



Breast Imaging

A review of computer aided detection in mammography

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ABSTRACT

Breast screening with mammography is widely recognized as the most effective method of detecting early breast cancer and has consistently demonstrated a 20–40% decrease in mortality among screened women. Despite this, the sensitivity of mammography ranges between 70 and 90%. Computer aided detection (CAD) is an artificial intelligence (AI) technique that utilizes pattern recognition to highlight suspicious features on imaging and marks them for the radiologist to review and interpret. It aims to decrease oversights made by interpreting radiologists. Here we review the efficacy of CAD and potential future directions.

1. Introduction

Breast screening with mammography is widely recognized as the most effective method of detecting early breast cancer [1] and has consistently demonstrated a 20–40% decrease in mortality among screened women [2,3]. In fact, a 2014 study by Webb et al. demonstrated that up to 71% of deaths from breast cancer are in unscreened women [4]. Despite its established efficacy, however, the sensitivity of mammography is suboptimal ranging between 70 and 90%, the upper limits of the range seen with the switch from screen film mammography to full field digital mammography (FFDM) as well as with the advent of digital breast tomosynthesis (DBT) [5–8]. Although limitation to sensitivity is inherent to the technique, studies demonstrate that up to 30% of interval cancers (those presenting clinically within a year of a mammogram reported as normal) and 20% of newly diagnosed cancers were present in retrospect on prior mammograms and can therefore be classified as missed cancers or false negatives [9–11]. Further retrospective review of false negative cases demonstrates that the most common reason for missed breast cancer is misinterpretation of perceived abnormality closely followed by overlooked abnormality [12].

Cultivated since the 1980s and approved by the Food and Drug Administration in 1998, computer aided detection (CAD) has been developed with the aim of decreasing oversights and therefore false negative rates of radiologists interpreting images [13]. CAD is an artificial intelligence (AI) technique that utilizes pattern recognition to highlight suspicious features on imaging and marks them for the radiologist to review and interpret. CAD search algorithms are developed by “training” the system with a set of images and includes the steps of pre-processing, anatomic region segmentation, feature extraction and

classification. Preprocessing involves improving the contrast of the images and tuning out the noise, thus teaching the system to ignore variations due to technique differences. This first step can present a limitation to a CAD system, in particular if the system is trained by images from a single institution, thus limiting its ability to dismiss normal variation due to differences in technique from other institutions. Anatomic region segmentation allows the system to more easily extract suspicious lesions from breast tissue, while feature extraction teaches the system to detect the same suspicious features that are assessed by a radiologist, such as microcalcifications or masses in the case of mammography. Classification is the final step which teaches the software to classify the lesions as benign or malignant [14,15]. This latter step is utilized by computer aided diagnosis (also termed CAD, sometimes CADx) systems not yet approved for clinical practice in mammography.

With Congress extending Medicare coverage to CAD in the *Benefits Improvement and Protection Act* of 2000, use of CAD increased to 10% of mammography facilities [16] with subsequent steady growth in CAD utilization seen with the conversion of screen film mammography to digital. In 2016 approximately 90% of Mammography Quality Standard Act (MQSA)-certified digital mammography facilities utilized CAD [17] despite conflicting evidence of CAD's diagnostic accuracy. It was in 2003 that simultaneous billing for digital mammography and CAD was permitted [18] with two of the major commercially available mammography CAD systems, R2 image checker[®] and iCAD Second Look[®] receiving FDA approval in 1998 and 2002, respectively [13]. The most recent American College of Radiology (ACR) 2018 practice parameter does not advocate for or against the use of CAD, stating that CAD and double reading “may slightly” increase the sensitivity of screening mammography and therefore may be used, however admonishes that

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the potential slight benefit may come at the expense of decreased specificity and increased biopsy rates [19]. Here we seek to outline the evidence summarizing the diagnostic performance of CAD and its future potential.

2. Single reader with CAD versus double reader

Prior to the introduction of CAD, double reading had been utilized in an attempt to increase the diagnostic performance of mammography. Studies have demonstrated that double reading can increase the cancer detection rate (CDR) by 15% with no significant change in the positive predictive value (PPV) [20]. In their review, Dinnes et al. concluded that double reading could improve the accuracy of mammography. They found that when used with arbitration, it resulted in an increased CDR and decreased recall rate (RR) [21]. However, double reading requires extensive time and resources, which may not be a viable option in many practices. In addition, multiple studies have demonstrated that double reading does not appear to be a cost effective option [22–24].

Older studies demonstrate mixed results when comparing the efficacy of CAD with double reading. A 2006 study comparing the efficacy of CAD with double reading in the United Kingdom Breast Screening Program found a 32% increase in recall rate with CAD versus second reading [25]. However, a later study comparing single reading versus double reading versus single reading with CAD found that CAD demonstrated a lower recall rate than double reading ($p < 0.0001$). The same study did however show an increased recall rate with utilization of CAD versus a single reader of 10.6 versus 10.2 ($p < 0.0001$) [26].

