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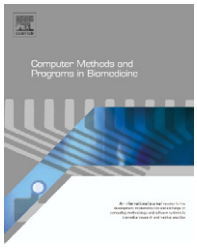

Computer-aided diagnosis: The emerging of three CAD systems induced by Japanese health care needs

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ABSTRACT

The aim of this paper is to describe three emerging computer-aided diagnosis (CAD) systems induced by Japanese health care needs. CAD has been developing fast in the last two decades. The idea of using a computer to help in medical image diagnosis is not new. Some pioneer studies are dated back to the 1960s. In 1998, the first U.S. FDA (Food and Drug Administration) approved commercial CAD system, a film-digitized mammography system, was launched by R2 Technologies, Inc. The success was quickly repeated by a number of companies. The approval of Medicare CAD reimbursement in the U.S. in 2001 further boosted the industry. Today, CAD has its significance in the economy of the medical industry. FDA approved CAD products in the field of breast imaging (mammography, ultrasonography and breast MRI) and chest imaging (radiography and CT) can be seen. In Japan, as part of the "Knowledge Cluster Initiative" of the government, three computer-aided diagnosis (CAD) projects are hosted at the Gifu University since 2004. These projects are regarding the development of CAD systems for the early detection of (1) cerebrovascular diseases using brain MRI and MRA images by detecting lacunar infarcts, unruptured aneurysms, and arterial occlusions; (2) ocular diseases such as glaucoma, diabetic retinopathy, and hypertensive retinopathy using retinal fundus images; and (3) breast cancers using ultrasound 3-D volumetric whole breast data by detecting the breast masses. The projects are entering their final development stage. Preliminary results are presented in this paper. Clinical examinations will be started soon, and commercialized CAD systems for the above subjects will appear by the completion of this project.

1. Introduction

Computer-aided diagnosis (CAD) has been developing fast in the last two decades. The main idea of CAD is to assist radiologists in interpreting medical images by using dedicated computer systems to provide 'second opinions'. The final medical decision is made by the radiologists. Studies on CAD systems and technology show that CAD can help

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to improve diagnostic accuracy of radiologists, lighten the burden of increasing workload, reduce cancer missed due to fatigue, overlooked or data overloaded and improve inter- and intra-reader variability. Two typical examples of application of CAD in clinical areas are the use of computerized systems in mammography and chest CT and radiography.

In this paper, three emerging CAD systems induced by Japanese health care needs are introduced. A brief review on CAD is provided in the following. For extensive reviews and current research and development of CAD on specific applications, readers are referred to elsewhere [1–13].

The idea of enlisting the help of a computer in the analysis of medical images is not new. In 1963, Lodwick et al. [14] investigated the use of a computer in diagnosing bone tumor. They further studied the usefulness of computer evaluation in diagnosing and grading of bone tumors [15]. In 1964, Meyers et al. proposed a system to distinguish normal chest radiographs from abnormal chest radiographs automatically by measuring the cardio-thoracic ratio [16]. In 1967, Winsberg et al. [17] described their study on computer analysis and detection of radiographic abnormalities in mammograms by means of optical scanning. The system automatically analyzes mammograms for abnormalities based on bilateral comparison. Another early computer system for breast cancer detection was reported by Ackerman and Gose [18] in 1972. The computer system was designed to classify breast lesions on xeroradiographs.

The year 1998 is one of the most important years in the history of CAD. It marked the transition of CAD technologies from the research phase to industrial practice with the success of the ImageChecker™ (R2 Technology, Inc., Sunnyvale, CA; later acquired by Hologic, Inc. in 2006) in obtaining a Food and Drug Administration (FDA) approval. The ImageChecker™ is a computer system intended to mark regions of interest on routine screening mammograms. The system was based on a prototype developed earlier at the University of Chicago [19]. Following the success of ImageChecker™, iCAD, Inc. (Nashua, NH) and the Eastman Kodak's Health Group (Carestream Health Inc. since 2007) also obtained FDA approval for their CAD system for mammography in 2002 and 2004, respectively. In 2002, R2 Technology, Inc. further obtained a FDA approval for its CAD system in use with full-field digital mammography. In breast magnetic resonance imaging (MRI), the CAD system CADstream™ was developed for the analysis and interpretation of breast MRI by Confirma, Inc. (Bellevue, WA). In breast ultrasonography, Medipattern Corporation (Toronto, Canada) first obtained a FDA approval for their B-CAD™ Software in 2005. The initial software product was designed to analyze breast ultrasound images by automatically segmenting and analyzing shape and orientation characteristics of suspicious lesions in user-selected regions-of-interest (ROIs). The B-CAD™ software is now available through Cedara Software Corp. (Mississauga, ON.)—a Merge Healthcare company. It should be mentioned that the approval of Medicare CAD reimbursement in the U.S. in 2001 has boosted the sale of CAD systems significantly. Today, it is estimated that more than 5000 mammography CAD systems are in current use in hospitals, clinics and screening centers in the U.S.

The success in CAD in mammography was quickly repeated in chest radiography. In 2001, the RapidScreen™, a CAD system for chest radiography developed by Deus Technologies (acquired by Riverain Medical in 2004) for the detection of early-stage lung cancer in association with solitary pulmonary nodules from 9 to 30 mm in size, obtained a FDA approval. In 2004, a CAD system for lung CT, the ImageChecker™ CT, developed by the R2 Technology, Inc. obtained FDA approval.

