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Detection and Diagnosis of Breast Diseases

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Abstract

Cancer is a disease that starts in a localized organ or tissue and then grows out of control. Breast cancer is an important health problem as in the Western world; it is the second most frequent cause of cancer death in women (after lung cancer). The incidence rate, however, rises dramatically over the age of 50 years. This is may be due to several risk factors, such as family history, genetics, early menstruation, late menopause, and other factors, that have not yet been identified. The problems of breast diseases have prompted global governments to put constant efforts to increase patient's recovery level against this disease. Early and accurate detection with mass screening programs helps improves a woman's chances for successful treatment. It also minimizes pain, suffering, and anxiety that surround patients and their families. The current and the most cost-effective technique used for screening and diagnosis of breast cancer is X-ray mammography. It is the state-of-the-art for earlier detection to improve both prognosis and survival rate. This is may be due to its good availability, high sensitivity, and relatively low cost/patient. The goal of this chapter is to introduce the problems caused by breast cancer. Starting with an overview of the requirement for breast tumor imaging and the diagnostic techniques used for breast cancer assessment are briefly described, highlighting the advantages and disadvantages of each technique. In addition, the problems associated with a relatively new functional breast imaging technique namely scintimammography were introduced and discussed. The intention that the chapter provide the reader with sufficient background on the available diagnostic techniques of breast tumor imaging approach, as well as an overview of the literature.

Keywords: breast cancer detection, molecular imaging, scintimammography

1. Introduction

Most women experience breast changes in their life. This is due to normal growth and changes in hormone levels. However, lumps, bumps, breast pain, nipple discharges, or skin irritation

are examples of breast problems that have similar symptoms. The vast majority of lesions and abnormalities occurs in the breast are not cancer but are far more frequent than malignant ones [1–7]. Benign breast constitutes a heterogeneous group of lesions including various abnormalities, inflammatory lesions, epithelial and stromal proliferations, and neoplasms [3–5]. However, cancer is a disease that starts in a localized organ or tissue and then grows out of control. Breast cancer is an important health problem as it is the most common malignancy in women in Western countries. It is the second most frequent cause of cancer death in women (after lung cancer) [8, 9]. The incidence rate, however, rises dramatically over the age of 50 years. This is may be due to several risk factors such as family history, genetics, early menstruation, late menopause medication, and other factors that have not yet been identified. The above problems have prompted global governments to put constant efforts to increase patient's recovery level against this disease. Early and accurate detection with mass screening programs helps improves a woman's chances for successful treatment. It also minimizes pain, suffering, and anxiety that surround patients and their families. The goal of this chapter is to introduce the problems caused by breast cancer, starting with the requirements for breast imaging, an overview of the methods for diagnosing breast abnormalities with the focus on molecular imaging of the breast.

2. Requirements for breast imaging

The goal of breast evaluation is to classify findings as normal physiologic variations, clearly benign, or possibly malignant. The size, shape, and appearance of the female breast are not constant but undergo a number of changes during the lifetime of women. For instance, changes occur with pregnancy, breast feeding, and during the menstrual cycle. In addition, the age of the subject not only influences the shape but also parenchymal density of the breast. That is why young women tend to have dense breasts (more fibro-glandular tissue), creating a rounded appearance. On the other hand, postmenopausal women have breasts containing a large amount of fat. This makes the X-ray mammogram far more effective in older women as the fat content is more radio-translucent (appears darker) compared to glandular tissue (appears under-exposed) in younger women [10]. The above discussion suggests that both the shape and parenchymal density of the breast impose particular constraints on the choice of imaging modality. The imaging technique should be powerful for initial detection and subsequent follow-up of the diseases.

At present, no single technique was used for all cases of breast cancer detection without showing certain clinical or technical limitations. This implies necessity to address the specific needs that can help for breast tumors imaging to overcome these limitations. For instance, breast compression often needed as it holds the breast still and enhances the spatial resolution. It also evens out the breast thickness and reduces scatter in X-ray or γ -ray imaging [11], thus increasing image sharpness. Moreover, it spreads out the tissue so that the overlying breast tissue will not obscure small abnormalities. Since the breast is an external organ and extends to the chest wall, it requires appropriate views to be obtained. For instance, in X-ray mammography, a lateral (from the side) view of the breast allows separation of the chest wall from

lesions deep within the breast. On the other hand, in single photon γ -ray emission imaging, one needs to separate the breast from the heart by employing an appropriate prone (face down) position. However, it has been claimed that with prone imaging view, there is a possibility of missing a small low-intensity medial lesion because of attenuation. This implies that another image is needed but in the lateral view. In addition, shielding the camera from the background cardiac flux is very useful in tumor detection in terms of contrast and resolution.

