1.3 million women will be diagnosed with breast cancer yearly worldwide and 465,000 of those will die from the disease [1].

Death rates in the USA have dropped regularly since the early 1990s. This can be attributed to earlier detection with screening mammography and more effective treatment. Nonetheless, it is expected that when figures become available there will have been 40,910 breast cancer deaths (450 males, 40,460 females) in 2007 in the USA [2].

Screening

X-ray mammography
Periodic X-ray mammography screening of age-appropriate asymptomatic women is currently the only imaging modality for which a preponderance of data is available to show a reduction in breast cancer mortality. Effective treatment requires early diagnosis. It is therefore essential that the quality of the performance and interpretation of screening mammography examinations be optimized for early cancer diagnosis. Congressional approval of the Mammography Quality Standards Act (MQSA) in 1994 has resulted in improved standards for mammography screening nationwide.

However, X-ray mammography screening has certain limitations, and breast density and age are important predictors of the accuracy of screening mammography. A study of 463,372 screening studies reported in seven USA tumor registries during 1996-1998 showed sensitivities for breast cancer detection of 87.0% for women with fatty breasts and 62.9% for women with radiographically dense breasts [4].

Magnetic resonance imaging (MRI)
Recently, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has emerged as a promising technique for detecting, diagnosing and staging breast cancer. Research has shown that DCE-MRI can be more sensitive than X-ray mammography for screening high-risk patients, and the American Cancer Society published guidelines in 2007 recommending annual screening with MRI for select patient populations beginning at age 30 [1].

However, although DCE-MRI has a high sensitivity for detecting enhancing malignant lesions, its specificity is less favorable [5].

Diagnosis

Imaging modalities, such as mammography, ultrasound and, more recently, DCE-MRI are used to investigate symptomatic patients and those patients recalled from screening mammography.

However, imaging alone is not enough. Percutaneous image-guided breast biopsy using either mammographic, ultrasound or MRI guidance is now the standard of care for further investigation of suspicious lesions at diagnostic imaging. These interventional procedures are used to provide definitive histologic diagnoses for suspect lesions.

Computer-aided visualization and analysis (CAVA)

The ever-increasing stream of images and other information makes heavy demands on the radiologists. Computer assistance has already proved its value and will undoubtedly play a greater role in the future.

Computer-aided detection (CADe)
In 1994, Vyborny [6] showed that the diagnostic accuracy of mammography is increased when
two radiologists examine the same mammogram, or when the same radiologist re-reads a mammogram. The rationale for CADe systems is the replacement of the second pair of human eyes with a set of “electronic eyes”.

The development of reliable, reproducible, low-cost CADe systems for breast cancer detection is of great practical interest. CADe systems are now commercially available and are widely used in clinical practice to aid the radiologist in the detection of breast cancer in screening mammography.

Computer-aided diagnosis (CADx) research system

CADe systems have already established themselves in clinical practice. The next logical step is towards computer-aided diagnosis (CADx).

CADx is an emerging field, with the goal of providing computer assistance to the radiologist, at the time of diagnostic decision-making. At least seven reported studies demonstrate a clear statistically significant advantage with the use of CADx. Despite the fact that the evidence for benefits, as measured in observer studies, is much stronger than the evidence in support of using CADe, there are currently no commercial systems available. Furthermore, unlike CADe systems, which are generally inferior to the performance of radiologists, studies have shown CADx systems are at least as accurate as the radiologists, and in some cases even more so [7, 8].

The lack of commercial CADx systems may be due in part to the perception that there is higher medico-legal liability associated with CADx systems, compared with CADe systems. CADe is used in screening mammography, where the radiologist decides whether the woman is cancer-free or whether she should return for diagnostic workup. CADx systems are designed for use at the time of diagnostic imaging, where the decision for routine follow-up, breast biopsy or surgery is decided. An incorrect decision at this stage can result in either unnecessary surgery or a missed cancer. However, given the higher performance of CADx relative to radiologist decisions, and the large number of positive observer studies, it is likely that CADx will prove to be a successful clinical tool.

Researchers have developed CADx systems for detecting and diagnosing breast tumors in mammography, ultrasound and MRI data. These systems all depend on accurate characterization of breast masses as benign or malignant. Many classification methods have already been developed. These methods include wavelets, fractals, statistical methods, vision-based methods and recently, artificial intelligence methods, such as artificial neural networks (ANNs) and support vector machines (SVMs) [9].

