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Computed-aided diagnosis (CAD) in the detection of breast cancer

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ABSTRACT

Computer-aided detection (CAD) systems have been developed for interpretation to improve mammographic detection of breast cancer at screening by reducing the number of false-negative interpretation that can be caused by subtle findings, radiologist distraction and complex architecture. They use a digitized mammographic image that can be obtained from both screen-film mammography and full field digital mammography. Its performance in breast cancer detection is dependent on the performance of the CAD itself, the population to which it is applied and the radiologists who use it. There is a clear benefit to the use of CAD in less experienced radiologist and in detecting breast carcinomas presenting as microcalcifications. This review gives a detailed description CAD systems used in mammography and their performance in assistance of reading in screening mammography and as an alternative to double reading. Other CAD systems developed for MRI and ultrasound are also presented and discussed.

1. Introduction

Digital mammography offers new opportunities that are not provided by conventional film screen mammography for the detection of breast carcinomas. The primary benefit comes from more reliable and efficient image management. The second one comes from novel uses of X-rays for breast imaging.

Mammography has long been established as the only screening examination capable of reducing breast cancer mortality. And yet, mammography has significant limitations with a sensitivity of 85–90% for breast cancer detection. However, if missed cancer cases are analyzed retrospectively, we discover that most of them exhibit some features on mammograms. The use of the computer to assist radiologists is particularly important in mammography because the radiologist is distracted when faced with a large pile of screening mammograms to examine, because breast architecture is complex, because subtleties are present among findings and because the probability of breast cancer is low. All contribute to false-negative interpretation in about 10–15% of cases. The most frequent reasons for missed breast cancers are the misinterpretation of a perceived abnormality (a lesion with a benign appearance, or an abnormal finding on a previous mammogram seen on only one view) which is slightly more common than overlooked cases [1]. The aim of the CAD system is to offer more objective evidence and increase the radiologist's diagnostic confidence. CAD systems have been developed to improve mammographic detection of breast cancer at screening by reducing the number of false-negative interpretations.

2. Technique and interpretation

The first Food and Drug Administration approval of a CAD device was in 1998. CAD is a neural network applying calcification and mass algorithms to highlight areas of suspicious findings to assist radiologists. The CAD system helps the radiologist by defining a region of interest on the mammogram. During this process, the system analyzes each mammogram using the software of the CAD system. Most CAD devices analyze the 2 views separately and independently.

CAD systems are available for both Screen-Film and Full-Field Digital Mammography (FFDM). With Screen-Film mammography, films need to be digitalized with a dedicated unit, then digitalized images are processed with a CAD algorithm and finally prompts are printed and interpreted by the radiologist. The whole process is costly, time consuming, and it had no success in countries without any reimbursement for CAD use (Europe). With FFDM the CAD system does not require a digitizer. Due to the higher signal-to-noise ratio and a better dynamic range of FFDM, more accurate information is extracted from the image which improves the computer's ability to discriminate between true and false lesions. With FFDM, CAD devices are easily implemented, the cost much lower, and CAD marks are immediately displayed after image acquisition.

Interpretation of mammography using CAD involves several steps. Fist the radiologist performs his/her own interpretation of the original mammograms. Then he/she activates CAD marks on the workstation or views the printed prompts to see if the CAD system

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Table 1
Studies evaluating the performance of CAD-assisted reading in screening mammography.

	True-positives	False-positives
Ciatto et al. [35]	+13.7%	+35.5%
Freer et al. [2]	+19.5%	+18.7%
Birdwell et al. [3]	+11.7%	+11.7%
Helvie et al. [36]	+10%	+9.8%
Gur. et al. [5]	+1.9%	
Khoo et al. [9]	+1.3%	+5.8%
Birdwell et al. [3]	+7.4%	+8.2%
Cupples et al. [37]	+16.8%	+7.8%

marked any regions of interest. Finally, the radiologist re-inspects the original mammogram in the area marked by the CAD to determine whether an abnormal finding was overlooked on the initial assessment. Two types of marks are displayed, one for microcalcifications and one for masses. A learning curve is necessary to manage the marks. One of the challenges of the CAD system is to become comfortable with the number of false marks. With experience, the majority of false CAD marks are readily dismissed. However, the use of CAD takes more time for the interpretation of screening mammography than it does without CAD.

