An overview of mammogram analysis

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A mammogram is an X-ray image of the human breast. It is used for the detection and diagnosis of changes in breast tissues. Asymptomatic women may be encouraged to undergo screening mammography on a regular basis after reaching a certain age. In most cases, mammograms reveal information that could yield the detection of suspicious lesions by breast radiologists (BRs). Hopefully, the detection is achieved before the lesions have advanced to a late stage of cancer, which makes it difficult to cure.

Lesions can be characterized as masses, calcifications, or architectural distortions. A mass is an accumulation of cells in one specific location that can be benign or malignant. Calcifications are tiny bright deposits of calcified milk. Calcification is characterized as benign or malignant based on its shape, size, contour, and its count in one location. Architectural distortion appears when lesions destroy the normal architecture of the breast with no presence of a mass. Since a mammogram is a two-dimensional (2-D) projection of a complex three-dimensional (3-D) object, this makes it challenging to identify all ill-defined lesions using mammography. Many factors, such as breast density, overlapping tissues, and the lesion's size, affect the accuracy of mammogram analysis.

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Computer-aided diagnosis (CAD) has been developed to assist radiologists in detecting breast lesions.

Breast anatomy

The breasts of female mammals are active organs that are responsible for nourishing the newborns with milk. The female hormones become active in the breasts during puberty. These hormones stimulate the breast glands to grow into a spherical shape. When a gestation period ends, the female hormones boost the terminal ductal lobule units (TDLUs) within the lobes to produce milk and transfer it to the nipple through the ducts. Figure 1 shows the anatomy of the breast with a magnified TDLU.

The breast lies on the superficial fascia that covers the anterior and lateral parts of the pectoralis major muscle. The space between the breast and the pectoralis major muscle is the retromammary space, which consists of adipose tissue and connective fascia. The breast tissues extend vertically from the clavicle bone located on the second or third rib to the abdominal wall located on

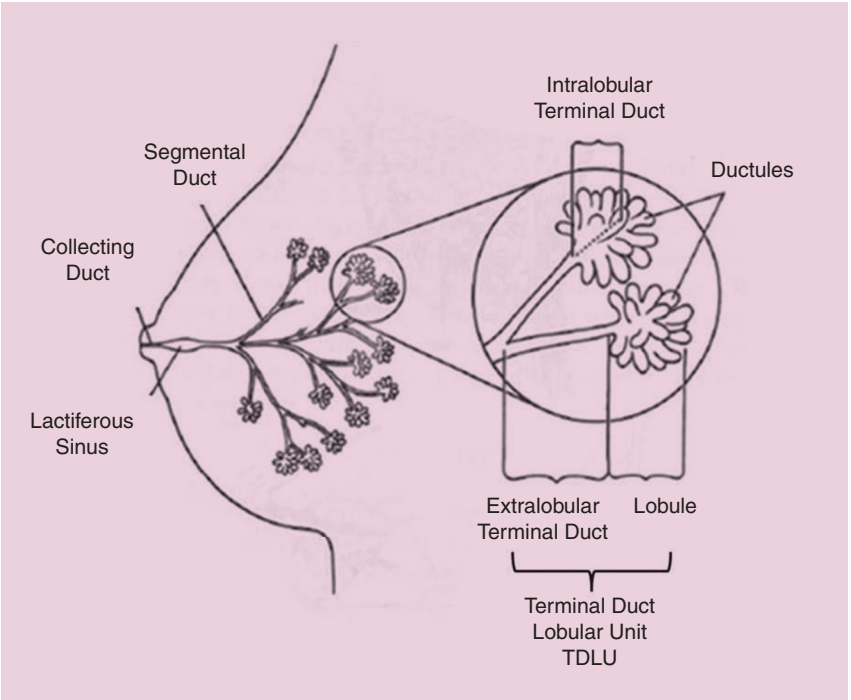

FIG 1 The anatomy of the breast. (Image used with permission from L. Tabár, 2014.)

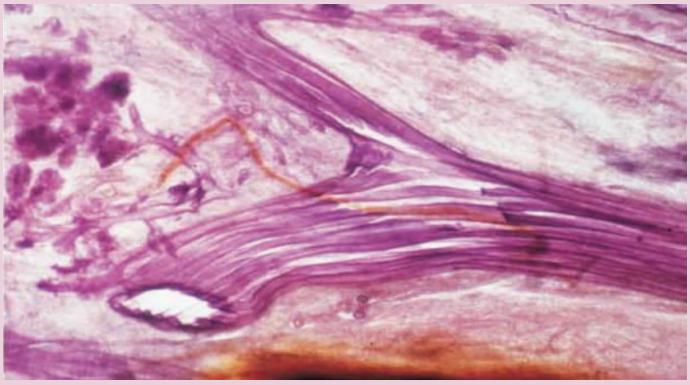

FIG2 The 3-D histology of a main duct. (Image used with permission from L. Tabár, 2014.)