ANN-based methods are especially popular because they can be implemented using parallel processing to efficiently handle large amounts of information, they can analyze and classify patterns even when the information is noisy, complex or incomplete, and they can adapt their behavior to a variety of training data.

Several research groups have reported encouraging results, using neural networks to classify breast masses on mammography [7] and MRI [8].

At the University of Chicago, Drs Maryellen Giger, Robert Nishikawa and Kunio Doi and colleagues have been developing CADx for mammography, ultrasound and MRI for the past 10 years. Their goal is to incorporate these CADe/CADx systems into clinical workstations and then to evaluate these systems in diagnostic breast imaging clinics.

CADx for mammography research

Drs Lina Arbash Meinel, Joseph M. Reinhardt, Lee Bennett and Ghassan Fallouh developed a research computer-aided diagnosis system for mammographic masses at the University of Iowa in collaboration with Damascus University, using one hundred and sixty breast mammogram cases from three different institutions (University of Iowa, IA, USA; Damascus University, Damascus, Syria; and American University of Beirut, Beirut, Lebanon) [10].

Each case contained at least one mass accompanied by the pathology results as the gold standard. Mass boundaries were extracted by a region-growing algorithm with manually-defined seed points. Texture and shape-based features (area, perimeter, compactness, radial length, spiculation, mean and standard deviation of normalized radial length, length of minimum and maximum axes and average boundary roughness) were used as inputs to two classifiers: backpropagation neural network (BNN) and K-nearest neighbors (KNN).

The backpropagation algorithm was used for training the BNN, where the output of each node is updated depending on the difference between the current output and the target (biopsy result). The classifiers were trained on 140 cases and tested on the remaining 20 data sets (an independent testing set). Each testing set was
Computerized algorithms for image analysis are often motivated by clinical observations. In recent years, consensus has been reached regarding the interpretation of breast MRI, through the work of a group of international experts, supported by the American College of Radiology (ACR) [16].

The standardized ACR breast MRI lexicon [17] shows that the enhancement pattern is an important diagnostic criterion: benign lesions are characterized by a homogeneous appearance while malignant lesions tend to exhibit heterogeneous enhancement. These clinical observations have provided a motive for further investigation of textural features, as a means of distinguishing between benign and malignant breast lesions on DCE-MRI [18].

**Development of a practical CADx system for MRI**

Using the clinical observations mentioned above, Drs Lina Arbash Meinel, Joseph M. Reinhardt and Alan Stolpen at the University of Iowa developed a research computer-aided diagnosis system designed to aid radiologists with different levels of experience in the diagnosis of lesions in breast MRI [8].

The research prototype uses a novel segmentation algorithm that requires the minimum of user interaction and is applicable to a wide variety of lesions and imaging protocols. Further details of the system are given in the Intermezzo.

A research pilot study [19] has shown that the computerized segmentation methods are more reproducible and reliable than manual methods.

**CADx for axilla research**

Lymph node status in patients with early breast cancer is a strong predictor for recurrence and survival. The identification of axillary lymph nodes containing metastatic cancer deposits has a significant impact on the type of therapy the breast cancer patient receives. There is prognostic significance associated with the number of metastatic lymph nodes, and the histopathology of axillary lymph nodes (ALNs) influences therapeutic planning for patients [20].
INTERMEZZO

Research

At the University of Iowa, a research computer-aided diagnosis system has been developed to aid radiologists in the diagnosis of lesions in breast MRI.

The first step was to provide a standard for evaluation. This was done by having an expert radiologist identify a selection of lesions that had also been confirmed by biopsy results.

Next, forty-two shape, texture and enhancement kinetics-based features were identified and assessed as diagnostic markers. The best of these features were used as inputs to the intelligent classifiers (Table 1).

Three classifiers were used: a BNN, an SVM and a Bayesian classifier (BC). Five human readers (a breast MRI expert, two mammographers and two body imaging fellows) manually classified 75 MRI datasets (80 lesions), both with and without CAD system assistance.

The ROC curve analysis showed that the BNN system significantly outperformed the other two classifiers with $A_z = 0.970$ and $p < 0.05$, as shown in Figure I.

![Figure I. The ROC curves of the Bayesian Classifier (BC), the support vector machine (SVM), and the backpropagation neural network (BNN) for classifying the MRI lesions.](image)

![Figure II. The ROC curves of the BNN system, human MRI expert without using the BNN assistance, and the human MRI expert using the BNN system assistance for classifying the 80 BMRI lesions.](image)

Also, all human readers significantly improved when aided by the CAD system ($p < 0.05$) as shown in Figure II.