In a direct comparison of CAD versus second reader, recall rates were not significantly different. Relative increased cancer detection rate was 0% for CAD (images were marked but reader dismissed) and 15.4% for double reader. This study had a small sample size with only two additional cancers detected, and did not reach statistical significance. These findings were supported by the authors' conjecture that the true added benefit of a second reader is the ability to discern the significance of a finding as opposed to simply identifying it [27].

Finally, a 2008 meta-analysis of 27 studies demonstrated that double reading with arbitration increases cancer detection rates and decreases recall rates. In contrast, single reading with CAD did not have a significant effect on the CDR while increasing recall rates [28]. The authors conclude that double reading with arbitration adds more value than single reading with CAD.

Despite these findings, CAD does offer a potentially viable option to those practices which cannot support double reading for staffing or financial considerations. For this reason, it is important to explore the performance of the addition of CAD to single readers.

3. Sensitivity

The sensitivity of CAD for detecting cancer is varied, ranging from 60 to 100% [29–37]. CAD does not appear to be affected by breast density [30–32,38] which is a limitation of screening mammography. A 2014 study investigated the sensitivity of two of the most widely available CAD systems in detection of 161 cancers that were identified during the DMIST trial. The authors found that with both of these systems, the sensitivity for detecting carcinoma was significantly increased with CAD ($p < 0.0001$ for each) [35]. However, also in 2014, the same group published a study investigating the sensitivity of CAD in the setting of mixed cancers and normal cases and found that there was no difference in sensitivity with the addition of CAD. Even though CAD had the potential to mark missed cancers, the radiologists were unlikely to change their opinions based on these marks [29]. In the same study, when looking at individual readers, only 28.6% in one group, and 26.7% in the other group demonstrated statistically significant increased sensitivity. Readers rarely changed their opinions after the addition of CAD [29].

A retrospective study which looked at 429,345 mammograms found

that the increased sensitivity following the addition of CAD from 80.4% to 84% was not statistically significant. In addition, it came at the cost of statistically significantly decreased specificity, decreased positive predictive value, and increased biopsy rates. Specificity decreased from 90.2% to 87.2% following the implementation of CAD which was statistically significant [43]. Supporting the lack of increased sensitivity with the addition of CAD, in their analysis of 625,625 digital mammograms, Lehman et al. found no difference in overall sensitivity, specificity, sensitivity for invasive cancer, or sensitivity for DCIS [37].

3.1. Sensitivity for calcifications

Although there may be no significant difference in overall sensitivity, CAD has repeatedly demonstrated an increased sensitivity for calcifications ranging from 80 to 100% [31–33,36,40–41]. Taplin et al. demonstrated that CAD marked more visible calcified lesions (86%) than masses and asymmetric densities (67%) ($p < 0.05$) [39]. A study which looked specifically at amorphous calcifications, demonstrated that CAD correctly marked the malignancies 100% of the time (36/36) and correctly identified 85% of the high-risk lesions [36].

3.2. Sensitivity for distortion

In a retrospective study where architectural distortion (AD) was felt to be visible by a group of expert breast imagers, application of CAD yielded 49% sensitivity for one of the CAD software systems and 33% sensitivity for the second. When CAD was applied only to those cases of AD which ultimately yielded carcinoma, a similar sensitivity was found [34]. Another study demonstrated a slightly higher sensitivity for AD of 71% [32]. Interestingly, several studies have demonstrated a higher sensitivity for invasive lobular carcinoma which frequently presents as AD. The sensitivity of CAD specifically for invasive lobular carcinoma ranges from 89 to 100% [33,41–42].

3.3. Sensitivity for malignant masses

Many of the studies break down the detection of malignant masses into pure masses versus masses with calcifications. The reported sensitivity for malignant masses ranges from 89 to 98% [30–31,33,38,41]. The sensitivity for malignant masses with calcifications ranges from 88 to 100% [30–32,38,41]. When combining several of the available studies, CAD detected 360/394 malignant masses for a sensitivity of 91% [30–31,33,38,41]. CAD detected 82/84 malignant calcified masses for a sensitivity of 98% [30–32,38,41].