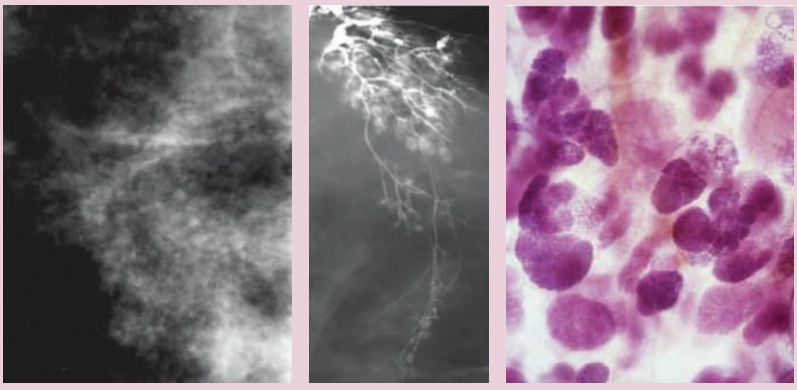

FIG3 (a) A mammogram, (b) a galactogram, and (c) a subgross histology with numerous lobules outlined by fat. (Images used with permission from L. Tabár, 2014.)

the sixth or seventh rib. Horizontally, the breast tissues extend from the axilla and the side muscles to the sternum bone.

The external anatomy of the breast consists of the skin, nipple, areola, tubercles, and several glands. The breast skin contains sweat glands, oil glands, and hair follicles. The nipple is located at the center of the breast or slightly below the center. The nipple's texture is soft to firm, with a flat, round conical, inverted, or cylindrical shape. The areola is the smooth, dark pink, circular area that surrounds the nipple. The areola consists of several small bumps that are known as the tubercles of Montgomery and are responsible for lubricating the nipple during the lactation period.

A network of lobes that is responsible for producing milk resides within the connective and fatty tissues. Each lobe is of a circular to pyramid shape with an individual duct that has its own opening on the nipple surface. Figure 2 illustrates a 3-D histology of a main duct. The branching ducts inside each lobe subdivide it into a number of lobules. Each lobe may contain ~10–100 lobules. Each lobule consists of several acini (ductules) and intralobular terminal ducts (ITDs). The ductules are located at the far end of the lobule and are the basic units responsible for milk production. The extralobular terminal ducts (ETDs) and the lobule form the TDLU. The connective tissues hold together and support the glands inside the breast. Fatty tissue is part of the connective tissues that gives the breast its smooth contours. A network of nerves, blood vessels, and lymph vessels reside within the connective tissues. Figure 3 displays lobules imaged using (a) an X-ray mammography image, (b) a galactogram, and (c) subgross histology techniques, respectively.

Breast cancer

Breast cancer is a life-threatening disease of unknown cause that affects women around the globe. According to the American Cancer Society, breast cancer is the second leading cause of cancer death

among women in the United States and the leading cause of death around the globe. The probability of developing breast cancer is higher among women who live in developed countries such as the United States, the United Kingdom, and Australia.

The statistics given in Fig. 4 demonstrate the female breast cancer incidence and mortality based on race and ethnicity in the United States for the period 2006-2010 according to the American Cancer Society. During 2014, the annual incidence of invasive malignant breast cancer in the United States was approximately 232,670 cases and 62,570 additional cases of *in situ* breast cancer. The estimated deaths were 40,000 cases. Women who live in southern European and South American countries have intermediate breast cancer incidences and death rates, while women in Asian and African countries have low incidences and death rates. This is partly related to low screening rates and incomplete reports in the developing countries. The low estrogen level in male bodies results in an atrophic breast organ with less probability of developing breast cancer compared to female bodies. During 2014, 2,360 new cases were expected to occur among men in the United States, with estimated deaths of 430 cases.

Breast cancer is initiated when abnormal cells line up along the duct or lobules. Most of the abnormal cells originate in the duct to form a ductal or duct cell carcinoma. Abnormal cells formed in the lobules are known as *lobular carcinoma* and are less common.