The multi-reader, multi-case (MRMC) analysis showed that the human reader performance with and without CAD system assistance can be generalized over the population of cases and still

### Features used as inputs to the classifiers

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intensity</strong></td>
<td>average relative intensity</td>
</tr>
<tr>
<td></td>
<td>RMS relative intensity</td>
</tr>
<tr>
<td><strong>Spiculation</strong></td>
<td>average spiculation</td>
</tr>
<tr>
<td></td>
<td>RMS spiculation</td>
</tr>
<tr>
<td></td>
<td>standard deviation of spiculation</td>
</tr>
<tr>
<td><strong>Radius</strong></td>
<td>average radius</td>
</tr>
<tr>
<td></td>
<td>RMS radius</td>
</tr>
<tr>
<td><strong>Perimeter length</strong></td>
<td>average perimeter length</td>
</tr>
<tr>
<td></td>
<td>RMS perimeter length</td>
</tr>
<tr>
<td><strong>Compactness</strong></td>
<td>average compactness</td>
</tr>
<tr>
<td></td>
<td>standard deviation of compactness</td>
</tr>
<tr>
<td><strong>Area</strong></td>
<td>average area</td>
</tr>
<tr>
<td></td>
<td>RMS area</td>
</tr>
</tbody>
</table>

*Table 1. Features used as inputs to the intelligent classifiers.*
Studies indicate that this novel segmentation algorithm overcomes the big challenge in breast MRI lesion segmentation, that is, the large variability in size, shape, amount and distribution of contrast uptake. This method needs minimal user interaction, and is applicable to a wide variety of lesions and imaging protocols.

**Pilot study**
To evaluate the performance of the computerized segmentation, a research pilot observer study was performed in preparation for a future clinical study [3]. This included testing the manual and computerized segmentation procedure, data analysis, defining required changes, and estimating the required number of observers and datasets.

The research pilot study included manual segmentations of 11 mass lesions by two observers and placement of seed voxels for automated segmentation. Both observers repeated the evaluation of each case in three different sessions to measure inter and intraobserver variation. Evaluation included manual tracing of the borders of the lesion on all slices and placement of seed points using a direct method and a robust method. These seed voxels were used to initialize the automated segmentation. The computerized segmentation involved robust seed point selection to minimize the impact of variations in seed-point placement, with automated thresholding and connected component analysis.

As part of research collaboration between Philips and the University of Chicago Hospitals, a novel three-dimensional (3D) algorithm was developed for the segmentation of suspicious lesions from dynamic contrast enhanced breast MR images.

[2]. This algorithm is for research and is not commercially available. The methodology consists of three steps:

- robust seed point selection; this interaction mode ensures robustness of the segmentation result against variations in seed-point placement
- connected component analysis at an automatically determined intensity threshold in the subtraction image
- a post-processing step that includes non-enhancing portions of the lesion in the segmented area and removes attached vessels.

Figure III shows segmentation results for a variety of breast lesions. Whether internal non-enhancing portions of the lesion are included in the segmentation depends on the application: while non-enhancing kernels are considered as part of the lesion for volume measurements, they will be excluded for other applications, such as analysis of kinetic enhancement patterns. The proposed method provides both types of segmentation results as shown in Figure IV.

Figure III. MR images of suspicious breast lesions and segmentation results obtained by the proposed method.

Figure IV. Depending on the use of the segmentation result, non-enhancing internal areas can be either included in or excluded from the segmentation result.

Figure V. Comparison of manual and computerized segmentation. First row: different mass lesions with seed point placed by the user. Second row: computerized segmentation results. Third row: Computerized post-processing to include non-enhancing portions of the lesion into the segmented area and removing attached vessels.
A post-processing step was performed to include non-enhancing portions. This produced 18 segmentations for each lesion (6 manual, 12 computerized) as shown in Figure V.

The segmentations were compared pair-wise using the measured size and overlap to evaluate similarity.

In the study results, the observed inter- and intra-observer variation was similar ($p > 0.05$). Segmentation with the robust seed-point placement was significantly ($p < 0.001$) more reproducible in measuring lesion size (SD 1.8%) than either manual contouring (11.7%) or directly placed seed points (13.7%). The percent overlap between two computer readings (median 82%) was significantly ($p < 0.001$) higher than either the overlap between two manual readings (66%) or the overlap between computer and manual readings (64%). If the 95% confidence interval of relative difference has a length of 5%, then the sample size is 50 cases using seven observers.