3. Interpreting imaging test

The usefulness of diagnostic imaging tests, which is their ability to detect a patient or subject with disease or exclude a patient or subject without disease. In other words, the idea in using any diagnostic test is to be able to correctly diagnose the disease and easily interpret the results. The latter is achieved by calculating the probability that a patient has a disease. The diagnostic test performance is usually measured by calculating four important statistical parameters or terms. These are the test's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) [12, 13]. **Table 1** illustrates these parameters and their relationship. In breast tumor γ -ray imaging, these parameters are dependent on clinical history, biological factors such as size, site, or location, the type of the lesion, and patient's age. The test parameters may also depend on the physical and the practical aspects as well as on the imaging technology parameters. Sensitivity and specificity are properties of a test that tell us how good the diagnostic test is at predicting the disease and whether it is to be used or not [12]. Sensitivity is the proportion of people with the disease who have a positive test for the disease [12]. Specificity is the proportion of people without the disease who test negative [12]. A high sensitivity test means that the test has a low rate of false-negatives and high specificity means that the test has a low rate of false-positives. In brief, the text here and **Table 1** simply provide a practical application, hence of what these concepts mean in clinical practice and how they can be used in practical settings to aid the diagnostic process.

In clinical practice, the decision to send patients for breast biopsies is arbitrary, i.e., there is no fixed test threshold. Instead, the decision is usually based on the needs of patients and clinicians for the different clinical situations. As a result, for any given image of a breast lesion, there is a kind of trade-off between the sensitivity and specificity, i.e., sensitivity can only

Test outcome	Condition as determined by "gold" standard		
	True	False	
Positive	True positive	False positive	⇒Positive predictive value
Negative	False negative	True negative	⇒Negative predictive value
	↓ Sensitivity	↓ Specificity	

Table 1. The main diagnostic test parameters [12, 13] demonstrating the practical application and the relationship of these four terms.

increase by decreasing the specificity of a test. For instance, if the decision is to only select patients with extremely abnormal images to have breast biopsy, then the test will become extremely specific but not very sensitive. In this case, many patients falsely diagnosed as not having breast diseases or breast cancer. On the other hand, if the decision is to send patients with borderline abnormal images to have biopsy, the test will then become more sensitive but less specific. As a result, many patients who do not have breast cancer sent for an unnecessary biopsy, i.e., the diagnostic tests are useless. This sensitivity specificity trade-off of the diagnostic test is accurately illustrated by the analysis of the receiver operating characteristic (ROC) curve at each test threshold or cut-point. This curve is a plot of the true positive rate against the false positive rate for the different possible thresholds of the diagnostic test. The area under the ROC curve is a measure of test accuracy, i.e., how well the test separates or classifies the patient population into those with the abnormality and those without. An area of 1 represents excellent performance test and an area of 0.5 represents a fail test.

To know the probability that the imaging test is giving the correct diagnosis, the positive and negative predictive values are needed. The PPV of a test is the probability of a patient having the disease following a positive test result [13]. The NPV is the probability of a person not having the disease following a negative test result [13]. These test performance measures are influenced by the probability of disease at any point in time of the total abnormality in the population tested [13]. The predictive values also vary as a function of disease prevalence and patient subpopulation. Thus, a combined measure of diagnostic performance, the likelihood ratio, is a clinically useful diagnostic test performance measure. Negative likelihood ratios measure the ability of the test to accurately rule out disease, and positive likelihood ratios measure the ability of the test to accurately detect disease. In summary, both sensitivity and specificity terms of a diagnostic test suffer from limitations in clinical practice, as they cannot estimate the probability of breast cancer in an individual patient. However, PPV and NPV help to overcome this problem, but they both vary according to disease prevalence and populations.

4. Diagnosis of breast disease

Breast lesion investigations may include self or clinical breast examination, X-ray mammography, and biopsy. In addition, a variety of other efficient complementary imaging modalities provide additional information to achieve a definite breast diagnosis. The following subsections give an overview of the main diagnostic techniques used for breast tumor imaging.