3. CAD performance

3.1. CAD-assisted reading in screening mammography

CAD-assisted reading is associated with a moderate increase in sensitivity and with a drop in specificity (Table 1). Freer et al. studied prospectively the effect of CAD on recall rate [2]. Among 12,860 mammograms, there were 986 recalls and 49 cancers. Eight of the cancers were detected with CAD alone which increases the detection rate by 19.5%. Birdwell et al. studied prospectively 8682 patients [3]. Ten percent of patients were recalled and CAD contributed 8% of total recalled findings and 7% of the cancers detected (2 of the 29 cancers found). Ko et al. prospectively interpreted 5016 mammograms without and with CAD in a working clinical environment [4]. The recall rate increased from 12% to 14% with the use of CAD. Of the 107 patients who underwent biopsies, 6% were prompted by CAD. The radiologist detected 43 of the 48 cancers without CAD and 45 of the 48 cancers with CAD (+4%). CAD missed 8 cancers that were detected by the radiologist. Gur et al. reported that no statistically significant increase in cancer detection between radiologists who used CAD and those who did not [5]. A more recent study of Fenton et al. published in the New England Journal of Medicine in 2007 [6], questioned the diagnostic contribution of CAD by concluding that the use of CAD is associated with reduced accuracy of screening mammogram interpretation, an increased rate of biopsies and is not clearly associated with enhanced detection of invasive breast cancer. They analyzed screen-film mammograms of 222.135 women, before and after the implementation of CAD. CAD increased sensitivity from 80.4% to 84%, decreased specificity from 90.2% to 87.2%, and increased the rate of biopsies by 19.7%, and the rate of detection of invasive cancer decreased by 12%. However, the rate of detection of ductal carcinomas in situ was increased by 34%. These differences observed in the rate of detection of breast cancer with the use of CAD has been reported to be due to the practice setting, the volume of cases interpreted by the radiologist, the number of radiologists dedicated to interpreting the mammograms and the experience of the radiologists with the CAD system [3].

3.2. CAD should be addressed as an alternative to double reading

Indeed it is well established that prospective double reading of screening mammograms increases the detection of cancer from 4 to 15% [7] (Fig. 1). Like double reading, CAD could increase the cancer detection rate and could be easier to implement and cheaper than double reading. Gilbert et al. showed that single reading with CAD yielded the same performance as double reading. The proportion of cancers detected was 199 of 227 (87.7%) for double reading and 198 of 227 (87.2%) for single reading with computer-aided detection ($P = 0.89$) [8]. However, the specificity of CAD is low with about 1 false positive mark per view (Fig. 2). These false positive marks may cause the radiologist to underestimate and disregard CAD findings. Khoo et al. studied the use of CAD as a second reader in 6111 women [9]. CAD increased sensitivity by 1.3%. However, of 12 cancers missed on single reading, 9 were correctly prompted by CAD, but 7 of these prompts were overruled by the reader. On the other hand, double reading increased sensitivity by 8.2%. This study highlights the need to learn to manage the marks and the need for preliminary training of the radiologist in the use of the CAD.