Breast cancer types

When the cancerous cells are localized in the ducts or lobules and have not invaded surrounding tissues or spread to other organs, they cause noninvasive or in situ breast cancer. Invasive or infiltrating cancer spreads beyond the duct or lobule to the surrounding breast tissues and it may metastasize to other body organs through the blood or lymphatic fluid. Noninvasive breast cancer, if not treated, could develop into an invasive one.

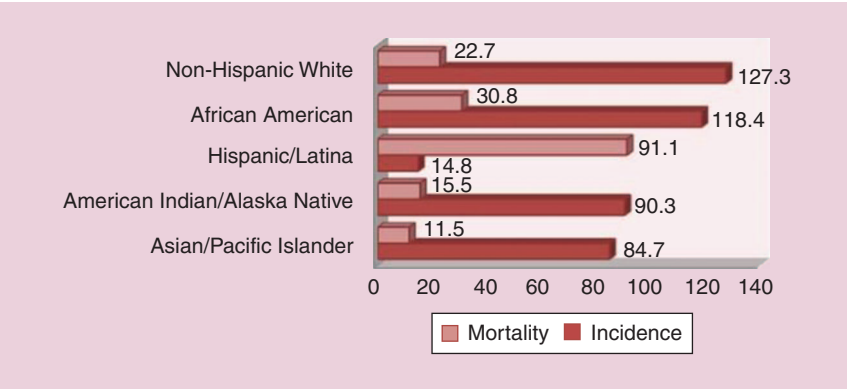

FIG4 Female breast cancer incidence and mortality rate by race and ethnicity, United States, 2006–2010. (Statistics courtesy of The American Cancer Society, 2014.)

The most common types of invasive breast cancers are infiltrating ductal carcinoma (IDC) and infiltrating lobular carcinoma (ILC). IDC initiates in ducts and accounts for 75% of all invasive breast cancer, while ILC starts in lobules or lobes and accounts for 15% of all in invasive breast cancer. Ductal carcinoma in situ (DCIS) is the most common noninvasive breast cancer. The distribution of the breast cancer subtypes is summarized in Fig. 5.

Signs of breast cancer

The primary signs of breast cancer include masses, architectural distortions, and calcifications. When large numbers of abnormal cells cluster together in one location they form a mass. Approximately 80–85% of noninvasive breast's carcinomas are of mass shapes. The density, margins, size, and shape of the mass determine the likelihood that a lesion is malignant. As seen in Fig. 6, masses that are round, oval, and lobulated are mostly benign. The most common malignant types of masses are nodular and stellate.

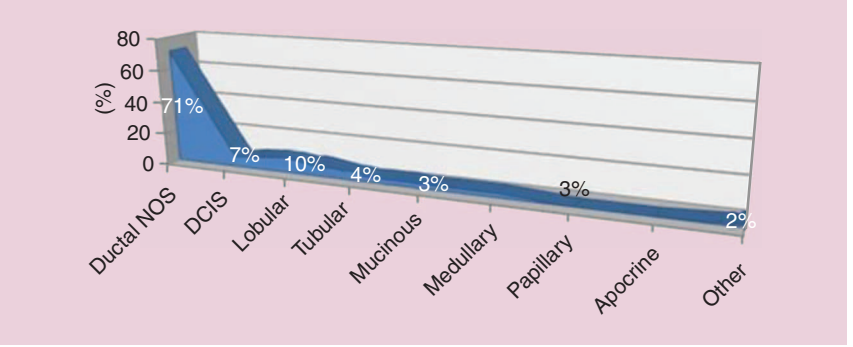

FIG5 The distribution of breast cancer subtypes. [Statistics courtesy of (L. Tabár, 2014).]

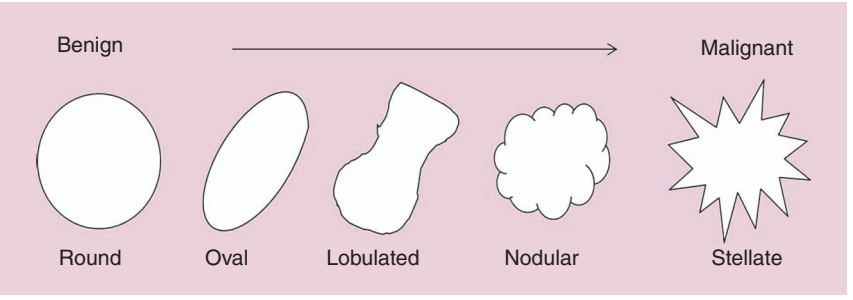

FIG6 A characterization of masses based on shape and boundaries. (Used with permission from Bruce and Adhami, 1996.)