In other applications, the MeVis LiverAnalyser/LiverViewer Software™, a software product for liver surgery planning and lesions segmentation, developed by the Center for Medical Diagnostic Systems and Visualizations GmbH, Bremen, Germany, obtained FDA approval. The MEDIAN Technologies of France also received a FDA approval in 2007 for its LMS-Liver, an image visualization and analysis software package for the evaluation of liver lesions in CT images. CAD in colonoscopy has been receiving a lot of attention in the last few years. A number of visualization and image analysis software systems dedicated to colonscopy were developed and approved by FDA. For instance, the CT colongraphy/navigator 2 software package by GE Medical systems, Inc, was approved by FDA in 2001 and the Syngo Colonography software package by Siemens Medical Solutions U.S.A., Inc. was approved in 2003. Both systems allow the user to examine the colon by examining the inside, wall, and outside of the colon on CT colon images. Ongoing efforts are made by a number of commercial companies including the R2 Technologies, Inc. in developing sophisticated colon CAD systems.

In Japan, research on CAD systems has been active. Eighteen "knowledge clusters" have been established in Japan under the "Knowledge Cluster Initiative" of the Japanese Government in 2002. These clusters are supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan under a Grant-In-Aid for Scientific Research with a budget of US $4.5 million per year per cluster over 5 years. The aim of the clusters is to promote industrial, academic and governmental cooperation in regional areas and to conduct innovative and technological research with a focus on the needs of industry. The clusters are based in universities and other research institutes in order to draw sources of advanced knowledge; hence, the name "knowledge cluster."

The Fujita Laboratory at Gifu University is part of the Gifu/Ogaki Robotics Advanced Medical Cluster with a focus on research in distinctive, new medical technologies and developing the state-of-the-art medical equipments such as surgery robots and medical diagnosis support equipments. Currently, there are three established cluster projects in the Fujita Laboratory, Gifu University, started since April 2004. These three projects are computer-aided detection (CAD) systems using brain magnetic resonance imaging and magnetic resonance angiography (MRA) images, retinal fundus images and ultrasound breast images, and are described in the following sections.

2. CAD for MR brain images

2.1. *Overview*

Cerebrovascular disease is the third leading cause of death by disease in Japan [20]. Therefore, the screening system, which is named *Brain Dock*, has been widely used for the detection of

asymptomatic brain diseases. The prevention of this disease is of paramount importance. MRI and MRA are very useful for the early detection of cerebral and cerebrovascular diseases. Lacunar infarcts, unruptured aneurysms, and arterial occlusions can be detected using MRI and MRA. These medical conditions indicate an increased risk of severe cerebral and cerebrovascular diseases. The presence of lacunar infarcts increases the risk of serious cerebral infarction, and a ruptured aneurysm is the major cause of subarachnoid hemorrhage (SAH).

It is important to detect lacunar infarcts, unruptured aneurysms, and arterial occlusions. However, visualization of these structures is not always easy for radiologists and neurosurgeons. For example, it is difficult to distinguish between lacunar infarcts and normal tissue such as Virchow-Robin spaces in MRI images. Small aneurysms in MRA studies are also difficult to distinguish from the adjacent vessels in a maximum intensity projection (MIP) image. CAD systems can assist neuroradiologists and general radiologists in detecting intracranial aneurysms, asymptomatic lacunar infarcts, and arterial occlusions and in assessing the risk of cerebral and cerebrovascular diseases. In this project, we use T1- and T2-weighted MRI brain images for the detection of asymptomatic lacunar infarcts [21,22]. We also employ MRA brain images for the detection of intracranial aneurysms [23] and for developing a new viewing technique to facilitate the detection of intracranial aneurysms [24] and arterial occlusions [25].

2.2. *Detection of lacunar infarct*

The CAD scheme for detecting lacunar infarcts in MRI is shown in Fig. 1. The cerebral region is first extracted from a T1-weighted image. Lacunar infarct candidates are extracted using a simple thresholding technique and a top-hat transformation on T2-weighted images. Twelve features are measured from each candidate and a neural network is used in the final classification of the lacunar infarcts [21,22]. Using the above procedure for detecting lacunar infarcts and a two-fold cross validation method in evaluating the results, our developed CAD scheme can achieve a sensitivity of 96.8% at 0.71 false positive (FP) per image in a dataset of 132 studies.

2.3. *Detection of unruptured aneurysm*

The overall scheme for the detection of unruptured aneurysm is shown in Fig. 2. Vessel regions are first extracted from MRA images using linear gray-level transformation. A gradient concentration filter is then used to enhance the candidate aneurysms and quadratic discriminant analysis is used for the final detection of aneurysms [23,24]. In a dataset of 100 MRA studies and using all data for training and testing, our current CAD scheme achieves a sensitivity of 93.8% at an FP detection of 1.2 per patient.

2.4. *Detection of occlusion*

The overall scheme for the detection of arterial occlusion in MRA studies is shown in Fig. 3, in which the scheme consists of two parts, i.e., (1) classification of eight arteries based on the comparison of the target image with the reference image, and (2) detection of arterial occlusion(s) based on the relative lengths of eight arteries [25]. For the classification of arteries, the segmented vessel regions are classified into eight arteries based on a comparison of the target image with a reference image. For the detection of an arterial occlusion, a classifier that uses the relative lengths of the arteries as features is employed in distinguishing between the normal cases and the abnormal cases with arterial occlusions. The sensitivity and specificity for the detection of abnormal cases with arterial occlusions are 80.0% and 95.3%, respectively, for the cases of 100 MRA studies including 15 arterial occlusions.