3.3. Factors influencing CAD performance

The performance of CAD in breast cancer detection is dependent on the performance of the CAD itself, the population to which it is applied and on the radiologists who use it. Most studies suggest that there is a clear benefit in using CAD in less experienced or low volume reviewers. Balleyguier et al. showed that the use of CAD is more useful for the junior radiologist with an improvement in sensitivity from 61.9% to 84.6% compared to a slight improvement from 76.9% to 84.6% for the experienced radiologist [10]. Feig et al. showed that the use of CAD by low-volume readers allowed an increased rate of both recall and cancer detection rates of approximately 19% [11]. CAD devices are particularly helpful in detecting breast carcinomas presenting as microcalcifications, with a reported sensitivity for microcalcification detection ranging from 86% to 99% [12–14]. CAD clearly increases the efficiency and confidence level of radiologists when searching for subtle microcalcifications. Moreover, the rate of false positive marks is about 0.6 marks/image and is lower than for mass detection. Yang et al retrospectively evaluated the sensitivity of CAD applied to FFDM in 103 cases of asymptomatic non-palpable breast cancers detected with screening and 100 cases of normal mammograms [15]. The overall sensitivity was 96.1%. The CAD system marked all 44 breast cancers that manifested exclusively as microcalcifications, all 23 breast cancers that manifested as masses with microcalcifications and 32 of the 36 lesions that appeared exclusively as a mass. On normal mammograms, the mean number of false positive marks per patient was 1.8 leading to a rate of 360 false positive marks for 1 cancer. Hall et al. showed that CAD clearly increases the efficiency and confidence level of radiologists when searching for subtle microcalcification clusters [16]. The main limitation of CAD is amorphous calcifications for which the CAD system has a limited value. Soo et al. in 85 cases of amorphous calcifications evaluated by CAD reported a sensitivity of 57% for the detection of malignant calcifications [17].

For mass detection, the sensitivity is lower ranging from 83% to 90% and is adjustable according to the specificity desired. There is also a higher rate of false positives for the detection of masses than for microcalcifications [from 0.72 to 1.82 marks/image] [18] (Fig. 2). Moreover, this sensitivity has been shown to be greater for masses with spiculation than for architectural distortions (sens 50%) [19]. Radiologists must consider that CAD was optimized for detecting small-sized opacities < 3 cm but should be aware of the possibility of false negatives for obvious and voluminous cancers (Fig. 3). Improving the performance of CAD in detecting masses is necessary and could probably be obtained by multiview-based analyses.