They account for 47.7% and 35.4% of the invasive cancers, respectively.

Massive lesions are mostly considered as the pathological evaluation of calcifications. Calcifications are tiny particles with different patterns. Calcifications are more likely to occur in young patients, with a probability of 63% for patients younger than 50 years old. Determining the malignancy of calcifications is a challenging task because of their fuzzy appearance and difficulty of distinguishing them from their surroundings, especially in dense breasts. The location, distribution, density, and the shape of the calcifications are commonly used to classify them as benign or malignant. Linear and segmental calcifications are of malignant nature while diffuse and regional are of benign nature.

Calcifications can be an early sign of breast cancer, as 30–50% of the early detected breast cancers were through the appearance of clusters of fine granular microcalcifications. Calcifications formed in the ducts through a bilateral process known as *secretory disease* and results in secretory-type calcifications. There are two mammographic presentations for the secretory type: intraductal and periductal forms. Intraductal calcifications have a long needle shape that reflects the duct shape, while periductal have hollow ring-like or tube-like shapes.

Another type of calcification formed in the duct is the casting type, which can be further subdivided into fragmented and dotted casting types. Calcifications formed in ducts are most likely to be malignant. Calcifications can be formed in the terminal ductal lobule units (TDLUs) as well, and examples of these calcifications are crushed stone-like and powdery, and cotton ball-like calcifications

Architectural distortion is the third-most prevalent sign of nonpalpable breast cancer. Architectural distortions accounted for almost 20% of the detected cancers along with asymmetry, single dilated duct, and developing densities. It is reported that 79% of the architectural distortions are due to invasive cancer in the breast tissue.

According to the Breast Imaging Reporting and Data System (BI-RADS), an architectural distortion occurs when the normal architecture of the breast is distorted with no definite mass visible. BI-RADS is published and trademarked by the American College of Radiology (ACR) based on the collaborative effort of many health groups. Architectural distortions include focal retraction or distortion at the edge of the parenchyma and spiculations radiating from a point. In addition, sometimes architectural distortions appear as the initial stage of an obvious mass shadow. Other signs of architectural distortions include asymmetrical thickening and straightening of fibrous connective tissues, asymmetric density in one breast, or fibrotic changes that produce a "purse-string" appearance.

Screening mammography

The main aim of using screening mammography is to detect malignant carcinomas while they are still localized in the breast. Many health organizations encourage asymptomatic women of a certain age to undergo screening mammography on a regular basis. Despite its popularity, screening mammography is a controversial issue. Some experts believe that the overdiagnosis and false positive rates, associated with using screening mammography surpass its benefits. Others argue that screening mammography is not 100% effective, since it produces numerous false positive rates. Some experts are proposing individualizing screening mammography based on the risk factors. At this point, women have to decide how often they want to perform screening mammography and embrace the risk associated with their decisions.

Breast cancer is a disease with ambiguous symptoms. In most cases, it takes several years for the disease to present physical symptoms, which may manifest during its late stages. Without the use of screening mammography, detection of these malignant deadly carcinomas may not be possible.

In the screening mammography procedure, a low-dose X-ray is passed through the breast tissues. Connective and fatty tissues, masses, and calcifications have different attenuation factors for the X-ray and appear with different brightness levels on the mammogram. Masses and calcifications usually appear brighter compared with other normal tissues. Figure 7 shows the mammographic representation for a) a mass, b) calcifications, and c) an architectural distortion, respectively. There are two standard projections for screening mammography: craniocaudal (CC) and mediolateral oblique (MLO) views. The CC view shows the medial part of the breast, and the nipple must be in the profile. The external lateral portion may also be included in the CC view, while the retromammary space is only shown in 20% of cases. The pectoralis major muscle appears in only 30–40% of the cases. Most of the breast tissues are captured within the MLO view. The retromammary space, as well as the pectoralis major muscle, must appear in the MLO to indicate correct positioning of the breast during the MLO procedure.

An accurate mammogram analysis depends on the quality of the images and the radiologist's skills and experience. Radiologists carefully examine the mammogram views to search for suspicious lesions, masses with ill-defined margins, breast asymmetry, and microcalcifications. Standard definitions established by BI-RADS are used to interpret the mammogram findings. These definitions help to maintain standardized terminology that facilitates communication between the radiologist and the physician.