4. Performance

Studies evaluating overall performance have demonstrated similarly mixed results. Cole et al. looked back at cases from the DMIST trial. In contrast to early studies, they only evaluated digital mammograms. The study included 300 cases (50% with a cancer diagnosis) to which one of two CAD systems was applied. While some of the individual readers had improved AUC with each of the CAD systems, there was no statistically significant difference for the average between the readers (15 readers with one type of CAD and 14 readers with the other) [29]. A large study by Fenton et al., demonstrated decreased accuracy with addition of CAD. Area under the ROC curve was 0.871 with CAD vs 0.919 without CAD ($p = 0.005$) [43]. Lehman et al., found similar results in their study. The area under the ROC went from 0.88 to 0.84 with the addition of CAD ($p = 0.002$) [37].

A 2002 study investigated which population of radiologists would benefit from CAD the most. The study included 12 radiologists (6 mammographers and 6 community radiologists) evaluating an enriched dataset of 110 cases. Addition of CAD increased AUC from 0.93 to 0.96 ($p < 0.001$) among all radiologists. Most notably, it negated a previously statistically significant difference in the sensitivity between the

two groups of radiologists [44].

5. Recall rate

A disadvantage of CAD is the large number of false positive markings made by the software. It is rare for a study to have no lesions marked by CAD. The average number of marks ranges from 1.5–5.1 per full exam [29,34,36,41]. A major criticism of CAD, therefore, is that the large number of markings leads to increased recall rates resulting in increased cost and anxiety for patients. There is mounting evidence supporting this concern with the majority of the studies showing increase in recall rates with the implementation of CAD. This increase ranges anywhere from 7.8–19% [20–22,45–50]. One study demonstrated that the percentage of calcifications recalled increased by 53%, while the number of masses recalled increased by 12% [45]. However, a single study which looked at a large practice with 24 academic radiologists, found that CAD had no significant effect on recall rates, at the same time this study demonstrated no change in cancer detection rates with the application of CAD [51].

6. Cancer detection rate

Review of the literature suggests an increased cancer detection rate (CDR) with the addition of CAD. Published values of this increase in the CDR range from 0 to 19.5% [25,45–48,50,52,53]. Consistent with the documented increased sensitivity for calcifications, many studies demonstrate an increased detection of DCIS. In their study, Freer et al. demonstrated that 7/8 additional cancers detected with CAD were DCIS [45]. Lehman et al. found no difference in the overall or invasive cancer CDR, nor differences in sensitivity for either invasive cancer or DCIS, however did find an increase in the CDR of DCIS $p < 0.03$ [37]. The lack of difference in sensitivity for DCIS likely stems from increased number of recall rates for calcifications with the addition of CAD as noted above. Morton et al. demonstrated an increased overall cancer detection rate (7.6%), mostly explained by increased detection of DCIS. In this study 62% (5/8) of additional detected cancers were DCIS [46]. Dean et al. demonstrated a 14.2% increase in the detection of DCIS with the addition of CAD [50].

Birdwell et al. looked at 115 missed cancers that in retrospect were detectable as determined by experienced breast imagers. When CAD was applied to these cases, it marked 86% (30/35) of the missed calcifications and 73% (58/80) of the missed masses [54].

7. Stage at diagnosis

A potential benefit of CAD is that its addition may lead to detection of earlier stage disease [18,45,47,50]. One study showed that CAD increased detection of stage 0 disease by as much as 42%, and increased diagnosis of stage I disease by 17% [45]. In 2009 approximately 1 of 9 DCIS diagnoses was attributable to the use of CAD in the Medicare population (aged 67–89) [55]. In a study of Medicare patients, Fenton et al. discovered that the addition of CAD increased DCIS incidence without any change in the incidence of IDC [18]. Furthermore, invasive cancer found with CAD was more likely to be Stage I/II versus III/IV. Similarly, although a non-statistically significant increase in cancer detection rate of invasive carcinomas 1.0 cm and under of 164% was seen in a study by Cupples et al., the authors demonstrated earlier stage at diagnosis to be the strongest predictor for earlier age at diagnosis with utilization of CAD [47]. The latter suggests that, absent CAD studies demonstrating mortality reduction, this may be a promising marker for improved screening outcomes with CAD. This appears to be a benefit of CAD—finding earlier stage disease, which has a greater likelihood of being treatable.

8. Emerging technologies and future directions

The inherent limitations of standard mammography secondary to tissue superimposition have been addressed with the development of digital breast tomosynthesis (DBT), which has proved to significantly increase the diagnostic accuracy of mammography by decreasing recall rates and increasing cancer detection rates [56–59]. Due to these added benefits, DBT is becoming more widespread in its utilization—a recent 2016 survey by the Society of Breast Imaging reports DBT 30% utilization rate in the United States, with higher prevalence in academic institutions [60]. However, two of the challenges of DBT include increased radiation dose and increased reading time. The former has been tackled with the creation of synthetic 2D mammograms out of the acquired DBT volume set, which has proved to be non-inferior to FFDM in its diagnostic accuracy, thus obviating the need for additional radiation from FFDM [61,62]. The increased volume and number of images with which a radiologist is faced when reading DBT, however, prolongs reading time and has the potential to lead to more missed findings due to reader fatigue [63–65].