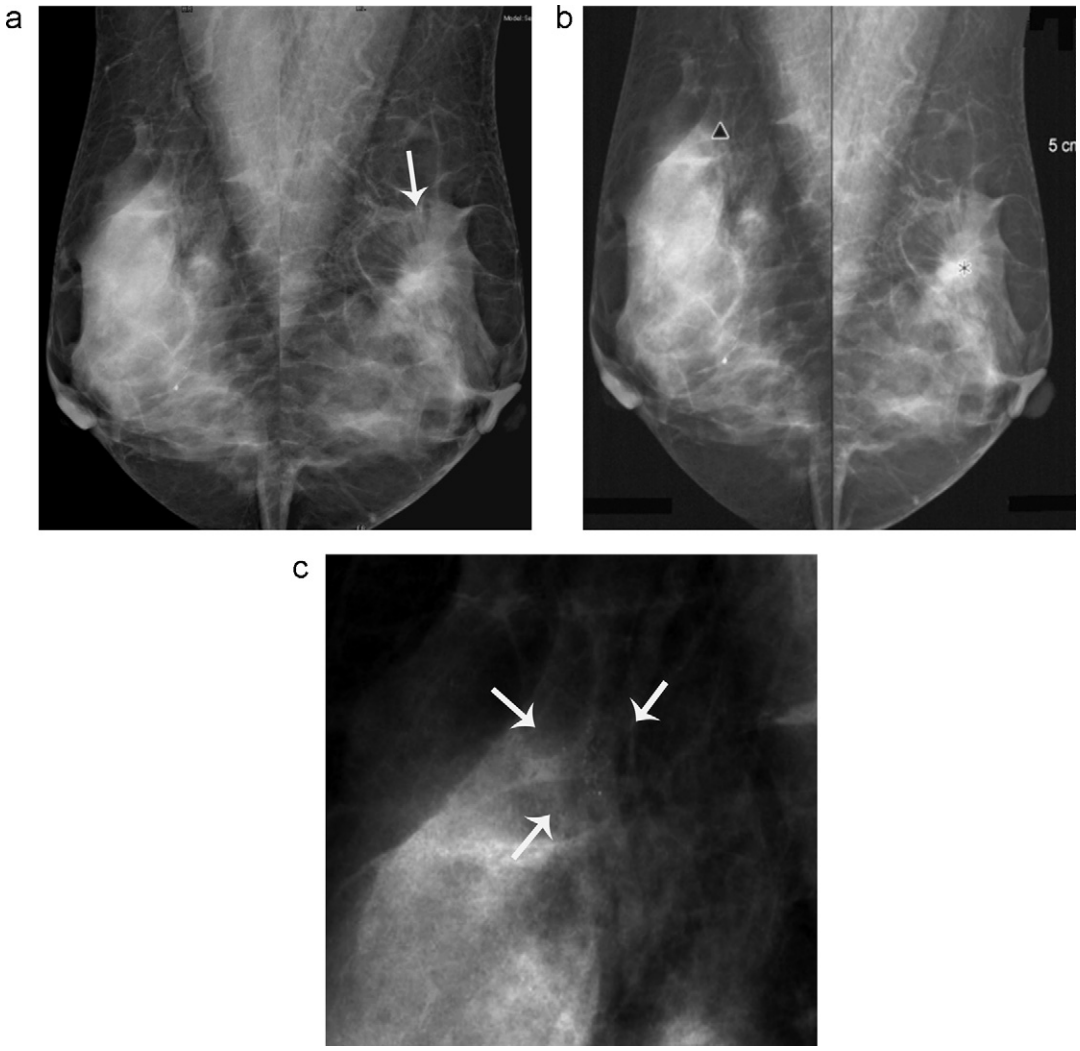


Fig. 1. 43 year old woman. Invasive ductal carcinoma of the left breast and ductal carcinoma in situ of the right breast. The mammograms in MLO views show a spiculated mass in the upper quadrant of the left breast (arrow). After activation of CAD marks (b), an additional lesion in the opposite breast was depicted corresponding in the magnification view (c) to a subtle cluster of microcalcifications. The speculated mass of the right breast was proved to be an IDC and the cluster of microcalcifications of the left breast was proved to be a DCIS at histology.

The performance of CAD may also depend on background breast density [20] and histologic findings in the tumor [12,21]. Brem et al. showed that overall, breast density did not exert an impact on CAD detection of breast cancer but decreased the sensitivity of mass detection. Of the 906 cancers studied using CAD, 89% were detected by CAD corresponding to 90% of cancer cases in nondense breasts and 88% of cancer cases in dense breasts. However, among the cancers that manifested as masses, 89% and 83% of cases were detected in nondense and in dense breasts respectively. Moreover other studies suggested that CAD could have a greater sensitivity for detecting invasive lobular carcinoma and ductal carcinoma in situ rather than for invasive ductal carcinoma.

4. MR and sonographic CAD

4.1. CAD in breast MRI

Since the beginning of the 90s, breast MRI has been used for the detection and characterization of breast lesions [22]. More and more applications of breast MRI are being evaluated in routine practice, from the detection of local recurrences through screening of high-risk women, to the staging of breast cancer in selected cases. MRI has a particular high rate of sensitivity (78–98%) but its specificity is still lacking (43–75%) [23]. These last years have seen the development of computed-assisted diagnosis software in order to facilitate the MR analysis and the report, or to try to improve the characterization of MR detected lesions. These software systems particularly develop the analysis of dynamic contrast-enhanced breast MRI and generate parametric maps with a detailed evaluation of the uptake kinetics of contrast agent in enhancing lesions. Most of the different commercially available systems exclusively analyze kinetic studies, without analyzing morphological parameters [24]. Confirma® generated the first commercially available software (Cadstream®) in 2004. This software is a dedicated automated software designed to automate the image processing and analysis functions usually performed by the radiologist in order to achieve greater efficiency [25].

Using CAD for breast MRI is different from CAD applied to mammography [26]: (1) in breast MRI, CAD analyses contrast kinetics and not morphology. (2) The method used to train the computer is based on a large data training set in mammography, and on direct specific enhancement patterns of interest specified by the