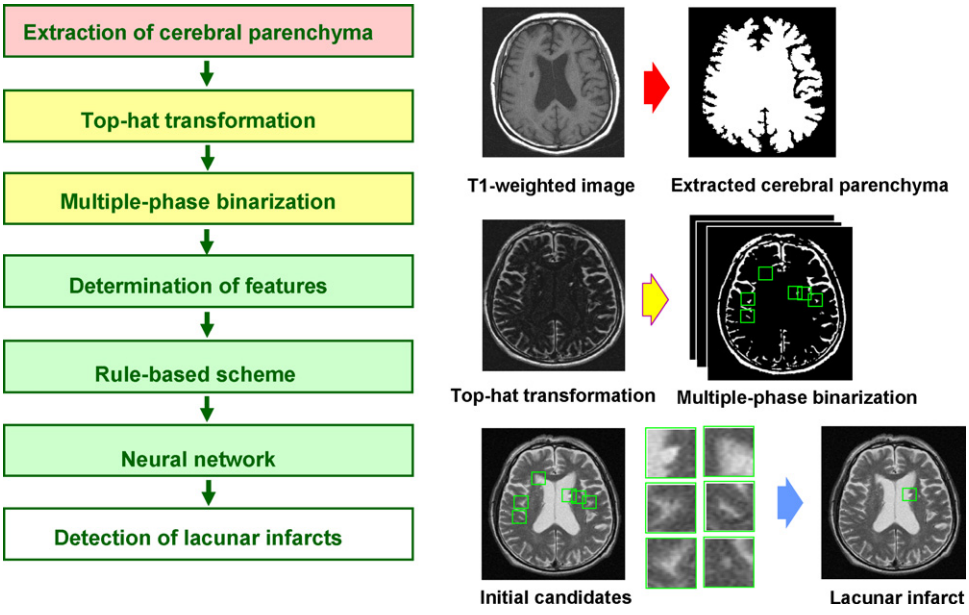

Fig. 1 – Overall CAD scheme for the detection of lacunar infarcts [22]. The detected lacunar infarct(s) is marked with a small square on the T2-weighted image, in which it appears as tiny round-shaped object with a "white" color, as shown in the bottom-right image.

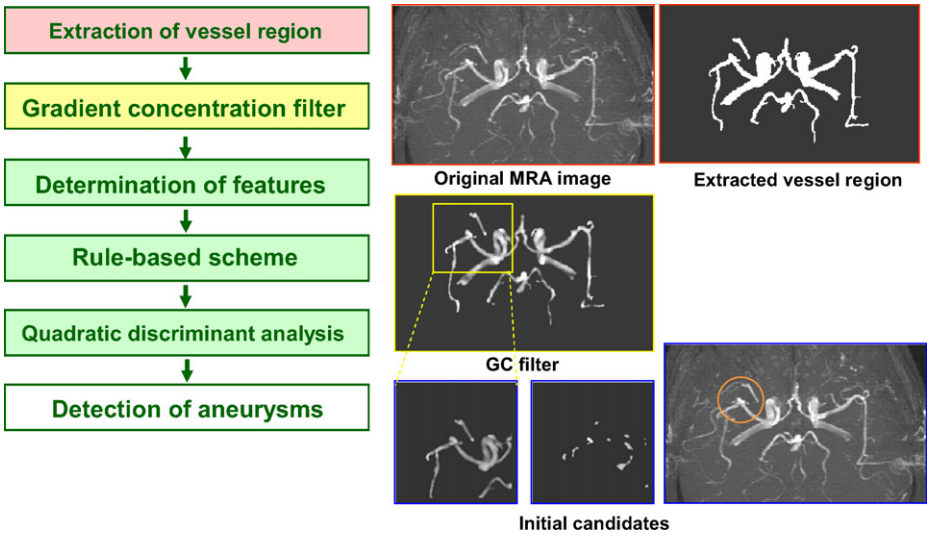

Fig. 2 – Overall CAD scheme for the detection of aneurysms [23,24]. An unruptured aneurysm is detected and is marked on the MIP image with a circle in the bottom-right image.

3. CAD for retinal fundus images

3.1. *Overview*

Retinal fundus images are useful for the early detection of a number of ocular diseases—if left untreated, can lead to blindness. Examinations using retinal fundus images are cost effective and are suitable for mass screening. In view of this, retinal fundus images are obtained in many health care centers and medical facilities during medical check-ups for ophthalmic examinations. Fig. 4 depicts the fundus images with glaucoma, diabetic retinopathy, and hypertensive retinopathy, which are targeted in this project. The increase in the number of ophthalmic examinations improves ocular health care in the population but it also increases the workload of ophthalmologists. Therefore, CAD systems developed for analyzing retinal fundus images can assist in reducing the workload of ophthalmologists and improving the screening accuracy.

3.2. *Detection of glaucoma*

In a population-based prevalence survey of glaucoma in Tajimi City, Japan, one in 20 people who are aged over 40 years was diagnosed with glaucoma [26,27]. Around the world, the number of people with glaucoma is estimated to be 60.5 million in 2010 and 79.6 million in 2020 [28]. Glau-