4.1. X-ray mammography and screening

Mammography is a low energy (25–32 keV) X-ray examination of the soft tissues of the breast. It uses the variation in density between normal mammary features and abnormal tissue structures (lesion) to produce the image. The X-ray images are either captured on a film or directly stored on a digital computer. The former is one of the widely used current techniques based on screen-film technology. X-ray mammography considered the gold standard in breast

imaging as it is fast, available, and has a lower cost than other breast imaging techniques. It has two main applications: as a screening method in asymptomatic patients and as a diagnostic method in symptomatic populations. The former application is extremely important and its introduction in the past three decades has significantly reduced the mortality rate of breast cancer in many countries [14, 15]. This is because the screening services accurately detect micro-calcifications and nonpalpable soft tissue masses, which have been beyond other imaging methods, due to the high spatial resolution ($\sim 50\text{--}100\ \mu\text{m}$). Normally, screening is achieved by exposing the breast to X-rays after gently compressed between two plates and then taking two views for each breast. A craniocaudal (imaging from above to below) and lateral views are generally taken. A lead grid is used to reduce scattering photons that reach the film. Diagnostic mammography evaluates the entire breast as well as characteristics of the mass. It is used for assessing the size of the lesion, for pre-surgical localization of suspicious areas of breast, and in the guidance of needle biopsies. The reported sensitivity (the fraction of patients actually having the disease and correctly diagnosed as positive) in lesion detection varied between 69 and 90% [16] depending on the breast density. The specificity (the fraction of patients without the disease, correctly diagnosed as negative) is the major drawback of conventional mammography. A variation in specificity between 87 and 97% and a low positive predictive value as low as 15% has also been reported [17]. This 'less than perfect' performance may be due to several confounding factors, e.g., poor mammographic technique, observer error, the lesions are nonpalpable or at a cellular level, and/or the lesions are obscured by the normal breast tissues. The presence of scars or tissue distortion may hide true small tumors on the mammogram. Nevertheless, conventional mammography remains a valuable and cost-effective technique for breast tumor diagnosis. Over the last three decades, considerable efforts are carried out to improve the current screen-film mammographic technique. These improvements include image quality, acquisition techniques, and interpretation protocol in order to reduce some of the mammographic limitations [18].

The use of digital imaging in general radiography has increased rapidly in recent years. This has extended to mammographic imaging. "Digital mammography" (DM) is a possible current direction in breast imaging compared to film-based conventional mammography. This is due to the presence of X-ray detector, which is considered the heart of DM. A number of technologies and several types of integrated digital detector system are in use nowadays. DM has the potential to improve contrast resolution compared with film-screen imaging. This is because DM detectors like other detectors characterized by sensitivity, spatial resolution properties, quantum detection efficiency, noise, and linearity of response.

This has improved diagnostic capability and relatively outweighs the potential reduction in limiting spatial resolution. DM technique offers many inherent advantages over the conventional screen film-based technology [19, 20]. For instance, processing with digital systems increase dynamic range (two to four times the dynamic range of typical film-screen), improved quantum efficiency, signal-to-noise-signal, and storage and display mechanisms.

Moreover, DM detector provides features for automatic control of exposure factors of the image acquisition. This represents the spatial pattern of X-ray transmitted by the breast tissue accurately. The use of computer-assisted image interpretation claimed to be helpful for

the physician. This may enhance different features such as computer-aided diagnosis, which may further improve the visibility of lesions and improve mammographic sensitivity [21]. Therefore, repeated exposures (which are sometimes, needed when using conventional mammography) are not required and this may reduce the radiation dose. The advantage of digital imaging systems compared with film-screen imaging is the ability to manipulate and possibly enhance the displayed image. The breast dose levels required by current digital imaging systems are, in general, similar to those of a modern mammographic film-screen combination. However, developments in detector design and optimization of beam quality may eventually result in a reduction in radiation dose. With the use of DM, a number of image processing operations can be introduced to correct for spatial nonuniformities in detector responses. In addition, it is also possible to improve the effective spatial resolution of the detector. It also overcomes a number of limitations inherent in the screen-film image receptor used in conventional mammography. Consequently, this improved the diagnostic image quality as well as reduced the doses to the breast tissues.

Furthermore, it does not need either cassettes or dark rooms or processors, and thus allegedly saves space and time in archiving and retrieving DM images. However, DM requires large disk space for saving image data. Despite several advantages, DM does not yet reach the level of detail to replace screen film mammography. However, with continuous technical improvements of the digital system, this may be expected to change in the near future. Both conventional and DM systems suffer from substantial technical and clinical limitations. For instance, these systems are unreliable in imaging patients with dense parenchyma tissue especially in the younger female population due to more glandular tissue. Mammographic findings are nonspecific (cannot always differentiate benign from malignant disease) and often underestimate the size of the detected lesion. X-ray-based imaging is also not useful for breast diagnosis following surgery or radiotherapy, as the patient's breasts in these cases have architectural distortion.