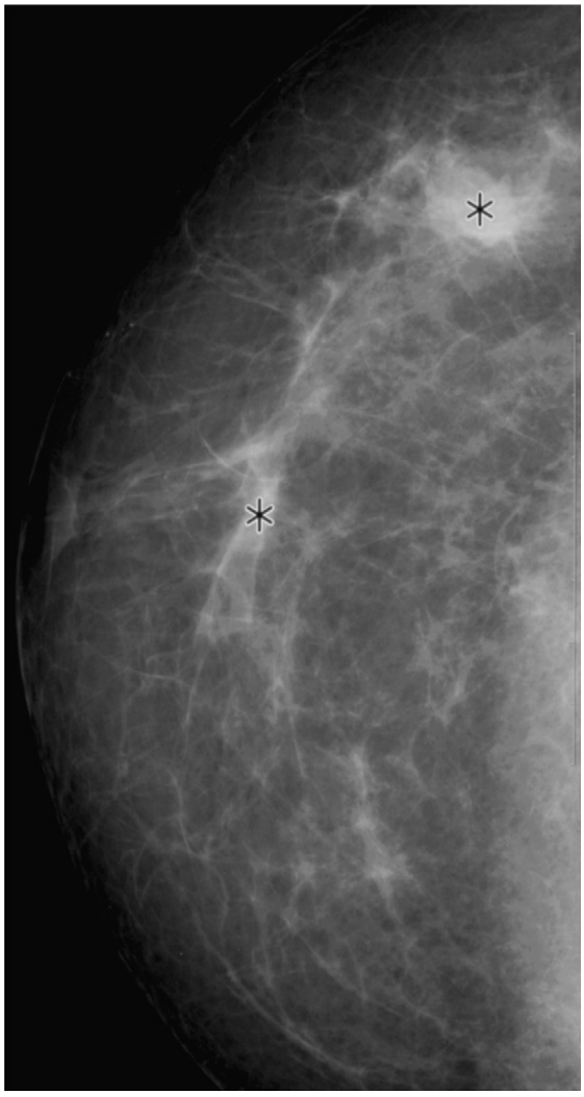


Fig. 2. 67 year old woman. Invasive ductal carcinoma. The CAD marks two masses (stars), one located in the outer quadrant corresponding to an invasive ductal carcinoma (true positive mark) and another located in the central area corresponding to normal parenchyma (false positive mark). These false positive marks may cause radiologist to underestimate and discount CAD findings.

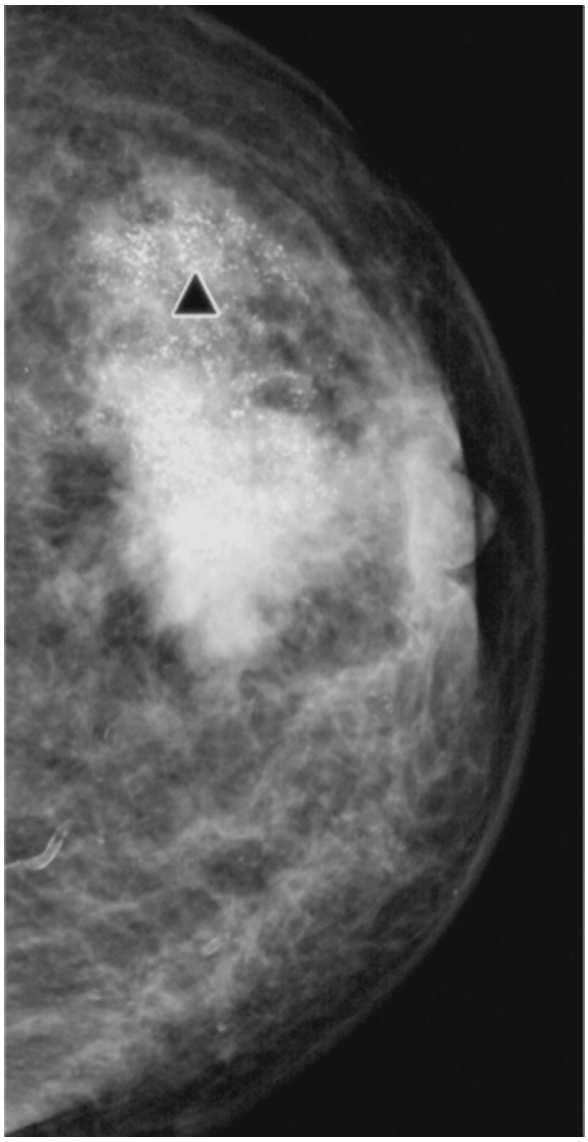


Fig. 3. 46 year old woman. Invasive ductal carcinoma associated with in situ component. The mammogram in CC view shows an obvious mass of the deep retroareolar area associated with microcalcifications in the outer quadrant. Only microcalcifications are marked by CAD (triangle) although the mass has not been depicted by CAD (false negative result). CAD focused on small-sized opacities < 3 cm and radiologists must be aware of the possibility of false negatives for evident and voluminous cancers.

radiologist and detected by the computer, in CAD MRI. (3) The expected clinical benefit is an increase in sensitivity in CAD mammography, a reduction in interpreting time and greater specificity.