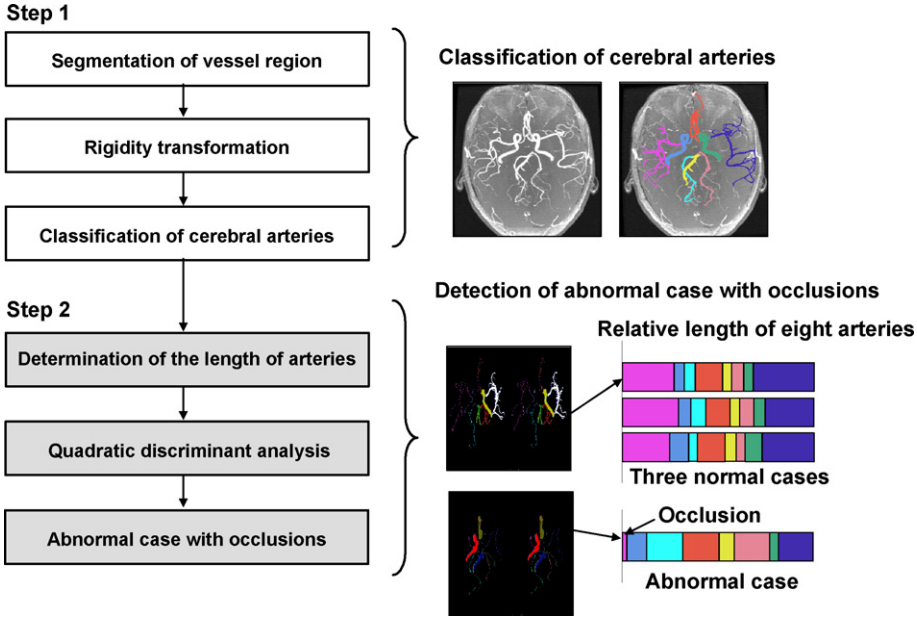

Fig. 3 – Automated detection of arterial occlusions cerebral arteries are, first, extracted and classified into eight different arteries. Occlusions are then detected based on the relative lengths of eight arteries [25].

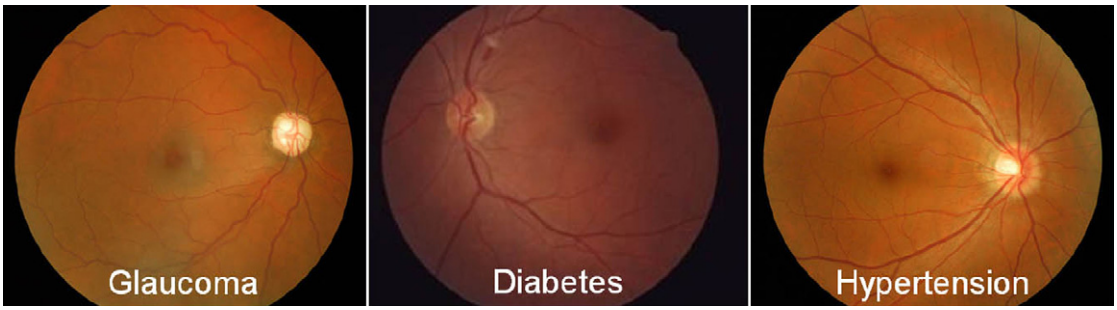

Fig. 4 – Retinal fundus images showing glaucoma, diabetes, and hypertension.

coma is the second leading cause of blindness in Japan and also worldwide. Although it cannot be cured, glaucoma can be treated if diagnosed early. Mass screening for glaucoma using retinal fundus images is simple and effective.

In the CAD system developed in this project, two different approaches are used for the detection of glaucoma. The first one is based on the measurement of the cup-to-disc (C/D) ratio. Blood vessels are first "erased" from the fundus image by image processing technique and the optical nerve head is located. The C/D ratio, which is the ratio of the diameter of the depression (cup) and that of the optic nerve head (ONH, i.e., disc), is evaluated for the diagnosis of glaucoma (Fig. 5). A total of 65 cases (47 normal and 18 abnormal) were included in the preliminary study. Using a rule-based classifier and with all cases included for training and testing, the sensitivity and specificity are reported at 77.8% and 74.5%, respectively.

We are also developing a method for measuring the depth of the cup by using our new digital stereo fundus camera along with an automatic reconstruction technique [29,30] in an extended project, as a part of the Regional New Consortium Projects from Ministry of Economy, Trade and Industry, Japan.

The second approach developed in this project for the diagnosis of glaucoma is based on the detection of retinal nerve fiber layer defects (NFLDs) using image processing techniques [31] and is shown in Fig. 6. Blood vessels in the original fundus image are erased and the optic disc is located as described previously. The fundus image is then transformed into a rectangular array before enhancing the NFLDs with Gabor filtering. The rectangular array, with the NFLDs highlighted, is then

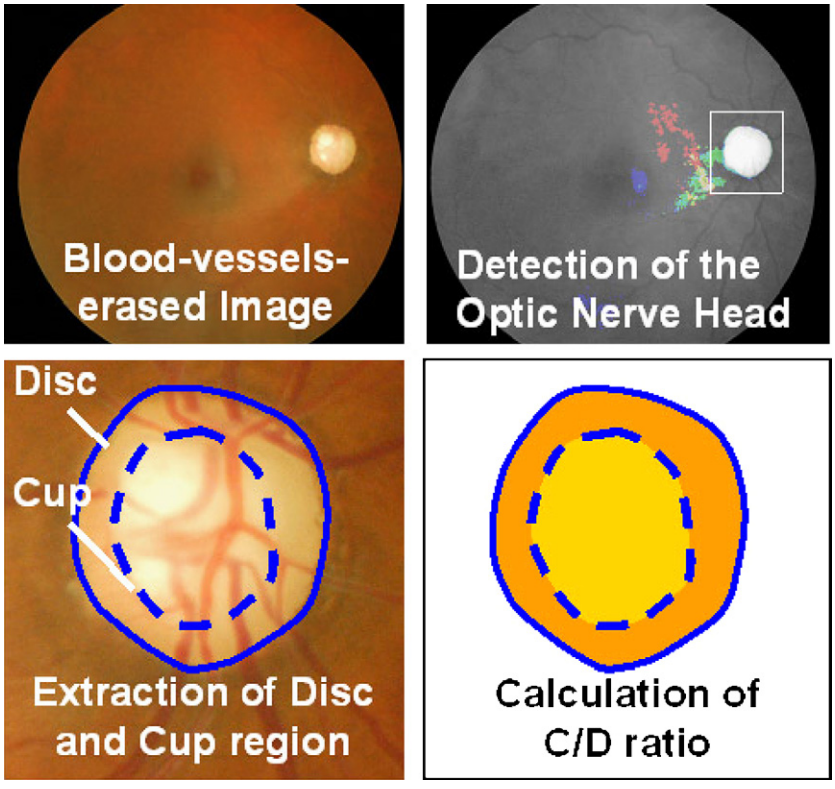

Fig. 5 – Diagnosis of glaucoma. (Left to right; top to bottom) Blood vessels are first "erased" from the original image and the optic nerve head is located. A fundus image with a C/D ratio greater than 0.60 is considered to be abnormal.