Moreover, both the tube spectrum and the peak potential (KVp) are important parameters affecting the image quality in film-screen and digital mammography. Automatic selection of proper target/filter combination in modern mammography systems may be affected by improper KVp. In conventional devices, the user depends on central laboratory calibration and has no easy way to calibrate the instrument during use. It is worth mentioning that X-ray mammography is not always useful for nonpalpable tumors. Another group of women with a known family history of breast cancer was recommended not to repeat X-ray mammography. In other words, those close carrying a mutation in BRCA1 (human gene called breast cancer 1, early onset) or BRCA2 (breast cancer 2) genes. Those groups are at high genetic risk of cancer. Some even have opted for preventative bilateral mastectomy. It is preferred not to repeat scan in this group due to X-ray dose and thus, a more sensitive diagnostic test would be advisable. Once the diagnostic tests particularly X-ray mammography indicates or suspects breast cancer, breast biopsies are then performed. Breast biopsy is an invasive procedure used to remove tissue or cells from the breast for microscopic examination. This technique generally performed under local anesthesia. Several types of biopsy are available depending on location, type, and size of lesion. Fine needle aspiration biopsy is performed by inserting a very thin needle to the lesion for taking a small sample of cells, fluid, or tissue. Core needle biopsy

is used with a large needle to remove a small cylindrical shape of tissue. Surgical biopsy involves removing part (incisional biopsy) or entire (excisional biopsy) lesion tissue.

In addition, a special wire localization technique may be used during surgery for deeply seated lesion. This technique usually performed under X-ray or ultrasound guidance. There are special instruments and techniques that help to guide the needle biopsy. These include stereotactic biopsy with a 3D mammographic technique to find the exact location of breast lesion and vacuum-assisted biopsy using a tube to gently suck the breast lesion and a knife to remove tissue. This technique is much less traumatic than open biopsy. Moreover, a sentinel node (the first lymph node to receive drainage from a breast cancer cell) biopsy may often be used to determine whether cancer cells have spread to other tissue. In summary, invasive breast biopsies play an important role for evaluating breast cancer particularly nonpalpable lesions. These surgical procedures are important for staging (see **Table 2**) and are considered the “gold standard” [17] to determine the presence or absence of breast cancer. However, invasive breast biopsy procedures are expensive, time consuming, and are often associated with emotional stress. It

Stage	Tumor size	Lymph node involvement	Metastasis
0	Carcinoma <i>in situ</i>	N0	M0
I	≤2 cm	N0	M0
IIA	No evidence of tumor	N1	M0
	≤2 cm	N1	M0
	2–5 cm	N0	M0
IIB	2–5 cm	N1	M0
	5 cm<	N0	M0
IIIA	No evidence of tumor	N2	M0
	≤2 cm	N2	M0
	2–5 cm	N2	M0
	5 cm<	N1	M0
	5 cm<	N2	M0
IIIB	Of any size	N0	M0
	Of any size	N1	M0
	Of any size	N2	M0
IIIC	Of any size	N3	M0
IV	Of any size	Any N	M1

Note: Beyond stage IIIB, the tumor is usually extended to either the skin or the chest wall and thus can be of any size. The N0 = no regional lymph node, N1 = metastasis in movable ipsilateral axillary lymph node(s), N2 = metastasis in ipsilateral axillary lymph node(s) fixed or matted, and N3 = metastasis in ipsilateral infraclavicular lymph node(s) or clinically apparent.

Table 2. The staging of breast cancer, adapted from Ref. [22].

also causes scar and tissue distortion that complicate the future mammography. As a result, additional imaging tests are being used to reduce the trauma, cost, avoid, or minimize unnecessary invasive breast biopsies, and more importantly to further improve breast cancer diagnosis.

4.2. Complementary diagnostic techniques

From the previous discussion, it is clear that there are some clinical situations where there are significant limitations to use mammography in isolation. In such cases, there is a great need to use sensitive tests to achieve a high confidence and accurate diagnostic decision. The use of breast biopsies is necessary if breast cancer is indicated or suspected in such cases. Of the performed breast biopsies, $\approx 60\text{--}80\%$ [17] are negative of breast cancer or have benign lesions. In these cases, breast biopsies are considered unnecessary. This has led many breast cancer experts to propose complementary imaging modalities to provide additional diagnostic information and reduce unnecessary breast biopsies. Over the last two decades, complementary diagnostic techniques such as ultrasonography (US), magnetic resonance imaging (MRI), and radionuclide breast imaging techniques have emerged as potential investigations for the detection and diagnosis of breast cancer. The radionuclide breast imaging technique, unlike X-ray mammography, is not affected by breast density. This has prompted a number of investigators to evaluate the feasibility of radionuclide breast imaging techniques in a screening context particularly for women with dense breast.