Screening mammography shortcomings and benefits

Screening mammography does not provide a perfect diagnosis. Similar to any other diagnostic tools, it includes false negative, false positive, and overdiagnosis rates. False negative detection can result in giving a

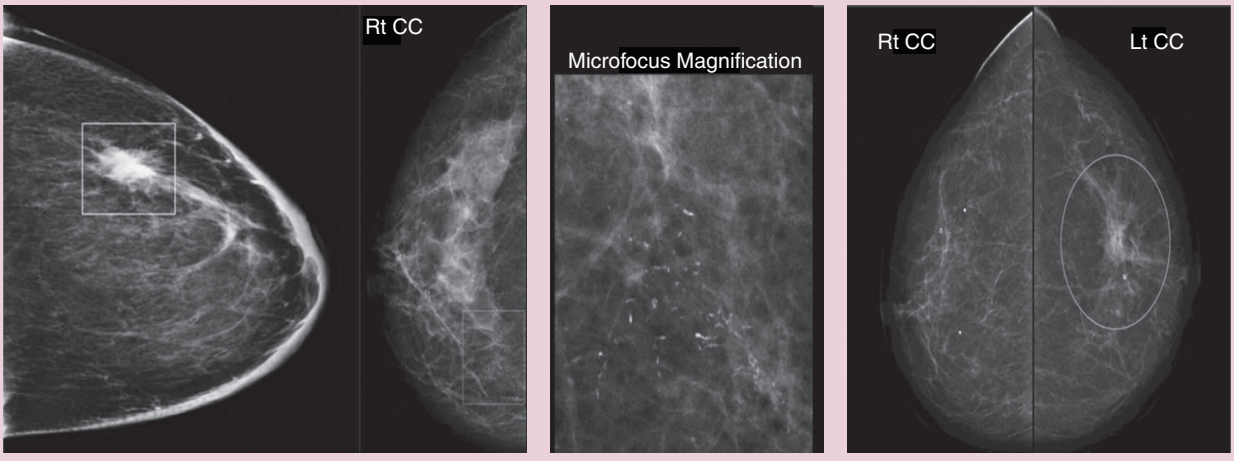

FIG7 A mammographic representation of (a) a mass, (b) calcifications, and (c) an architectural distortion. (Used with permission from L. Tabár, 2014.)

patient the assurance of a cancer-free body while she may be developing a carcinoma. On the other hand, a false positive places the emotional pain of having cancer on the patient, as well as having her go through multiple tests and biopsy procedures while her body is, in fact, cancer-free. Screening mammography by itself is a stressful procedure that costs time and money and produces anxiety. This procedure requires compressing the breast, which may be uncomfortable, and, of course, exposure to X-rays. Therefore, as mentioned previously, individualizing the procedure may be the best option.

One advantage for screening mammography is its effectiveness in detecting nonpalpable malignant lesions in asymptomatic women. It has been documented that the carcinomas found during screening mammography are usually detected during the early stages of the disease. Patients with early detected cancers have higher survival rates and more successful treatment options in comparison to patients with cancer detected at later stages.

Computer-aided diagnosis

On any given day, radiologists examine numerous mammograms. Biopsy, magnetic resonance imaging (MRI), and exaggerated mammogram views are tools used by radiologists to examine breast areas that need further attention. Unfortunately, 10–30% of breast lesions are overlooked by radiologists during routine screenings. A retrospective study (including malignant cases only) showed that in 48% of the cases, minimal signs were visible on prior mammograms. Furthermore, 9% of malignant cases were visible on screening mammograms obtained two years earlier. Also, the sensitivity in locating lesion in mammograms for women with BRAC1 or BRAC2 gene mutations is found to be low in the 16–40% range.

One of the reasons behind the high false negative rates is the interpretation of a large number of mammograms by radiologists on a daily basis for detecting a small number of cancers. One obvious solution is to double read each mammogram by two radiologists to confirm the findings. Clearly this solution produces more accurate interpretation for mammograms, from 81.4% to 88%. Additionally, the double reading of screening mammography has increased the detection rate of breast cancer by 4–15%.

This practice is not always implemented in countries that lack a sufficient number of BRs. An alternative solution may be through developing an automated diagnostic system that uses a fast computational environment for providing a second opinion. For many years, research has been conducted in the area of mammogram analysis for that purpose. The main goal of developing such a system is to improve the accuracy and consistency of mammogram interpretation by radiologists and to detect small gradual changes in the breast tissue.