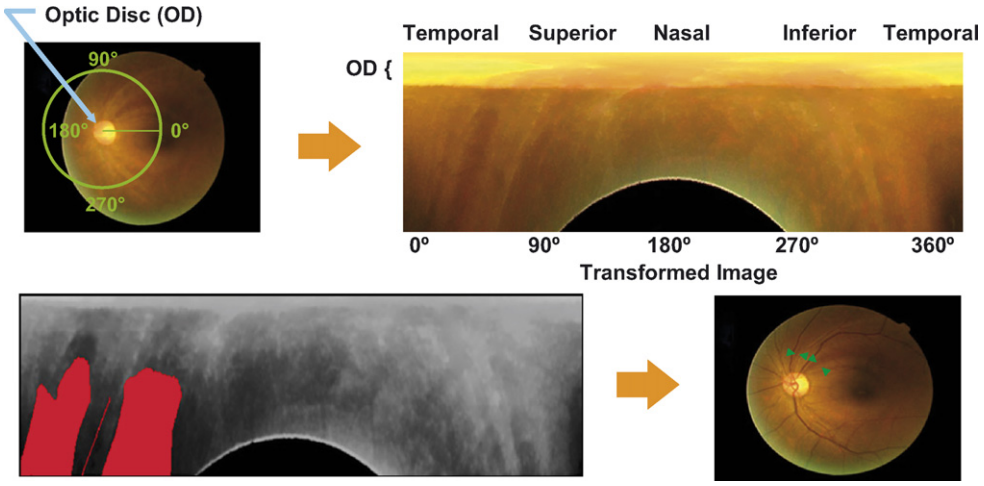

Fig. 6 – Detection of NFLDs [31]. (Top) The fundus image is transformed into a rectangular array by reading out the pixel values using polar coordinates. (Bottom left) Gabor filtering is applied to enhanced the NFLD regions (indicated in red). (Bottom right) After the elimination of FPs, the rectangular array is back-transformed and the detected NFLDs are marked using pairs of green arrows (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

back-transformed after false positive reduction. Using 26 normal and 26 abnormal fundus images with 53 NFLD regions, and a rule-based classifier with all cases included for training and testing, this approach can identify 71.7% of true positives at 3.2 FPs per image.

3.3. *Detection of diabetic retinopathy*

In Japan, the number of people with adult diseases such as diabetes and hypertension is increasing every year. Diabetic retinopathy is the leading cause of blindness in Japan; this is

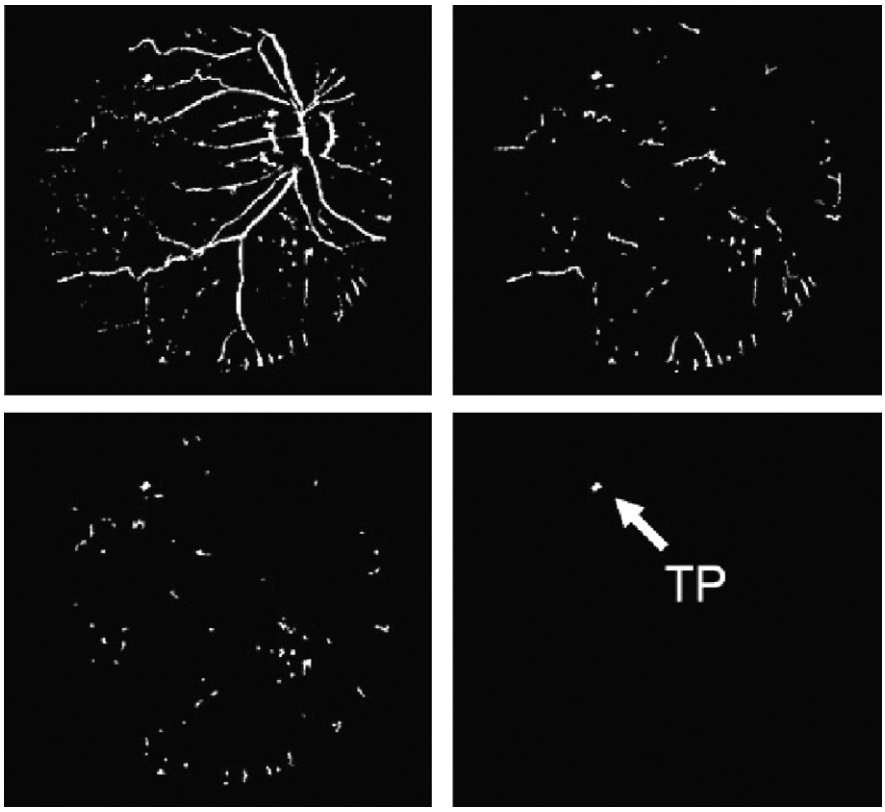

Fig. 7 – Detection of hemorrhages [32]. (Left to right, top to bottom) Initial extraction of hemorrhages with blood vessels; blood vessels are identified and erased; elimination of funicular shape regions; elimination of FPs using feature analysis. TP denotes true positive detection.