4.2.1. Ultrasonography

US uses high frequency acoustic waves that reflect at boundaries with different acoustic properties. It is a noninvasive technique, easily available, and relatively cheap. Breast US provides unique information in assessing both palpable and nonpalpable breast abnormalities. For instance, it clearly differentiates between solid masses and cystic lesions. It is considered to be useful in cancer staging, measuring tumor sizes, easy accessing lesions located in peripheries, and reducing the number of unnecessary biopsies. It allows accurate needle placement during biopsy and is very useful for aspiration of cysts. The members of the European group for breast cancer screening recommended using US as a complementary method to X-ray mammography. In addition, the use of high frequency transducers has improved spatial resolution and thus claimed to be useful in axillary node evaluation. However, breast US technique is time consuming and operator/observer dependent. It has also a number of other limitations that may be due to the overlapping in sonographic characteristics. For instance, it cannot detect calcifications (micro calcifications or macro calcifications) in ductal carcinoma in situ (DCIS). It could also miss solid lesions especially in a fatty breast and if detected cannot determine whether a solid mass is benign or malignant. For these reasons, US is not used in some institutions as a screening technique for asymptomatic breast cancer as it is difficult to ensure that the entire breast has been scanned.

4.2.2. Magnetic resonance imaging

Magnetic resonance imaging (MRI) images is created by the recording of signals generated after radio-frequency excitation of nuclear particles exposed to strong magnetic field. Breast

MRI is a nonionizing tomographic functional technique that may be used when the diagnosis is uncertain with mammography [23]. The technique is valuable for specific clinical indications such as patients with (1) axillary adenopathy (enlargement or inflammation of lymph gland), (2) possible tumor recurrence after surgery or radiotherapy, (3) lesions overlying implants, or (4) those requiring staging of multi-focal carcinoma (two or more discrete lesions in one breast) [24]. Breast MRI with dedicated breast coil has excellent soft tissue resolution that enhances the ability to both identify the location and in some cases determines the full extent of the lesion. The use of intravenous contrast agent, gadolinium, which accumulates in tissues with a dense blood vessel network, also increases the sensitivity of breast MRI [16]. However, the reported specificity (ability to determine if lesion is benign or malignant) is 56–72% [24]. This technique has a limited application in patients with implanted metal devices or other metallic materials inside the body. In addition, several clinical limitations have been reported in the literature suggested not to use MRI in pre-menopausal women. For example, changes that do occur in the T_1 value of the breast tissue during the menstrual cycle [24] mean that patients should be scanned between the 6th and 16th day of the cycle. In summary, researchers have concluded that breast MRI is very sensitive, but not very specific and thus, cannot be used alone to rule out cancer. MRI is limited by lack of availability and inconsistent quality, and the technique is too expensive for routine use in breast cancer screening in the general patient population.

4.2.3. Radionuclide breast imaging techniques

The need to improve breast cancer detection and to reduce unnecessary invasive breast biopsies has stimulated researchers to investigate functional imaging modalities. These techniques produce a range of different imaging approaches such as positron emission tomography (PET), single photon emission computed tomography (SPECT), planar imaging, and dedicated imaging instrumentation with and without breast compression. These imaging techniques of the breast potentially offer additional information in breast cancer diagnosis. This is because these imaging methods rely on the physiological and biochemical characteristics of a lesion. Thus, it is considered as the best hope to differentiate between benign/normal and malignant diseases. These functional techniques are also used to assess and monitor the effect of cancer prevention drugs. The current radionuclide imaging techniques used for breast tumor imaging are briefly discussed.