The Cadstream® software analyses MR acquisition data before and after dynamic contrast injection and creates angiogenesis maps, based on curve extraction and thresholding [26]. A 50% or 100% enhancement threshold can be chosen to analyze the images and create the curves. To classify areas on MRI with "significant" enhancement, pixel values on the unenhanced and the first contrast-enhanced images are compared. If the pixel value increases to a definite threshold, the pixel is colored on the screen (Fig. 4). If the pixel value does not increase to the threshold, no color enhancement is visible. Moreover, the pixel is colored in red on the screen if the pixel value on the late phase of enhancement decreases by more than 10% compared to that of the earlier phase, which corresponds to a washout (Fig. 5). If the pixel value increases by more than 10%, it is colored in blue on the screen, indicating persistent enhancement. Finally, if the pixel value does not change by more than 10%, it is colored in green on the screen for plateau enhancement. Thresholds can be adjusted depending upon the dosage and rate used for contrast injection. The software can automatically display automated subtraction, multiplanar and MIP reconstructions on the screen for a rapid analysis by the radiologist. By placing a ROI on a suspicious lesion, it is also possible to obtain an automated volume of the lesion and a structured report based on the BIRADS MR lexicon® (Figs. 6 and 7). Lehman et al. evaluated this software in 33 suspicious lesions that were detected on MRI and biopsied under MR guidance [25]. All malignant lesions showed significant enhancement and were correctly identified by the software, with a sensitivity of 100%. The false positive rates for the CAD software compared to the radiologist's analysis were reduced by 25% at a 50% threshold, by 33% at an 80% threshold and 50% at a 100% threshold for enhancement. Thus, in this study, CAD MR software yielded a high accuracy with improved specificity without

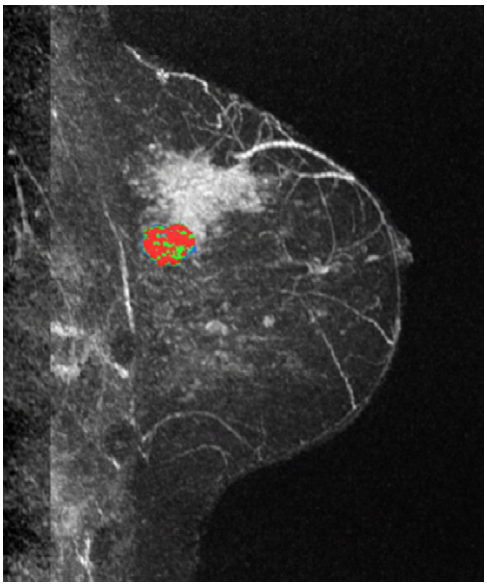


Fig. 4. 52 year old woman. 15 mm Invasive ductal carcinoma of the left breast. Dynamic breast MRI, MIP reconstruction, and CAD analysis (CADSTREAM, Confirma®). The malignant lesion is well depicted in the image, including colored pixels corresponding to the 50% and 100% enhanced part of the mass.

decreasing sensitivity. These results were confirmed in a recent study, comparing three commercially available CAD MR systems: Cadstream (Confirma®), 3TP Server Version 2.2.4 (CADsciences®), and Mammatool, a new CAD system (Digital Image Solutions®) [24]. MRI studies of 21 patients were analyzed with all these three software programs. All 10 carcinomas were considered as malignant lesions by the three CAD softwares. In addition, 131 further benign lesions were marked in Cadstream, 133 in 3TP and 99 in Mammatool, which had the lowest false positive rate. Nevertheless, the Mammatool software had the lowest score in subjective quality criteria, mainly due to poor ergonomics from the user's point of view.