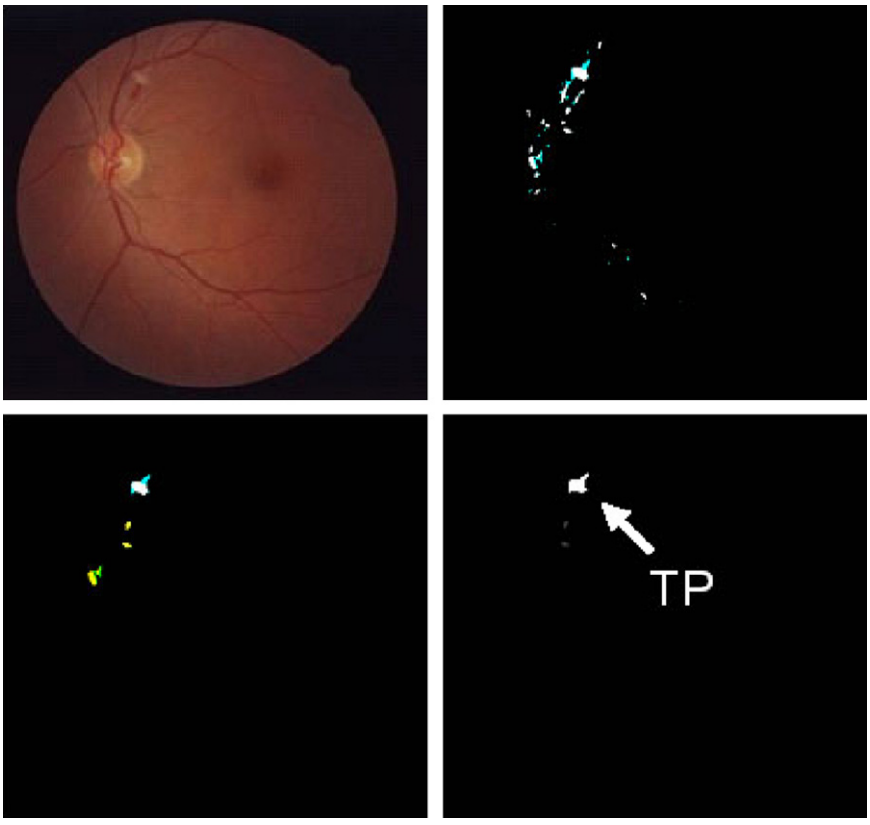

Fig. 8 – Detection of exudates [32]. (Left to right, top to bottom) Original retinal fundus image; initial detection of exudates; FPs reduction using shape analysis; FPs reduction using feature analysis. TP denotes true positive detection.

a complication associated with diabetes. The probability for diabetic patients developing diabetic retinopathy within 10 years of the onset of diabetes is high. To prevent this disease, people aged over 40 years or those who are at a risk should attend mass screening or have regular eye examinations. In an ophthalmologic examination, ophthalmologists look for the presence of hemorrhages (including microaneurysms) and exudates in the retinal fundus images.

Figs. 7 and 8 show the detection schemes developed for hemorrhages and exudates, respectively. For hemorrhage detection, the initial extraction includes both the hemorrhages and blood vessels. The blood vessels are subsequently identified and eliminated. In addition, the funicular shapes included in the initial extraction are also identified and eliminated. Further FP elimination is performed using feature analysis. A similar procedure is used in the exudates detection [32].

A rule-based classifier and linear discriminant analysis were employed in the hemorrhage detection scheme. In this preliminary study, the training set included 20 abnormal cases and the testing included 35 case with hemorrhages and 90 normal cases. Evaluation was case based and the sensitivity and specificity for hemorrhage detection were found to be 80.0% and 87.7%, respectively. A rule-based classifier and linear discriminant analysis were also employed in the exudate detection scheme. The entire dataset of 109 cases (13 with exudates and 96 normal) were used for training and testing. Evaluation was case based and the sensitivity and specificity for exudates detection were found to be 76.9% and 83.3%, respectively.

3.4. *Detection of hypertensive retinopathy*

Hypertensive retinopathy can also benefit from the analysis of retinal fundus images. With severe hypertensive retinopathy, the damage to the optic nerve or macula can be permanent. Fig. 9 shows the hypertensive retinopathy detection scheme based on the measurement of the vascular diameter [33]. Our scheme comprises the extraction of blood vessels, classification of arteries and veins, and detection of arteriolar narrowing by the artery-vein diameter ratio (A/V ratio). A rule based classifier was used in the detection scheme and an A/V ratio <0.67 is considered as abnormal. In a preliminary study using 39 normal and 44 abnormal cases with arteriolar narrowing in the fundus images and a two-fold cross validation technique, the system can identify 76.2% of true positives at 1.4 FPs per image.