4.2.3.1. Positron emission mammography

In PET, a small amount of positron emitter radiotracer, ^{18}F fluorodeoxyglucose (FDG), is administered intravenously to the patient [25]. It is then distributed in the body, and as it decays, the radionuclide emits a positron in any random direction. If the positron while travelling interacts with an electron within the body, the two particles then annihilate and produce two γ -rays of 511 keV each. Either a whole body scanner or a breast-specific positron emission mammography (PEM) camera [26] is used to detect the two γ -rays in coincidence (two events that are detected within ≈ 12 ns). PEM is increasingly used in North America not only in cancer diagnosis but also in staging, planning, and monitoring anticancer therapy. This information can be helpful in eliminating unnecessary axillary dissection [27], biopsies,

and in determining the appropriate treatment. The diagnosis of viable tumor tissue following chemotherapy is another application of PET [28, 29]. Imaging with ^{18}F -FDG has shown considerable promise in breast cancer imaging, but the exact role is still in evolution. Wahl [30] recommended that it is best applied to solve difficult clinical cases in specific patients rather than routinely. There are at least four reasons that limit the wide use of PEM for routine cancer diagnosis. The first one is the high cost (over £2 million) of PET coincidence imaging equipment, i.e., cyclotron, scanner, and radiochemistry facility [25]. The second one is the difficulty of producing and labeling the short half-life PET radionuclides [21]. The third reason is the lack of medical centers with the required experience to develop more advanced methodology appropriate for breast oncology. In particular, more data is still needed concerning the metabolism of different PET radiopharmaceuticals in breast tumors. The final reason is the lack of oncologists with a high knowledge of PET methodology [30].

4.2.3.2. Scintimammography

Scintimammography (SM) is a promising noninvasive functional imaging technique. It has been proposed to complement X-ray mammography and to improve patient selection for biopsy. This single photon imaging of the breast involves injecting the patient in the arm vein with a small amount (555–740 MBq [31]) of radiopharmaceutical. The most commonly used radiopharmaceutical for SM is $^{99\text{m}}\text{Tc}$ labeled sestamibi. After injection, the radiopharmaceutical distributes in the breast tissue as well as in other body organs. It accumulates more in the target object (breast lesion) with uptake ratio nearly 9:1 tumor-to-background-ratio (TBR) [32]. A standard full-size clinical gamma camera is then used to scan the patient and thus measure the 3D distribution of the radioactivity. SM imaging using full size clinical γ -camera includes a range of different imaging approaches such as planar (2D) imaging or SPECT technique. The latter technique gives a 3D image but is not widely used because it is difficult to accurately localize the lesion [33]. In contrast, planar SM is the technique that is more widely used in clinical practice because it provides better lesion localization particularly the prone images with lateral views [33]. In this case, the gamma camera is usually equipped with a low energy high resolution (LEHR) parallel-hole collimator and two views (prone and supine) are taken, to the diagnosed breast. Since the energy imaged is 140 keV representing the photopeak, 20% energy window (symmetric $\pm 10\%$) is often used and thus, centered over the photopeak. The main clinical applications of planar SM imaging are summarized here and the details are found in literatures [33–39]. In brief, SM with a general purpose γ -camera introduced to evaluate patients with dense breast tissue and prior to breast biopsy [34]. The technique is considered valuable for many clinical applications such as evaluating the axillary lymph nodes, investigating patients with micro calcifications [35], assessing multi-focal and multi-centric breast cancer diseases [36]. It is also useful for imaging patients following surgery, chemotherapy, hormonal replacement therapy, and radiotherapy as well as for patients with breast implants [33]. The technique may also assist in the differentiation of benign and malignant breast abnormalities by measuring the radiotracer uptake in the lesion as compared with surrounding breast tissue. Studies such as Refs. [37, 38] suggested that SM may be used as a second-line diagnostic test in cases where the sensitivity of mammography is decreased or there is a doubt about the presence of a lesion.

In summary, SM using conventional γ -camera is considered as a useful complementary imaging modality to aid the diagnosis and the detection of breast cancer [39]. It may also help to assess patients recommended for biopsy and this may reduce the number of unnecessary or benign breast biopsies. However, the major drawback of the current standard clinical gamma camera SM imaging systems is the use of mechanical collimator. This causes the camera imaging system to utilize a very small fraction, $\sim 0.01\%$, of the total number of the emitted photons. This limits the statistics and hence the quality and diagnostic value of the observed images. The collimator sensitivity and resolution are a trade-off and the camera is also limited by its intrinsic spatial resolution. As a result, these factors make it difficult to practically image cases of smaller, nonpalpable lesions (<1 cm) that may be deep seated or those close to the chest wall. These have stimulated the development of newly dedicated (breast specific) instruments that used for breast tumor imaging applications.

