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# Breast imaging: A survey

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## Abstract

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Breast cancer is the second leading cause of death in women. It occurs when cells in the breast start to grow out of proportion and invade neighboring tissues or spread throughout the body. Mammography is one of the most effective and popular modalities presently used for breast cancer screening and detection. Efforts have been made to improve the accuracy of breast cancer diagnosis using different imaging modalities. Ultrasound and magnetic resonance imaging have been used to detect breast cancers in high risk patients. Recently, electrical impedance imaging and nuclear medicine techniques are also being widely used for breast cancer screening and diagnosis. In this paper, we discuss the capabilities of various breast imaging modalities.

**Keywords:** Breast cancer, Breast magnetic resonance imaging, Breast ultrasound, Mammography, Thermography

## INTRODUCTION

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Breast cancer starts in the breast cells of both women and men. Worldwide, breast cancer is the second most common type of cancer after lung cancer (10.9% of cancer incidence in both men and women)[1] and the fifth most common cause of cancer death[2]. The National Breast Cancer Foundation has estimated around 200 000 new breast cancer cases and 40 000 deaths every year in women. In men, these statistics are 1700 and 450, respectively[3]. According to the National Cancer Institute, an estimated 207 090 new cases and 39 840 deaths from breast cancer (only women) are expected to occur in the United States, despite recent advances in treatment[4]. Given such circumstances, early diagnosis of breast cancer is considered vital, because statistics have shown a five-year survival rate of 96% for those whose cancer was detected in the early stages[3].

The breast is composed of identical tissues in both men and women, and hence, breast cancer also occurs in men. Breast cancer incidence in men is approximately 100 times less than in women, but men with breast cancer are considered to have the same statistical survival rates as women[5-7].

In this paper, our focus is on breast cancer detection modalities which use breast images obtained by various techniques for analysis and subsequent detection. For better survival odds and reduced use of treatments and therapies and, therefore, fewer side-effects, many imaging modalities are continually being developed to diagnose this disease as early as possible. Some of these modalities are used for screening purposes, some for diagnostic purposes, and a few others for adjunctive evaluation. Techniques that enable mass level screening should be cost-effective and efficient enough to reach the masses. Once breast cancer has been detected in screening tests, more detailed evaluations are usually performed using diagnostic modalities which may also be used for initial diagnosis.

Adjunctive modalities are used to provide the doctors and clinicians with additional confidence in their initial diagnosis. The currently used modalities include mammography, breast ultrasound, thermography, magnetic resonance imaging (MRI), positron emission tomography (PET), scintimammography, optical imaging, electrical impedance based imaging, and computed tomography (CT).

Since cancer is a complex disease with varied pathology, many variations of the basic detection technique used in each of these modalities have been carried out over the years in order to improve the detection efficiency[8]. The main aim of this paper is to provide a discussion on the capabilities of each of these modalities, which are presented in the following sections.

## VARIOUS MODALITIES USED FOR BREAST CANCER DETECTION

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This section presents a review of the various modalities used for breast cancer detection.

### Mammography

Mammography is the most common method of breast imaging. It uses low-dose amplitude-X-rays to examine the human breast. Cancerous masses and calcium deposits appear brighter on the mammogram. This method is good for detecting Ductal Carcinoma In Situ (DCIS) and calcifications. Currently, mammography is the gold standard method to detect early stage breast cancer before the lesions become clinically palpable. Mammography has helped to decrease the mortality rate by 25%-30% in screened women when compared with a control group after 5 to 7 years[9]. Randomized trials of mammographic screening have provided strong evidence that early diagnosis and treatment of breast cancer reduces breast cancer mortality[10].

It is very difficult to detect cancer in the early stage using mammographic screening. However, additional screening tests may reduce the death rate from breast cancer. The mammography screening test has been shown to lower the death rate in randomized controlled trials conducted with the general population[11-13]. Mammographic imaging has proved to be scientifically more suitable for screening, and hence, may be used for general screening[12]. Patients with abnormal breast findings were screened using mammography, sonography and magnetic resonance (MR) mammography[14]. Carcinoma *in situ* was diagnosed in 78.9% and 68.4% of patients using mammography and MR mammography, respectively. A combination of all three diagnostic methods performed better in detecting invasive cancer and multifocal disease. However, the sensitivity of mammography and sonography combined was identical to the performance of MR mammography (i.e. 94.6%).