4. CAD for ultrasound breast images

4.1. *Overview*

In Japan, breast cancer has the highest incidence rate among all the cancers in women [34]. It is also one of the most common causes of cancer death for women in many Western

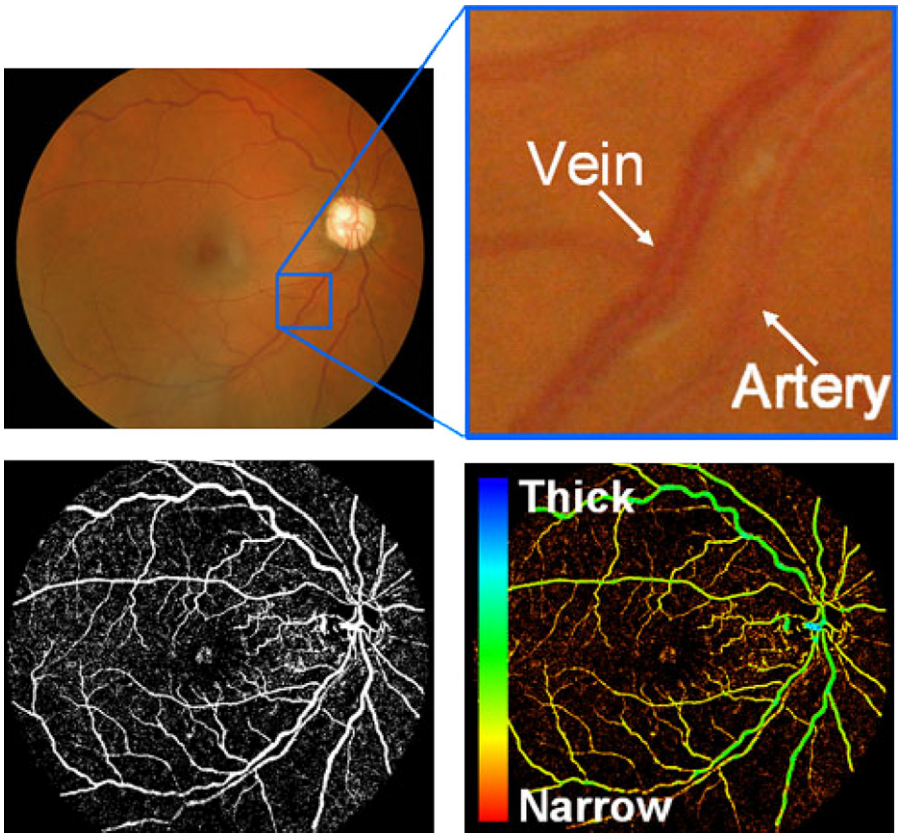

Fig. 9 – Detection scheme of hypertensive retinopathy [33]. (Left to right, top to bottom) Original retinal fundus image; magnified view showing the difference in the diameter between a vein and an artery; extraction of blood vessels; the ratio of the size of the artery to that of the vein (A/V ratio) is determined. An A/V ratio <0.67 is considered as abnormal.

countries. Early detection of breast cancer is the key to simpler treatment and a better prognosis. In view of this, many countries, including Japan have introduced breast cancer screening programs. Mammography is widely used in breast cancer screening. Its effectiveness in detecting breast cancer in women aged over 50 years, typically with less dense breast tissues, has been established. However, mammography is less effective for younger women or women with dense breast tissues.

In Japan, women typically have denser breast tissues than their counterparts in Western countries. Consequently, the image contrast between cancerous breast mass tissues and

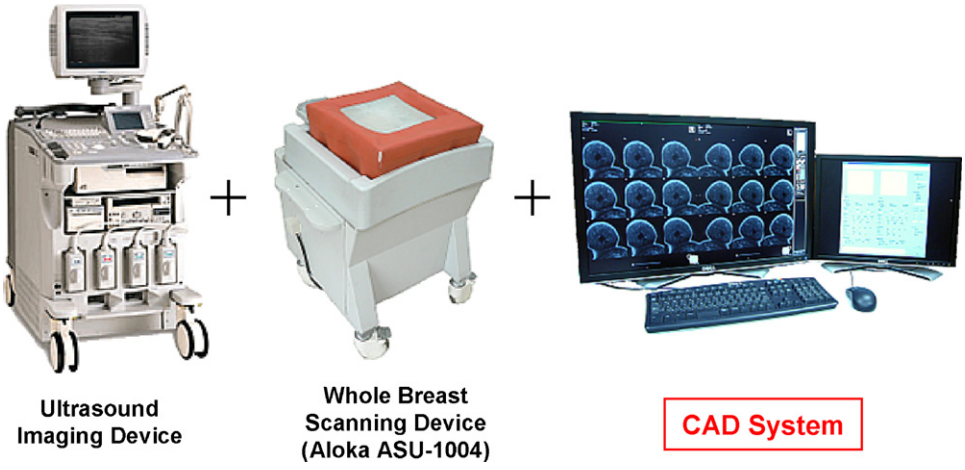

Fig. 10 – An overall system for breast cancer screening using ultrasound images. The system consists of an ultrasound imaging device and a whole-breast scanning device for whole breast volumetric data acquisition. A workstation is also included for the purpose of pre-processing and analysis of the images acquired by the scanning device from the patient and as a viewer for the visualization of the images along with the CAD results [35].