4.2.3.3. *Dedicated breast cameras*

Recent years have seen considerable interest by scientists in developing new compact medical imaging detectors. These instruments proposed for different clinical applications with the aim to improve image quality by building cameras of suitable size and shape for the part of the body under investigation. Among these designed detectors is the small-dedicated gamma camera for functional breast tumor imaging. The justification for this development is that a standard full size clinical gamma camera designed for whole body imaging and thus, is not been optimized for breast tumor imaging. In other words, there are a number of shortcomings with such general purpose gamma camera such as the limiting sensitivity. On average (50% [40]) for lesions <1 cm such as DCIS particularly, the medially located tumors. In addition, several studies [41–52] have pointed out that due to the large FoV of the camera and the bulky collimators, it is difficult to position the camera close to the breast, and thus, imaging breast tissue adjacent to the chest wall may not be possible. This may, ultimately, decrease the spatial resolution of the camera imaging system and thus affect the diagnostic value of the test in detecting such a small lesion size. To overcome some of the limitations offered by conventional gamma camera on breast imaging, Gupta et al. [41] reported the first preliminary clinical data that performed with breast-specific detectors and then compare it with the data obtained from standard full-size camera. A limited number of patients were investigated in this study but interestingly reported a higher sensitivity for the dedicated camera. Following this and due to the large research activities, new generation of detectors have been designed and developed for breast tumor imaging. For instance, the position-sensitive photo-multiplier tubes (PSPMT), semiconductor arrays, and scintillation crystals are coupled to an array of solid-state photodetectors. **Table 3** summarizes the features and the physical parameters of some of the currently under investigation and the commercially available dedicated breast camera. In general, these small FoV detectors have led to the improvement of the overall spatial resolution of such imaging system.

The commercially available dedicated breast camera has two detectors and is designed and optimized to image only the breasts. It possesses a high intrinsic spatial resolution and the camera is also equipped with ultra-high resolution parallel-hole collimator and thus, optimized

Cameras and study (reference)	Crystal sizes (mm ³)	FoV sizes (cm ²)	Intrinsic resolution (mm)	Spatial resolution (mm)	Energy resolution (%)
CsI(Tl) [47]	2 × 2 × 3	10 × 10	2	9	n/a
CsI(Si) [49]	3 × 3 × 6	21 × 21	3	6.5	n/a
NaI(Tl) [50]	3 × 3 × 6	15 × 20	3	6.3	10%
LumaGEM NaI(Tl) [42, 50]	2 × 2 × 6	12.8 × 12.8	2.2	3.4	10%
LumaGEM 32000S/12K ² (CZT) [51]	2.5 × 2.5 × 5	16 × 20	1.58	2.5	6%
LumaGEM (CsI) 5600 crystal [52]	3 × 3 × 6	10 × 10	1.7	n/a	n/a

All cameras are based on PSPMT(s) principle. The CZT detector array absorbs the γ -rays directly and converts their energy into electrical signal without the conversion to visible light as in the case with a scintillation detector. The spatial resolution is measured with general purpose collimator at 10 cm distance except the LumaGEM cameras that based on ultra-high resolution collimators.

Note: n/a, not available.

Table 3. Physical characteristics and specifications of dedicated gamma cameras proposed for scintimammography.

for high-resolution SM. The main advantage of such cameras is the ability to separate the breast from the chest wall by positioning the camera close to the breast. Thus, the camera can be used in areas with limited space (e.g., medial view can be possible), where the use of a full-sized camera is impractical or impossible. The use of moderate breast compression capabilities may improve both the signal-to-noise ratio (SNR) and the spatial resolution [42] and thus increase the sensitivity for detecting smaller lesions. The proposed clinical indications for such dedicated cameras are similar to the full size clinical gamma camera SM. There are some recent clinical studies associated with using these dedicated gamma cameras. For instance, a clinical preliminary study by Brem et al. [43, 44] using dedicated breast camera demonstrated a slight improvement in resolution and tumor sensitivity particularly for lesions ≤ 1 cm. Rhodes et al. reported [45] on SM, performed on 40 women with small mammographic abnormalities (<2 cm) scheduled to undergo biopsy. The SM examination identified (33/36) malignant lesions confirmed at biopsy. The authors concluded that this preliminary study suggested an important role for the dedicated SM camera in women with dense breasts.