In digital tomosynthesis mammography, the basic mammography technique has been modified to acquire 3D views of the breast[15]. In another variation called ductography, contrast agents are used to determine the presence of a mass within the ducts. A recent development of mammography is contrast-enhanced digital mammography (CEDM) which uses an intravenous injection of an iodinated contrast agent in conjunction with a mammography examination[16]. Diekmann et al[17] evaluated the diagnostic benefits of CEDM over conventional mammography. They found an increase in sensitivity from 0.43 to 0.62 on using CEDM, and also observed better sensitivity in the case of dense tissues. This is a potentially useful benefit as it is known that conventional mammography is not very sensitive in detecting cancer in dense breast tissues.

### Breast ultrasound

Ultrasound imaging is used to detect breast lesions and it is used as an adjunct tool for detecting the location of the suspicious lesion. The ultrasound transducer directs high-frequency sound waves into the breast tissues and detects the reflected sound waves. These detected waves are used to display 2D images. As the sensor is moved over the breast, continuous real-time images can be captured. Ultrasound can be used as an adjunct to mammography for clinical examination in the assessment of both palpable and impalpable breast abnormalities. Ultrasound screening in asymptomatic women causes unacceptable false positive and false negative outcomes[18]. Hence, there is little evidence to support the use of breast ultrasound in breast cancer screening.

Mammography alone misses many cancers in dense-breasted women. The diagnostic yield of mammography with an automated whole breast ultrasound (AWBU), for women with dense breasts and/or at elevated risk of breast cancer, is better[19]. A study by Kelly et al[19] showed that 87% of cancer detections added by AWBU were found in the 68% of studies in women with dense/very dense breasts. Hence, AWBU resulted in significant cancer

detection improvement compared with mammography alone. Kopans[12] has suggested that sonography should always be used with mammography or other imaging techniques. It alone will not be able to detect lesions accurately. Another study that supports the use of mammography and ultrasound together is the ACRIN 6666 trial. The results of this study indicated that incorporating a screening ultrasound with mammography would detect an additional 1.1 to 7.2 cancers per 1000 high-risk women, however, at the expense of an increased false positive rate[20]. Breast cancer is common among Japanese women in their late 40s with small and dense breasts. It was shown that the performance of ultrasound was similar to that of mammography in detecting breast cancers in these women[21]. The authors of this study have also suggested that the combination of mammography and ultrasound is a suitable method for breast screening in Japan. A very recent specific study which was conducted to evaluate the efficiency of whole breast ultrasound based on BI-RADS final assessment categories in women with mammographically negative dense breasts[22] has reported that ultrasound is useful for dense breast evaluations.

Advancements in ultrasound technology include 3D ultrasound that formats the sound wave data into 3D images[23], automated ultrasound for a good overall view of the breast[24], Doppler Ultrasound[25], and sonoelastography[26].

### Breast thermography

Cancerous and pre-cancerous tissues have a higher metabolic rate resulting in growth of new blood vessels supplying nutrients to the fast growing cancer cells. As a consequence, the temperature of the area surrounding the pre-cancerous and cancerous breast tissue is higher when compared to the normal breast tissue temperature. The breast has been recognized to exhibit a circadian rhythm, which reflects the physiology. There is evidence to indicate that these rhythms, associated with malignant cell proliferation, are non-circadian[27,28]. The relationship between breast skin temperature and breast cancer has been examined[29,30]. Measurable changes were observed in skin temperatures between clinically healthy and cancerous breasts. The cyclic variation in temperature and vascularization of the normal breast thermograms under a controlled environment were studied[31]. The results of this study help in the analysis of normal and abnormal breast thermography.

Nowadays, breast thermograms are widely used for the accurate detection of breast cancer[32-38]. Thermography is a promising screening tool because it is able to diagnose breast cancer at least ten years in advance. However, both analysis and interpretation of thermograms depends on analysts.