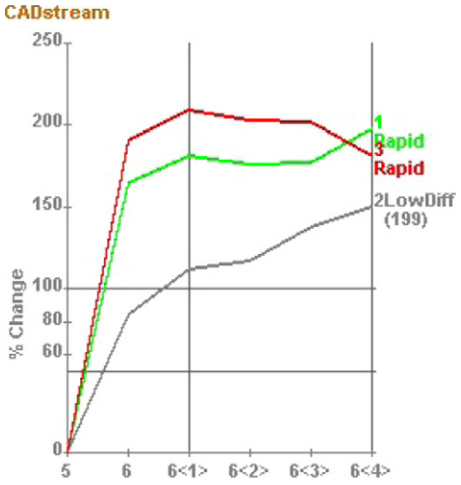


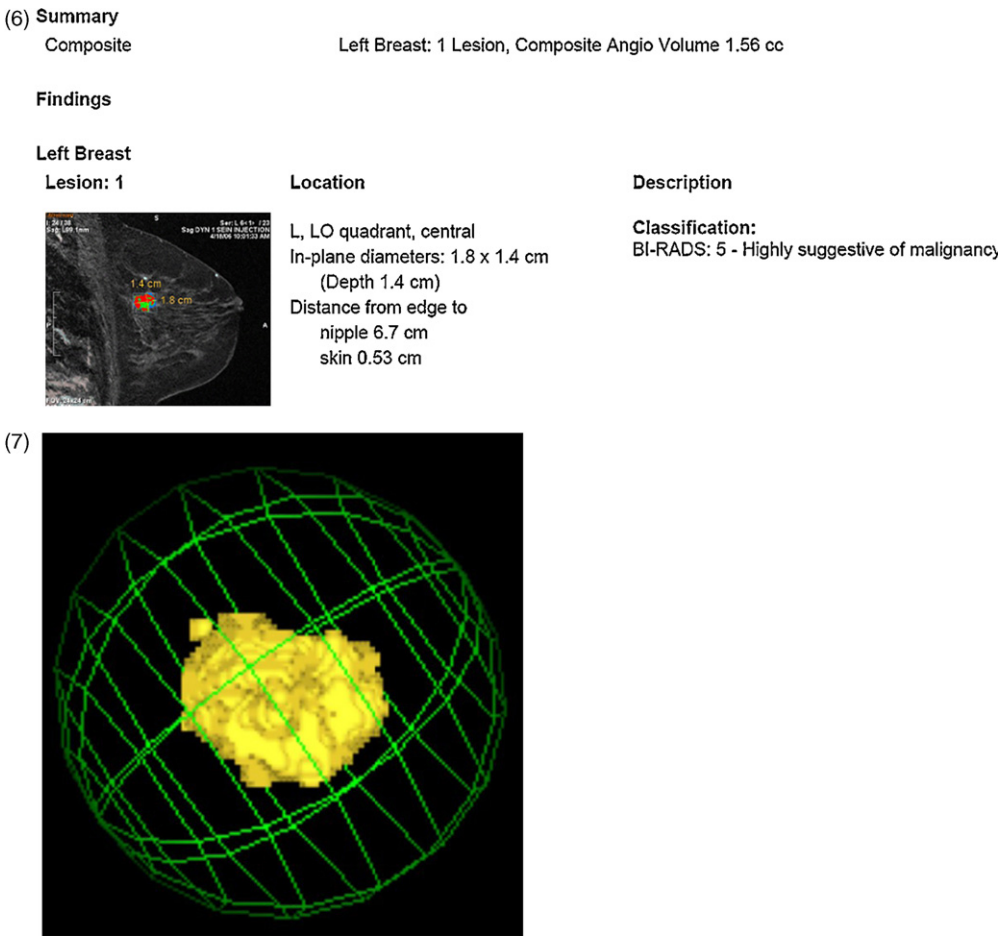
Fig. 5. 52 year old woman. 15 mm invasive ductal carcinoma of the left breast. Dynamic breast MRI, enhancement curves, and CAD analysis (CADSTREAM, Confirma®). Same patient. Enhancement curves are automatically generated by the CAD software; the different types of the curves are visible within the same lesion. Most of the lesion shows a significant enhancement curve with a washout, suggestive of malignancy.