In conclusion, the research pilot study showed that the computerized segmentation methods, especially with robust seed-point selection, are more reproducible and reliable than manual methods in terms of measuring the size and shape of a breast lesion.

**Acknowledgment**

We would like to thank Dr. Dezheng Huo from the University of Chicago for performing the statistical analysis of the research pilot study.

**References**


Surgical dissection is the gold standard for ALN staging. However, this procedure is invasive and may be accompanied with complications, such as lymphedema, numbness, seroma formation and limitation of shoulder movement. Imaging is also used for axillary nodal assessment, but current methods are at a relatively primitive stage and improvements in technology are needed.

At the University of Chicago Drs. Greg Karczmar, Hiro Abe, Akiko Shimauchi and colleagues plan to develop high-resolution MRI methods for axillary lymph nodes, both in vivo and in vitro. CADe/CADx techniques will then be applied for diagnostic evaluation. The plan is to optimize 3D ultrasound imaging of lymph nodes, and to develop coils specifically designed to image axillary node MR imaging in vivo.

The University of Chicago has already obtained pilot in vitro MRI data at high field strength, 9.4T, for MR imaging of excised breast specimens before they are evaluated at pathology, as shown in Figure 2. These techniques will be applied to in vitro imaging of excised axillary dissection specimens. The current pathologic methods used to assess lymph nodes are time-consuming and the goal of MRI of tissue specimens is to increase the efficiency and accuracy of pathologists, by demonstrating areas of the lymph nodes that are most likely to contain cancer.

This preliminary work suggests that normal lymph nodes have very bright and uniform intensity on T2 weighted images and on T2* weighted images. Lymph nodes that contain cancer, even small foci of cancer in the order of 500 µm in diameter, may be detectable, based on lower and variable image intensity. Specialized detectors will be designed and built to optimize sensitivity and spatial resolution for scans of lymph nodes. Nodes will be scanned with 100 µm resolution in-plane and 500 µm thick slices over the entire node using spin echo imaging and high spectral and spatial resolution imaging (a new MR method developed at the University of Chicago). Spin echo images will be acquired with TE of 20 ms and 80 ms and TR of 4 seconds using a fast spin echo method to reduce acquisition time. Spectral/spatial images will be acquired with spectral resolution of 5 Hz. Scans will require no more than 60 minutes and the tissue will be maintained at 16 °C throughout the entire scan, before transportation to the pathology laboratories for routine clinical evaluation.

Researchers at Philips Research and the University of Chicago are developing a multi-modality computer-aided diagnosis system for staging...
axillary lymph nodes. This represents a new approach to staging ALN, using a reliable and non-invasive method. The opportunity to avoid unnecessary surgery and the associated side effects while reducing costs is of great interest. This system is a research prototype and is not yet commercially available.

As a first step towards designing the multimodality CADx system, segmentation algorithms to distinguish the ALN from the surrounding tissues were developed. For ALN segmentation on MR images, the method described by Thomas Buelow et al. [21] was used. This method was successfully adapted from breast data to the ALN, and was tested quantifiably on ten datasets as shown in Figure 3.

For segmentation of ALN on ultrasound images, a model-fitting algorithm was used. The geometric model of choice was an ellipse. This low-parameter representation is a reasonable approximation of the shape of the 2D ultrasound image projection. Several techniques for robust ellipse fitting to noisy data are known from the literature [22]. A robust sampling technique and minimization of quadratic algebraic error to fit ellipses to image edge data, and the subsequent application of specific optimization criteria, were successfully implemented as shown in Figure 4.

Biomarkers and advanced imaging techniques

Researchers at the University of Chicago are developing markers using advanced imaging techniques to assess breast density and parenchymal structure. The general hypothesis is that combining automated analyses of the breast parenchyma and biomarkers will improve the assessment of breast cancer risk. Integrating advanced CADe/CADx functions and biomarkers into a diagnostic system would allow radiologists to accurately screen more young women and identify those at high risk. Physicians could then counsel these women regarding prevention measures involving lifestyle changes and the use of preventive therapies.

Computer-aided visualization and analysis (CAVA)

Data, data management, data analysis and visualization tools are essential for progress in the medical imaging environment, and are necessary for clinical practice, research and education. In the ever-increasing realm of data-intensive patient information, sustainable, scalable, agile and secure, cost-effective integration resources and methodologies need to be developed in order to encompass the entire medical information framework.