### MRI

MRI uses the hydrogen nucleus (single proton) for imaging purposes because this nucleus is abundant in water and fat. The magnetic property of the hydrogen nucleus is used to produce detailed images from any part of the body. The patient who is examined using MRI is placed in a magnetic field and a radio frequency wave is applied to create high contrast images of the breast. In dynamic contrast enhanced-MRI (DCE-MRI)[39], a contrast agent is injected before the images are captured. This technique has been found to be more sensitive than mammography[40].

Application of state-of-the-art imaging modalities, namely MRI, magnetic resonance spectroscopy (MRS), nuclear imaging, and optical imaging, for precise identification of human breast tumors and their use in monitoring chemotherapeutic responses has been discussed[41]. MRI helps in investigating vascular changes associated with neoangiogenesis[42]. It is popular in diagnosis, and is now being used to assess tumor response to treatment. It is predicted that new contrast agents and improvements in measurement and analytical methods will help the use of MRI in investigating the vascular dependence of tumor growth and the activity of vascular-directed therapies.

Breast MRI is a widely used imaging modality for the early detection of breast cancer[43]. Early results suggest that MRI can dramatically improve the yield of screening certain at-risk populations. Further work may be performed to clarify the role of breast MRI in the early detection of breast cancer. Recent work on breast MRI with 3 Tesla magnets, showed that MRI had a higher spatial and temporal resolution and a better signal to noise ratio[44].

Numerous studies have demonstrated that malignant tissues have elevated levels of choline-containing compounds, suggesting that these compounds may serve as non-invasive markers for detecting malignancies[45]. *In vivo* non-invasive MRSI uses equipment that is almost identical to the normal MRI apparatus but with specific sequences for spectroscopic signal acquisition to visualize the total choline content in the breast. MRS improves the specificity of

MRI further, and it can predict response to therapy and/or evaluate very early response to chemotherapy. In a study using MRS, the specificity was observed to be 87.5% which was significantly higher than that obtained using MRI (62.5%)[46]. Novel contrast agents are being developed to provide more sensitive and more specific discrimination of benign from malignant lesions. MRS and MRI are rapidly becoming standard capabilities of clinical MR systems with magnets 1.5 Tesla or stronger[47]. The promising results from multiple institutions reported so far suggest that MRS, along with MRI, can improve the clinical assessment of breast cancer in the future. Numerous multicenter trials may still be needed before these new techniques can be widely used to guide diagnostic decisions and to predict response to therapy. Brain and prostate cancers also exhibit increased choline levels, and hence, MRS is suitable for assessing these cancers[48].

In another version of MRI, namely diffusion weighted imaging (DWI), image contrast arising out of the differences in the motion of water molecules between tissues is utilized for imaging. No external contrast agents are needed. The Apparent Diffusion Constant (ADC) parameter was found to be higher in tumor tissues compared to normal tissues, and hence, this ADC has been used in the assessment of metastatic breast cancer response to chemoembolization[49]. DWI-MRI has also been used for evaluating a variety of other cancers including liver, prostate and pancreatic carcinomas[48].

In MRI based elastography, a periodic motion is generated by a mechanical shaker to one side of the breast and the resulting displacement field inside the breast is captured by MRI to determine the elasticity parameters[50]. This technique relies on MRI's ability to detect slight motion. MRE studies have also been tried to assess prostate cancers[48].

MRI is useful for women with a higher risk of breast cancer, has good image resolution, is effective for evaluating dense breasts, helps to evaluate inverted nipple, allows the simultaneous evaluation of both breasts, helps to determine whether lumpectomy or mastectomy is the best treatment, and it has no side effects as there is no radiation[51]. The limitations of this technique are that it is not good at diagnosing ductal carcinoma *in situ* (DCIS), may lead to many false positives, is slow (30 min to one hour), more expensive, and may not show all calcifications. Recently, an analysis was conducted to study the correlation between film mammography and MRI in screening breast cancer in high-risk women[52]. The authors found no significant correlation, and suggested that using both modalities for screening is likely to improve the odds of detecting early stage cancers.

### Positron emission tomography

Positron emission tomography (PET) is a nuclear medicine imaging technique which is used to produce three dimensional images. It detects a pair of γ rays, which are emitted from the radionuclide that is introduced into the human body. Malignant tumors are characterized by increased glucose metabolism compared with normal cells. This produces a good contrast between cancerous and normal cells in PET images. It provides information about the chemical functions inside organs and tissues. However, PET is very expensive and yields poor resolution images. Furthermore, the patient is subjected to radiation exposure. PET has been used frequently to predict treatment response in several cancers[48].