Besides these encouraging results, it is remarkable that all the commercially available or "home-made" systems are based on kinetics analysis, whereas it is currently known that it is more important for the radiologist to consider the morphological analysis in order to achieve an accurate analysis [27]. Some companies and physicians are working on implementing a morphological analysis in MRI CAD software to improve both sensitivity and specificity [28]. These improvements could lead to greater accuracy and ease of use in a routine practice.

4.2. CAD in breast ultrasound

The morphological analysis is a key tool in diagnosing benign and malignant lesions in breast ultrasound. Morphological criteria used to describe a mass should include the shape, number of lobulations, ratio of width and anteroposterior dimension and posterior shadowing [29]. These criteria are integrated into the Ultrasound BiRADS lexicon published in 2003. Breast ultrasound CAD systems were recently developed for the analysis of breast ultrasound images. The first commercially developed software is B-CAD from Medipattern® (Toronto, Canada). Other "home-made" systems have also been developed by working teams in imaging research [30–32]. General physics principles are usually the same. In order to describe a mass or a cystic lesion in the computer software, the sonographic features must be quantified into computerized sonographic features. To analyze the mass, shape and margin, characteristic classes could be determined. Several different morphological criteria can be extracted: shape, roundness, contours analysis, convexity, solidity, spiculation of the margins, etc. [29]. Texture analysis is also a useful criterion for describing a mass in a selected ROI. Posterior enhancement or shadowing, which are parametric criteria, can also be extracted and measured by the different software [29]. In B CAD, the radiologist places a mark in the center of the nodule on the screen, and the system automatically draws the contours of the lesion, to extract the different morphological parameters. The drawing may be inaccurate, but the radiologist can manually readjust the margins to achieve adequacy. The CAD system analyzes the extracted parameters and proposes an evaluation. Some ultrasound CAD systems are also able to propose a BI-RADS category and a structured report.

In most of the studies, the use of dedicated CAD software for breast ultrasound improves the accuracy in classifying benign and malignant breast lesions [33] but the performance of CAD can vary according to the type of lesion [benign or malignant, cystic or solid] [30]. In a recent study, 1046 lesions on 2266 images were analyzed by an ultrasound CAD system [30]. Sensitivity in detecting malignant lesions was 100%, and specificity was only 30%, as the expected specificity of the radiologist was 77%. These differences are probably linked to the fact that the radiologist has a greater capacity to analyze the risk of malignancy when he/she is aware of the familial and personal history, previous mammograms etc. A literature analysis of ultrasound CAD accuracy is ambiguous: some studies show the poor specificity of the different systems [30], while other authors underline the great value of CAD in terms of specificity, allowing a decrease of up to 53% in the need for biopsy [34]. The performances of CAD systems is usually better in the case of suspicious lesions, with a high risk of malignancy compared to benign lesions. Usually the Cystic lesions are the least difficult to deal with using a CAD system, whereas the other benign solid lesions are more difficult to analyze [30]. Similarly, specificity is often lower in case of benign nodules. Nevertheless, an ultrasound CAD system can be used as a teaching tool for junior radiologists, especially to familiarize them with the different terms of the breast ultrasound BI-RADS lexicon.



Figs. 6 and 7. 52 year old woman. 15 mm invasive ductal carcinoma of the left breast. Dynamic breast MRI (structured report, Fig. 6), automated volume (CADSTREAM, Confirma®) (Fig. 7). Same patient. Structured report with location of the lesion within the breast and BIRADS category can be displayed. Volume of the lesion can also be automatically calculated.

5. Conclusion

CAD systems are image analysis tools intended to reduce the number of false negative mammograms that can be caused by subtle findings, radiologist distraction or complex architecture. The use of a CAD system helps the radiologist as a second reviewer to evaluate screening mammograms. However, CAD must not be responsible for omitting the step of the complete evaluation of mammograms by the radiologist. A CAD system cannot and should not replace the radiologist as either or final interpretation.

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