Over the last twenty years there has been an exponential growth in knowledge and techniques, including new imaging modalities such as CT, MRI, PET, fMRI, MEG, the development of molecular medicine and entirely new drug therapies for cancer. Patients’ expectations are also higher. They expect immediate access to high

Figure 2. Excised breast cancer specimen examined with high field strength (9.4 T) MRI. The specimen shows a normal lobulated intramammary lymph node, located adjacent to a small spiculated cancer.

Figure 3. Segmentation of axillary lymph node on MR images.
quality treatment, access to specialized knowledge and participation in management of their condition.

These developments are particularly evident in breast imaging, which is in a state of rapid technological change as a result of recent clinical trials that have demonstrated significant benefits from digital modalities, especially digital X-ray mammography and MRI. In fact, breast imaging today requires multiple modalities, including ultrasound, mammography, MRI and SPECT/PET. Most often these modalities are used on the same patient at multiple encounters throughout the patient’s lifetime.

Furthermore, breast imaging cannot be considered in isolation. Breast imaging is practiced in an integrated manner with medical, surgical and radiation oncology, and has a central role in disease management and decision making.

The future

Modalities
Currently, there are imaging modalities dedicated to breast examinations (such as digital mammography and dedicated ultrasound systems) while others are shared with other departments (such as MRI, SPECT and PET-CT). Exogenous intravenous contrast media are used for dynamic contrast enhanced MRI scans, and there is potential for new contrast media and targeted agents developed specifically for breast imaging. Testing new modalities, diagnostic agents and their combination, while integrating them into clinical practice, is a major goal of breast imaging at the University of Chicago.

Many new technologies show promise for further improvement in diagnostic performance, such as MRI-CADe/CADx or multimodality-CADe/CADx, as well as breast CT and optical methods.

Data management
Developments in imaging modalities and quantification are producing an ever-increasing stream of data that must be managed if physicians and allied health professionals are to deliver consistent optimal patient care. Radiologists, in particular, need easy access to a wide variety of patient and imaging data, from heterogeneous sources, to formulate meaningful analyses and to contribute effectively to patient diagnoses and management decisions.

The availability of non-image information, e.g. the patient electronic medical record (EMR), launched from the PACS workstation, with automatic selection of pertinent case-specific data, would greatly facilitate the reporting procedure and overcome the chronic problem of insufficient clinical data to accompany radiologic requisitions.

The current approach to clinical breast imaging workflow is piecemeal and unsatisfactory. There is a proliferation of user environments and constant interface difficulties. At present, there is no solution for the integration of multimodality breast studies from a variety of heterogeneous modalities. The development of a new viewing environment is needed for optimal interpretation of routine clinical multimodality images, and also for incorporation of the advanced computer-aided analysis tools, developed specifically for breast imaging by Philips researchers and colleagues in the medical physics section. Structured reporting, with audit analysis tools to comply with federal MQSA regulations, is also needed.

Multi-modality CADe/CADx
Multi-modality CADe/CADx systems are the way forward. From a technical point of view, a CADe/CADx system designed for a single modality will likely make assumptions that are only applicable to that modality. A multimodality CADe/CADx system simultaneously considers complementary anatomical/physiological information provided by the input modalities in combination. On the basis of a richer feature set, such a system can characterize lesions more accurately than a single modality CADe/CADx system, thus leaving fewer unresolved cases. This could particularly improve the specificity of diagnosis over a single modality approach, thereby leading, for example, to a reduction in the number of unnecessary procedures (biopsies and surgeries).

Each CADe/CADx system tends to have a unique mode of interaction. Integrating different
modalities into a multi-modality CADe/CADx system can streamline the clinical workflow, thus reducing time-consuming tasks that add no value, such as multiple loading of input images and repetitive arrangement and alignment of the display. This leaves valuable time for diagnosis and therapy planning.

**Computer-aided diagnosis (CADx)**

There are already systems available for detecting breast cancer on mammograms, and lung cancer on chest radiographs and CT scans, while other systems are currently under development for other areas of radiology, such as colonography, cardiac imaging, bone imaging, brain imaging and many others.

While CADe systems are in use clinically, CADx systems are not yet commercially available. In our view, CADx is the way forward.

**Acknowledgements**

We would like to thank Thomas Buelow, PhD and Martin Bergtholdt of Philips Research Hamburg, and Ursula Kose of Philips Healthcare, for their valuable contributions.

We would also like to acknowledge the important clinical discussions with Dr. Hiroyuki Abe and Dr. Akiko Shimauchi of the University of Chicago.

---

**References**