Single photon emission computed tomography (SPECT) and PET use radiolabeled isotopes[53]. Both imaging modalities provide unique opportunities to study animal models of breast cancer with direct application to human imaging. MRI and PET are complementary and valuable in monitoring response and assessing residual disease of locally advanced breast cancer treated with neoadjuvant chemotherapy[54]. Their study suggested that the combined use of MRI and PET were complementary and offered advantages over clinical breast examination. PET was more accurate in predicting pathologic non-response, and the response evaluated using MRI correlated well with macroscopic pathologic complete response.

Scintimammography (SMM), SPECT and PET can be used as adjunct imaging tools for detecting and staging breast cancer, however, they cannot replace invasive procedures, due to insufficient sensitivity to detect small (less than 1 cm) tumor deposits[55]. SMM is useful for assessing palpable breast masses in women with dense breasts. Several enzymes and receptors have been targeted for imaging breast cancers with PET. Fluorodeoxyglucose is useful in the detection and staging of recurrent breast cancer and assessing its response to chemotherapy.

PET used to complement mammography is known as positron emission mammography (PEM), and it has been

reported that PEM may not be adversely affected by breast density, hormone replacement therapy, and menopausal status of the patient[56].

### Scintimammography

The scintimammography imaging technique uses a radioisotope to visualize lesions of the breast. It is difficult to detect breast cancer in dense breast tissue using mammography. As a result, mammogram-based breast cancer detection techniques yield a high number of false positives. Scintimammography with technetium tetrofosmin (Tc-99 tetrofosmin) provides better precision in the diagnosis of women with dense breasts. It is suitable for dense breasts, can image breasts with implants, can image large and palpable abnormalities, and it can be used when multiple tumors are suspected[57]. A high-resolution breast-specific gamma camera was used to evaluate the occult breast cancer in women at high risk of breast cancer[58]. The authors found that high-resolution breast-specific scintimammography was able to detect small (< 1 cm), mammographically occult, nonpalpable lesions not otherwise detected by mammography or physical examination in women with increased risk for breast cancer. The joint use of mammography and 99mTc-methoxy isobutyl isonitrile (MIBI) scintimammography to reduce the number of biopsies required in patients with suspected breast cancer has been studied[59]. The total number of biopsies performed was reduced by 34%. In scintimammography with Tc99m compounds, the value of planar Tc99m sestamibi scanning for auxiliary lymph node evaluation was presented[60]. Their work confirmed that non-tomographic Tc99m sestamibi scintimammography had a very low detection rate for auxiliary lymph node involvement and may not be suitable for clinical assessment of breast cancer. The sensitivity and specificity of Breast-Specific Gamma Imaging (BSGI) for the detection of breast cancer by using pathologic results as the reference standard was determined[61]. BSGI showed high sensitivity (96.4%) and moderate specificity (59.5%) in the detection of breast cancers.

### Optical imaging

Optical imaging uses near infrared (NIR) wavelength light to detect lesions inside the breast. Diffuse optical imaging (uses NIR light to penetrate into the breast), diffuse optical tomography (uses NIR light of wavelength 700 to 1000 nm), and optical mammography (uses laser light) are the different types of optical imaging which use different wavelengths of light to detect breast lesions.

Diffuse optical imaging (DOI) is a noninvasive optical technique which uses NIR light to quantitatively characterize the properties of thick tissues[62]. Factors affecting the DOI performance are intrinsic and extrinsic contrast mechanisms, quantitation of biochemical components, and image formation/visualization. Currently, the new direction is to develop standardized DOI platforms that can be used as stand-alone devices or in conjunction with MRI, mammography, or ultrasound which can provide new insights for detecting disease in mammographically dense tissue, distinguishing between malignant and benign lesions, and understanding the impact of neoadjuvant chemotherapies.