Although there are limited large scale studies to date of this publication, computer-aided detection systems may prove of utility in interpretation of DBT. Active research in this field suggests an improvement in DBT CAD performance compared to that of DM CAD with sensitivities approaching 93% [66–68], likely secondary to better mass border depiction and conspicuity on individual tomosynthesis slices as well as decreased false positive rate of asymmetries resulting from overlapping tissue. Given this evidence, the first tomosynthesis based CAD system (iCAD PowerLook®Tomo Detection Software, GE Seno-claire) received FDA approval in March of 2017 for the detection of masses, architectural distortions and asymmetries [69]. Unlike traditional CAD for standard mammography, this tomosynthesis based CAD system is designed to be used concurrently throughout study interpretation. The software detects suspicious soft tissue densities utilizing the 3D tomosynthesis planes and highlights these, blending them into a CAD-enhanced 2D synthetic image. The 2D synthetic image supplies further navigation information of each of the soft tissue lesions and their corresponding 3D plane location which allows the radiologist to quickly review the 3D volume set in order to confirm or dismiss the finding [70].

Multiple approaches are also currently being investigated for CAD detection of microcalcifications. This is a more challenging endeavor as there are mixed observations in the efficacy of DBT itself in identifying microcalcifications, with some studies demonstrating lower detection sensitivity and conspicuity, potentially stemming from a large 3D volume set to be evaluated [71–73]. There is promise of these varied DBT CAD approaches for detection of microcalcifications. Some techniques utilize the synthetic mammogram while others use the actual 3D volume projection images. Still others create a novel planar projection image generated from a DBT volume containing only the high frequency information filtered specifically for microcalcifications. Recent studies evaluating the efficacy of these techniques yield CAD sensitivities ranging from 85 to 90% [74–76]. Further validation was seen in a 2015 multicenter study by Marra et al. which demonstrated 89% sensitivity of DBT CAD combined for all lesion types, including microcalcifications in 175 diagnostic and screening mammograms [77].

Finally, recent evidence suggests the potential of addressing one of the major shortcomings of DBT—increased reading time—by the addition of CAD. Balleyguier et al. demonstrated statistically significant reduction of DBT reading time with the addition of CAD system of 23.5% in a small enriched data set of 80 cases [78]. Of note, and reaffirming prior studies on the added diagnostic accuracy of CAD cited above, no improvement in diagnostic accuracy was seen with the addition of CAD. The study demonstrated a non-statistically significant improved AUC curve for readers without CAD and a further trend toward decreased specificity and increase in false positive rates by the addition of CAD. Similarly, a larger 2018 study by Benedikt et al.,

supported by funding from iCAD, demonstrated a 29% reduction in DBT reading time with the addition of CAD without statistically significant improvement in diagnostic accuracy [68]. Although CAD for DBT could be a valuable addition by improving workflow and aiding in calcification detection, larger scale studies will be necessary to fully assess the diagnostic accuracy of tomosynthesis based CAD systems in order to more scrupulously weigh its clinical benefit.

9. Conclusion

Although some data point to a benefit of CAD in particular subsets of cases, as demonstrated with its increased CDR for DCIS, suggestion of earlier stage at diagnosis, and improved diagnostic accuracy for lobular carcinoma, the overall body of evidence in support of CAD is equivocal at best and mostly unconvincing. One of the largest studies to date evaluating the diagnostic accuracy of CAD in nearly half a million mammograms read by 271 different radiologists failed to find a statistically significant metric of improved performance with the addition of CAD [37]. Similarly, more recent studies investigating the potential of CAD in improving reading time of DBT demonstrate no improvement in reader operating curves by the addition of CAD, including a study funded by the industry [68,78]. This is largely because CAD's original purpose was to replicate what radiologists already did well, find the majority of imaging apparent cancers rather than highlight the imaging occult [79].

While traditional CAD systems were pre-taught performance algorithms from reader input, the new generation of AI systems have the ability to constantly integrate new information. This ability may increase the utility of future CAD systems thus encouraging their use by the medical community. The promise is evident in the burgeoning field of radiomics, which is based upon the hypothesis that biomedical images contain more information than is appreciated by the naked eye, information that reflects underlying pathophysiology and which can be extracted via quantitative image analyses [80]. This, coupled with the ability of the new generation of neural networks to learn and adapt suggest that emerging advanced AI CAD systems should not be dismissed and may have a potential for success. As the medical field continues to incorporate the use of artificial intelligence systems into practice, the future success of CAD would stem from providing prognostic rather than solely diagnostic support to the radiologist, in essence, serving as a consultant to the imaging consultant.

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