The developed system is known as CAD. In the medical community, CAD is a second observer for screening mammography because human decision-making and observation mechanisms are considered more reliable and trusted in comparison to those made by machines. Ideally, CAD should improve the quality of service provided to patients, and patients should not suffer from faults due to device failures. CAD is considered one of the major research subjects in medical imaging and diagnostic radiology.

The CADs have two stages: detection of suspected lesion locations and reduction of false-positive rates. The first stage should provide high sensitivity in detecting carcinomas, while the second stage should have high specificity to reduce the false-positive rate. The CAD outcome is illustrated as a set of marks on the mammogram identifying suspicious lesions.

The importance of CAD

In 1998, the U.S. Food and Drug Administration (FDA) approved CAD

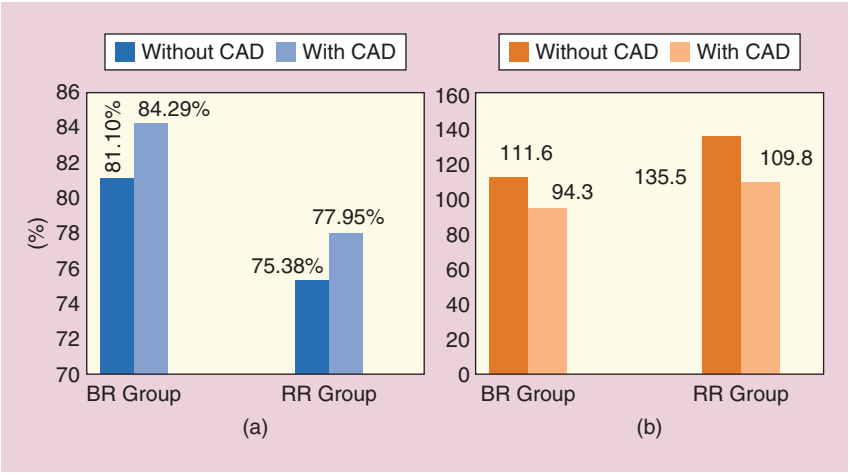

FIG8 (a) Sensitivity and (b) reading time (in minutes) for BR and RR groups. (Statistics courtesy of Young, 2014.)

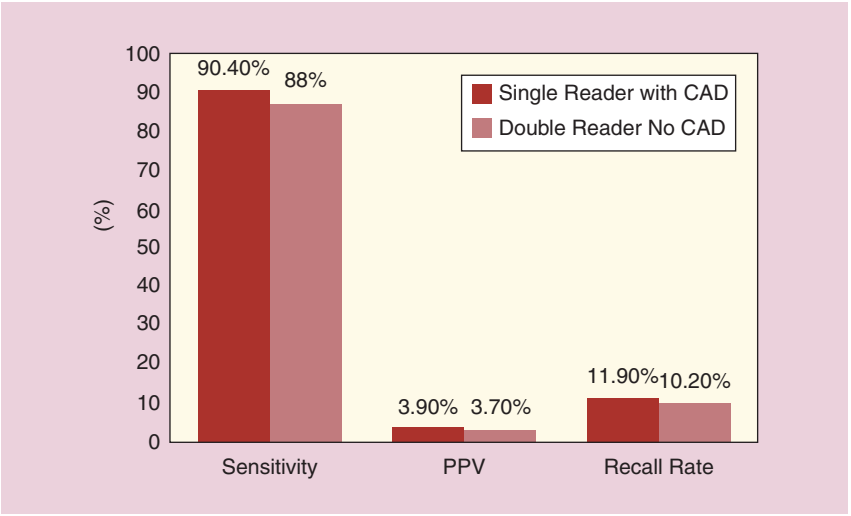

FIG9 Comparing the performance of a single reader with CAD and double readers without CAD. (Statistics courtesy of Gromet, 2008.)

to be a part of the screening mammography procedure. CADs have proven to be particularly effective in increasing the cancer detection rate, and CAD has been beneficial in reducing false-negatives. Measuring CAD sensitivity has shown that it has the ability to mark most of the asymptomatic breast cancers. Many studies demonstrated that CAD has improved the diagnostic performance of resident radiologists and reduced the reading time.

In a retrospective study done by (Young, 2014), 100 cases of both CC and MLO views were examined by seven BRs and 13 radiology residents (RRs), with and without the use of CAD. These cases included 15 with malignant masses, 15 with benign masses, 15 with benign microcalcifications, and 40 with normal tissues. The results for each group's sensitivity are shown in Fig. 8(a). The reading time with and without the use of CAD are given in Fig. 8(b).