Optical imaging offers complementary features to radiologic imaging techniques, primarily the quantitative imaging of hemoglobin saturation and concentration, and the selective imaging of specific gene expression with high sensitivity, because background signals can be suppressed using enzyme-activated fluorescence probes[63]. This method can also characterize vascularization, permeability, and a plethora of contrast agents with high sensitivity, without using harmful radiation, and probably at less cost.

### Electrical impedance based imaging

Our body tissues offer impedance to the flow of electric current. Studies have shown that cancerous breast tissues have lower impedance when compared to normal tissues. Electrical impedance tomography (EIT) and electrical impedance scanning (EIS) are the two types of electrical impedance based imaging techniques available. In EIT, 2D or 3D images are reconstructed from a large number of impedance values which are captured by placing electrodes around the breast surface in a circular fashion. However, in EIS or electrical impedance mapping (EIM), a planar electrode array is used and there is no need for complicated reconstruction algorithms which are used for EIT.

Zou et al[64] presented a review of the noninvasive impedance imaging techniques for breast cancer detection, such as EIT and EIM. They suggested that an invasive impedance technique can be more effective by combining it

with other cancer indicators. They have proposed the possibility of improving EIM using a pair of electrode arrays, one for exciting the breast surface and the other for measuring the impedance. They concluded that magnetic induction tomography and other magnetic induction based impedance imaging techniques are promising. The T-SCANTM technology and its use as a diagnostic tool for breast cancer detection was discussed by Assenheimer et al[65]. They used theoretical models with simplified geometries to show that the display of planar two-dimensional maps of the currents detected at the breast's surface related to the electric field distribution within the breast. The differences in the distribution of the various tissue types can be used to discriminate between various pathological states. They also suggested that low frequency impedance measurements can be used in breast cancer diagnosis. EIS has been found to provide a rather high sensitivity for the verification of suspicious breast lesions[66].

The possibilities of using electrical impedance mammography for the investigation of mammary gland state in women with different hormonal status was studied[67]. They found that electrical impedance mammograms from different groups had clear visual distinctions and statistically significant differences in mammary gland conductivity. Further investigations on histomorphological characteristics of false negative and false positive lesions may be needed to gain further knowledge about the bioelectric characteristics of breast lesions.

### CT

CT uses X-rays to capture 2D images or slices of the examined body parts. Subsequently, different algorithms are used to generate corresponding 3D images which provide anatomical information such as the location of lesions. Usually CT has low contrast, and hence, iodinated contrast media is injected intravenously to increase the contrast of the CT images. The iodine contrast injection dramatically enhances the visualization of tumors. The diagnostic accuracy of CT perfusion in differentiating metastatic from inflammatory enlarged axillary lymph nodes in patients with breast cancer was evaluated[68]. They showed that CT perfusion may be an effective tool for studying enlarged axillary lymph nodes in patients with breast cancer. The study presents information on vascularization of lymph nodes, helping to understand the changes occurring when neoplastic cells implant in lymph nodes. The lifetime attributable risk (LAR) of cancer incidence associated with radiation exposure from 64-slice computed tomography coronary angiography (CTCA) was studied and the influence of age, sex, and scan protocol on cancer risk was evaluated[69]. These estimates, which were derived from simulation models, suggest that the use of 64-slice CTCA was associated with a non-negligible LAR of cancer. This risk varies markedly and was considerably greater for women, younger patients, and for combined cardiac and aortic scans.

A hybrid technique combining PET and CT is useful for staging potential metastatic cancers[70]. This technique has the combined advantages of both CT and PET: tumor location is better captured by CT and PET indicates a metabolically active or malignant tumor based on glucose uptake. CT often incidentally identifies lung nodules during exams for other lesions in the thorax. Therefore, recently, a dedicated breast CT prototype that has a high-resolution, isotropic, rotating detector was developed. Subjective evaluation of breast CT images revealed excellent anatomical detail, good depiction of microcalcifications, and exquisite visualization of soft tissue components which belong to the tumor when contrasted against adipose tissues[71].