In another study, Brem et al. [46] evaluated 94 women (median age 55 years) who presented with normal mammographic and physical examination results but all subjects were considered at high risk of developing breast cancer. Of these women, 35 had a history of previous breast carcinoma or atypical ductal hyperplasia. The authors concluded that with this camera, they could depict small (8–9 mm) nonpalpable lesions in women at a high risk of breast cancer. In summary, while these studies using breast-specific cameras are promising, all are considered preliminary in nature because they are based on very few cases. Additional studies with a larger sample size are needed to accurately assess and reach scientific conclusions concerning these proposed cameras. They also need to be cost competitive with the general

purpose gamma cameras in order to be widely used in breast tumor imaging applications. In addition, the smallest lesion sizes that can be detected with these cameras claimed to be 3–3.3 mm [47] compared to 4–5 mm [48] with conventional camera. However, the evidence published to date did not demonstrate a statistically significant difference in lesion detection. The spatial resolution of these proposed cameras may further improve by increasing the pixel size but there are practical limitations in the development of cameras with small pixel sizes, including cost and detector design. More importantly, due to the use of collimator, these dedicated cameras suffer from low detection efficiency.

4.3. Summary of the role of different imaging modalities

In many centers, the current evaluation and primary diagnosis of breast are based on combination of physical examination, mammography, and breast biopsy. Mammography represents a significant contribution and remains the gold standard for breast tumor imaging. This is because mammography is relatively simple, cost-effective, and relatively, highly sensitive. However, in many clinical cases, mammography may be nonspecific and lesions may not be detected. This is because the breast lesion can be indistinguishable from normal breast tissue or obscured by the dense parenchyma. Mammography is also not reliable following radiation therapy, surgery, and hormonal replacement therapy. Consequently, breast biopsies are used for many cases as a second-line diagnostic test to evaluate a suspicious lesion. Unfortunately, many breast biopsies are performed on normal patients, which results in high cost and patient's stress. Thus, other noninvasive imaging techniques are needed and can be used as complementary functional methods to minimize unnecessary breast biopsies.

MRI and US are adjunctive imaging techniques to mammography. Breast US is relatively inexpensive and is currently the commonest complementary method. This technique is also useful particularly when there is a cyst in the breast, but has lower accuracy in solid lesions. Breast MRI with contrast is a sensitive and relatively specific technique for some certain indications but are too expensive to be used routinely. Both MRI and US are useful tools in breast diagnosis, in particular for solving problems in selected applications. For the aforementioned reasons, the use of complementary imaging techniques, to aid in the diagnosis, is necessary. Thus, additional imaging methods are needed for investigation, detection, and diagnosis of breast cancer. Functional breast γ -ray imaging techniques have aided breast cancer diagnosis.

Among the currently used techniques are planar SM with ^{99m}Tc labeled sestamibi and PET with ^{18}F -FDG. Both radionuclide techniques have been emerged as potential investigation for the detection and diagnosis of breast cancer. Consequently, it is increasingly used particularly for imaging patients with dense breasts. Having discussed commercial imaging methodologies, various weaknesses in each approach has led to the need for new complimentary imaging methods. Of these approaches, SM is one of the most promising approach. The current research in this area is focusing on dedicated collimator-based cameras. These dedicated cameras also suffer from low detection efficiency. In addition, this is an unattractive option for many health providers, due to limited clinical applications of such an imaging system. This provides the motivation for investigating the application of collimator-less method in breast tumor imaging. A gamma camera, employing a low energy high resolution (LEHR)

parallel-hole collimator is used, to generate an image of the resulting radionuclide distribution. The LEHR collimator geometrically selects γ -photons from a predetermined direction and as a result, a very small fraction of the total emitted photons reaches the detector. Thus, this limits the detection efficiency and spatial resolution of the observed image—collimator are trade-off.

Factors like these have generated massive research aimed to improve the accuracy and efficiency of the current SM imaging systems and reduce the overall costs of breast surgical biopsies procedures but without the need for the new dedicated camera instrumentation development. This is one of the primary motivations to carry out research using a simple coded aperture (CA) mask, instead of a collimator, coupled to a standard clinical gamma camera for breast tumor imaging without the need for a new dedicated camera instrumentation development. This is particularly attractive at general hospital level, where the cost of running an additional dedicated imaging system may be prohibitive. In addition, the smallest lesion sizes that can be detected with dedicated cameras claimed to be 4–5 mm compared to 8–10 mm with conventional camera. The spatial resolution of these proposed cameras may further improve by increasing the pixel size, but there are practical limitations in the development of cameras with small pixel sizes, including cost and detector design. CA imaging as originally developed for astronomical applications is well suited for detecting faint pseudo-point like objects in a nonzero background. Thus, it appears to be well matched to the imaging objectives in SM. While related prior work has also considered, this approach is characterized by gross simplifications in terms of clinical reality [53, 54].

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