It has been shown by (Groment, 2008) that CAD increases the sensitivity for screening mammography in comparison to double-reader practices as seen in Fig. 9, where PPV is defined as the positive predictive value for the detection of carcinomas within one year of the screening date. Research conducted by (The, 2009) computed the CAD detection rates for different factors that include breast density, mammographic presentation, tumor size, and histopathology. The results are given in Fig. 10. When CAD was used, the p-value for breast density, histopathology, and tumor size categories were 0.274, 0.922, and 0.138, respectively. CAD's false positive rate was 2.3 per case, where a case includes four images: the right and left views of both MLO and CC.

CAD systems methodology

A general block diagram for algorithms used in CAD is demonstrated in Fig.11. This block diagram consists of three phases: training, testing, and evaluation. The training phase includes two steps: preprocessing and feature extraction. In the preprocessing step, image filtering and transformations are applied to provide higher-quality mammograms and to filter out excess noise. In the feature extraction step, features that best characterize the lesions and normal breast tissue are extracted. Feature extraction can be done manually or by using algorithms such as edge detection, segmentation, and morphological operations.

Classification phase classifies the extracted features into benign and malignant features. The extracted features are used to teach the patterns to the machine. Classification is based on thresholding approaches or even through the use of machine-learning algorithms, such as neural network, support vector machine, and boosting algorithms.

Finally, the algorithm is evaluated using reliable methodologies such as receiver operating characteristic. The developed algorithm must meet criteria in the sensitivity, specificity, and positive predictions measurements. The developed algorithm is tested using a mammogram data set. The mammogram data set consists of numerous cases with malignant and benign findings. The mammogram data set is subdivided into two subsets: training and testing.

CAD systems shortcomings

The main aim of using CAD systems for screening mammography is to increase the sensitivity of breast cancer detection with no impact on the recall rate. However, in many

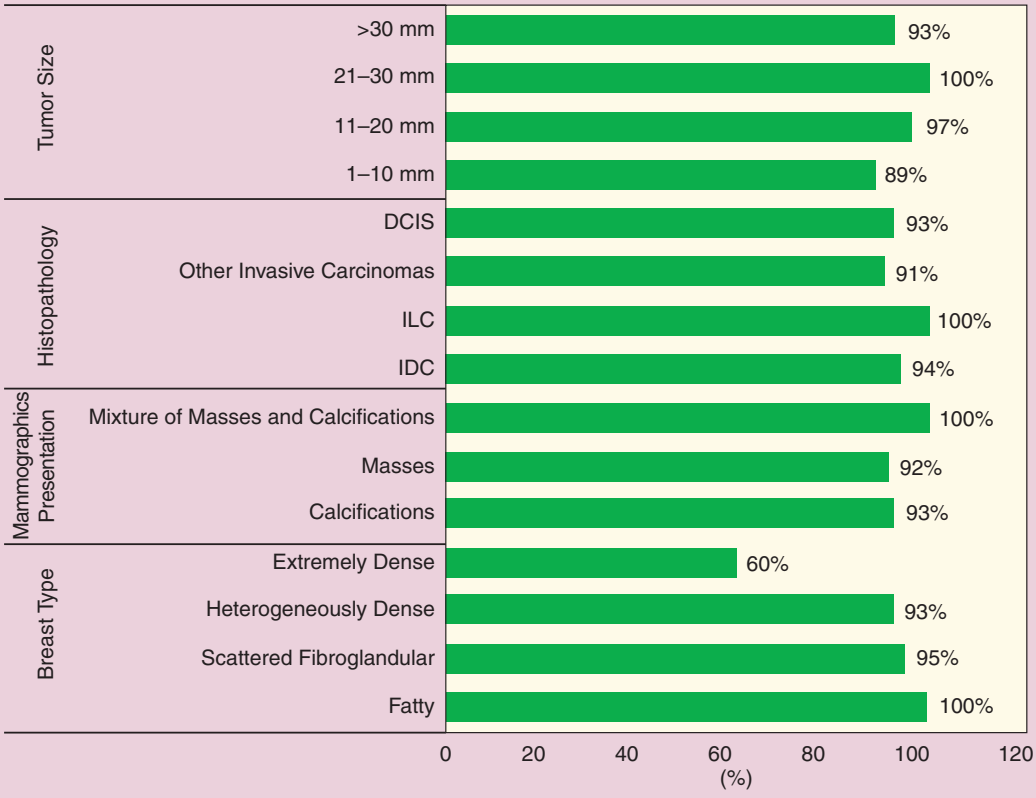

FIG10 CAD detection rate based on different factors. (Statistics courtesy of The, 2009.)