## BIOMARKERS

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A disease cannot be easily and straight-forwardly diagnosed based on symptoms as the initial symptoms may point to a group of diseases with similar features. Moreover, in the case of cancer, it will be too late to make a diagnosis based on symptoms, as symptoms appear when the tumor is relatively large. Therefore, for early detection, the modality must be capable of detecting cancer in asymptomatic women. By the time a tumor is detected by most of the current imaging modalities, molecular changes would have already occurred in the suspected area. Detection of such molecular changes, therefore, would be our best bet to capture the presence of cancer at its earliest stages. A biomarker is a measurable phenotypic parameter that characterizes an organism's state of health or disease, or a response to a particular therapeutic intervention[72]. Diagnostic assays using such biomarkers have good potential in early cancer detection.

Studies have demonstrated the utility of direct examination of the cytomorphology of exfoliated cells in detecting breast cancer[73]. The molecular analysis of tumor biomarkers in nipple aspirate fluid (NAF) or in ductal lavage has also been found to be useful for the detection of breast cancer[74]. However, the cytomorphology-based analysis is subjective, and most women may not produce NAF. Lipids, carbohydrates, polyamines, proteins, and

nucleic acids have also been studied as potential biomarkers for early breast cancer detection. A detailed review of the biomarkers used for early detection can be found in[75]

Response to therapy is first observed at the molecular and cellular level and then at the anatomical level. Therefore, biomarkers are useful in predicting treatment response. In current clinical practice, the standard markers used for general prognosis assessment and the prediction of therapy response are the hormone receptor (ER and PR) status, HER-2/neu status, and the labeling of Ki-67 antigen.

ER and PR testing have been used as markers for the prognosis and the prediction of response to anti-estrogen therapy[76-77]. The HER2/neu is a protein that has higher aggressiveness in breast cancers. Amplification of the *HER2/neu* gene and over-expression of the HER2/neu protein have been observed in 10%-34% of invasive breast cancers[78]. The human Ki-67 protein expression is associated with cell proliferation. The Ki-67 labeling index, which is a fraction of Ki-67-positive tumor cells, is often correlated with the clinical course of cancer. A detailed review of the emerging biomarkers used for breast cancer management (prognosis and treatment response prediction) has been carried out by Ross et al[79].

The term molecular imaging was defined by the Commission on Molecular Imaging of the American College of Radiology as "the spatially localized and/or temporally resolved sensing of molecular and cellular processes *in vivo*." Molecular imaging explores either changes in metabolic rate, cell proliferation rate, hormone expression, gene expression, or protein production. The main modalities for molecular imaging are PET, SPECT, MRS, and optical imaging; PET imaging being the most widely used modality. PET has been used for the in vivo quantification of ER. Since [18F]-16α-[fluororestradiol] (FES) has shown most promise in quantifying the functional ER status of breast cancer, it has been used as a tracer in PET-ER imaging[80]. PET-ER imaging (FES-PET) can therefore predict the likelihood of a patient's response to hormonal therapy, and thereby, determine the suitability of the patient for this type of treatment. The results of some related studies can be found in[81]. Jeraj et al[82] have presented a comprehensive review of the various functional and molecular imaging techniques used in oncology. They have presented the effectiveness of such imaging techniques for a variety of cancers.

## CONCLUSION

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Current breast imaging modalities play a vital role in assisting clinicians in the primary screening of cancer, in the diagnosis and characterization of lesions, staging and restaging, treatment selection and treatment progress monitoring and in determining cancer recurrence. In this paper, we have discussed the capabilities of the different breast imaging techniques that are currently used in clinical setups. It is evident from the material presented in this paper that no single modality is completely useful in all areas of breast cancer management. Therefore, research is continually being carried out to improve the existing modalities and develop new modalities based on the physical, chemical, and biological properties of cancerous breast tissue that differentiates it from normal and benign tissues. Cancer is a disease with no specific cure, and its treatment involves a wide variety of side-effects. Moreover, the survival rate is largely dependent on early detection. A disease with such disturbing and life-threatening factors warrants a huge amount of research to develop modalities (screening, diagnostic, adjunct, standalone, and hybrid) that help in early detection and in finding a possible cure. Currently, research on modality development is moving towards imaging at the molecular level. This type of imaging will also help in understanding the nature of cancer growth and development which in turn might lead us closer to finding a possible cure for this disease. Moreover, the use of computer-aided diagnosis techniques has been widely advocated for the improvement of cancer detection efficiency and for reducing the inter-observer variability that is associated with the subjective human interpretation of the images obtained.

## Footnotes

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