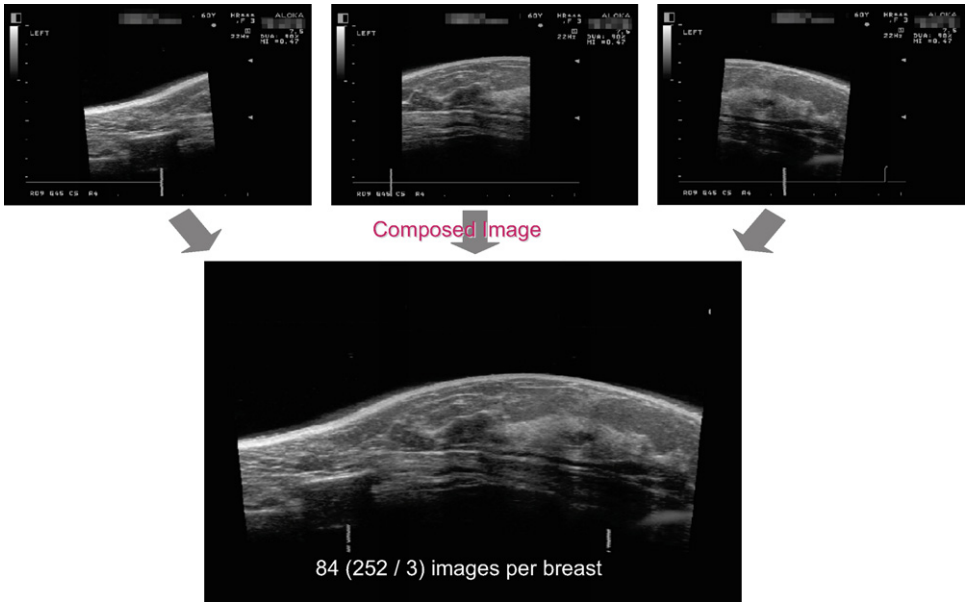

Fig. 11 – The 3-D whole-breast volumetric data is constructed by "stitching" together the images from the three sweeps (only one slice is shown) [35].

the dense breast tissues in mammographic images is low; thus, the detection of breast cancer over a background of dense breast tissue is difficult. Ultrasonography, on the other hand, is effective in distinguishing and characterizing breast masses set in a dense-breast-tissue environment. Currently, breast ultrasound is primarily used for the diagnosis of breast cancer, as opposed to the screening of breast cancer. There is a growing need for ultrasound examination to be available for breast cancer screening in women with dense breast tissues.

4.2. *Whole breast scanner and CAD*

Current diagnostic ultrasound breast images are obtained using conventional hand-held probes. Here, the results of the examinations are operator dependent and the reproducibility is poor. Moreover, the procedure is lengthy if the whole breast is to be scanned.

Fig. 10 shows our system developed for breast cancer screening using ultrasound images. An automatic whole-breast scanner (ASU-1004, Aloka Co. Ltd., Japan) is used

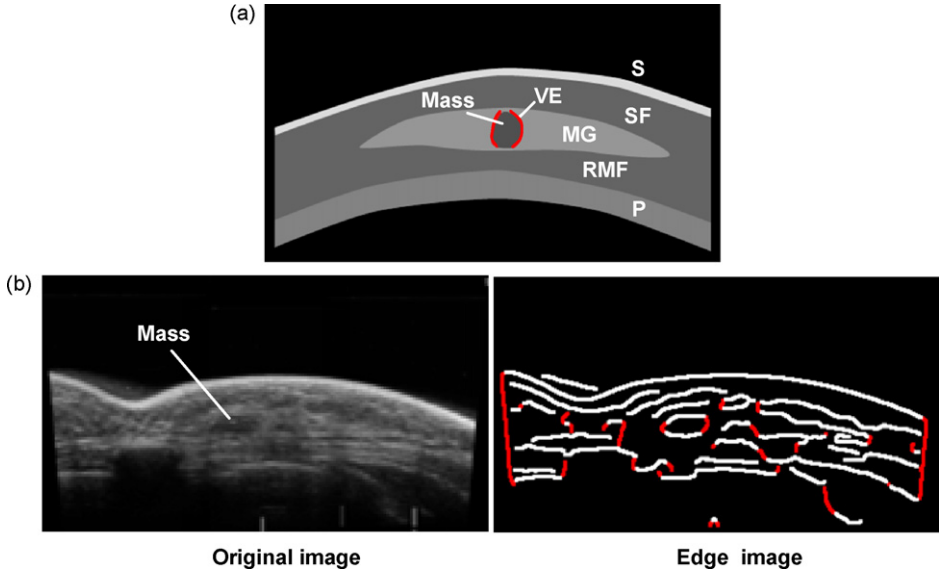

Fig. 12 – Illustration of the detection of a hypoechoic breast mass. (a) Schematic diagram of structures in a breast ultrasound image where S is skin layer, SF is subcutaneous fat, MG is mammary gland, RMF is the retro-mammary fat, P is pectorals and VE is a near-vertical edge of the mass. (b) The original breast ultrasound image and the processed edge image are shown [35].

in acquiring and screening breast images. The scanner is an automated water path system and can scan the whole breast in sweeps. A 3-D volumetric whole breast data is reconstructed from the original scans in the workstation, which has a capability of the image viewer with CAD function [35] (Fig. 11).

Using a Canny's detector, the edge information in the ultrasound images is enhanced and analyzed (Fig. 12). Normal structures in breast ultrasound images typically do not contain vertical edges. The detection of vertical edges in the image suggests abnormal structures [35]. Based on 109 whole-breast ultrasound patient cases and using all cases for training and testing, our CAD system for breast-mass detection achieves a sensitivity of 80.5% at 3.8 FPs per breast. A CAD system that uses a bilateral subtraction technique to reduce the FPs detected by the mass detection scheme has also been developed [36]. It was found that a scheme for FP reduction based on the bilateral subtraction technique can effectively reduce FPs because 67.3% of the FPs was reduced without removing a true positive region.

5. Conclusion

As part of the "Knowledge Cluster Initiative" by the Japanese government, three CAD projects are being developed in the Fujita Laboratory, Gifu University since 2004. The three CAD projects are motivated by the Japanese health-care needs which extend to the health-care needs in Asia and Western countries. All of the three CAD projects are proceeding very well thus far. Although the three CAD projects are works-in-progress, preliminary results are presented in this paper. For clinical evaluations of the three systems, much larger databases are required. The acquisition of large databases for clinical evaluation and improvement in the algorithms are the next milestones of the projects. According to our plan, commercialized CAD systems in the field of brain MR images, fundus images, and breast ultrasound images will appear by the completion of this project (March 2009).

Conflict of interest

None declared.

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