studies, CAD has been found to increase the recall rate. CADs are effective in identifying lesions associated with the presence of calcifications, masses of large size, and mixtures of masses and calcifications. Nevertheless, CADs are not mature enough to detect all the carcinomas, as 10–15% of breast cancers are missed by CAD. Another shortcoming for CAD is the reduced sensitivity for dense breasts; when the breast density increases, the screening mammography becomes a challenging task.

CAD is considered a nonharmful tool with no direct impact on the patient's safety. In many cases, CAD has been found to reduce the false negative rates and to increase the detected carcinomas, especially in the early stages.

The current CADs contain a reference database of malignant and benign findings. The reference database is used to locate and determine the malignancy of future findings in new mammograms using pattern recognition algorithms. CADs contain no algorithm to compare temporal mammograms for the same patient. Temporal mammograms are acquired during different sessions over a period of time—months or even years—for the same patient. Registering temporal mammograms help to locate gradual malignant changes in the breast tissue in the early stages of the disease.

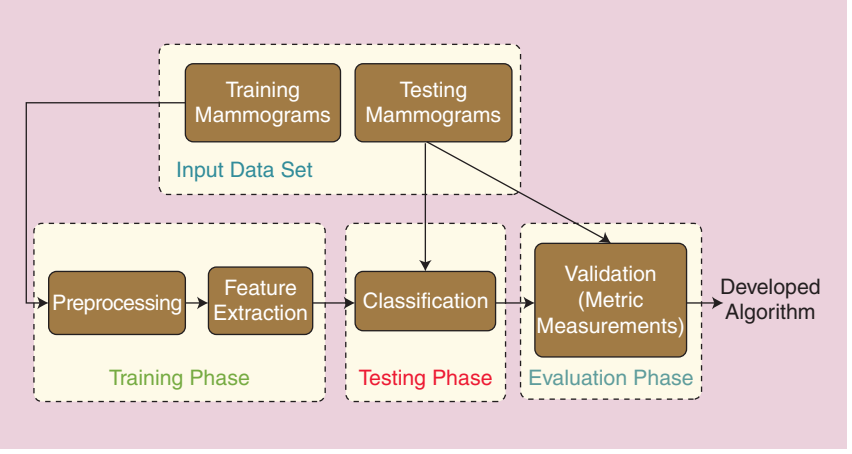

FIG11 A general block diagram for algorithms used in CAD.

An architectural distortion destroys the normal pattern of the parenchymal tissue due to carcinomas cells. Current CADs do not include detection of these distortions. More research needs to be conducted for automating detection of breast architectural distortions.

Conclusion

Early detection of breast carcinomas increases the survival rate with more successful treatment options. To detect breast lesions at their early

stages, a screening program has been launched around the globe. In this procedure, modalities such as mammography are used to acquire X-ray images for the breast tissue and to differentiate between normal and abnormal breast patterns. Screening mammography could be helpful to those with a family history of having breast cancer or with signs that could be indicators of developing cancer.

Nevertheless, screening mammography remains a controversial issue; it lacks the consistency and suffers from factors including false-negative, false-positive, and overdiagnosis rates. Screening people at a higher risk of developing breast cancer is more preferable than recommending it for all women after a certain age.

For every 1,000 screening cases, 100 are called back for extra investigations, and fewer than ten are of a malignant nature. Routine examination of large numbers of mammograms by radiologists is a challenging task. The advancement in technology has urged scientists and engineers to develop an automated system that could assist radiologists to read a large number of mammograms. The automated system is recognized as CAD and uses digital image processing algorithms to interpret mammogram information.

Many health facilities have found CAD to be helpful in reading screening mammograms. However, CAD lacks the consistency in interpreting the overlapped challenging patterns of the breast. As a result, many normal cases have been called back for extra unnecessary investigations. CAD is effective in identifying carcinomas associated with the presence of calcifications, masses of large sizes, and a mixture of masses and calcifications. Nevertheless, many carcinomas are missed by CADs. Almost all CADs neither incorporate algorithms to register temporal mammograms nor include algorithms to detect architectural distortions.

In conclusion, more research needs to be conducted for automated detection of breast architectural distortions as well as mammogram registration.

Read more about it

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