Breast Cancer Biomedical Imaging

Subjects: Others

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With the exponential increase in new cases coupled with an increased mortality rate, cancer has ranked as the second most prevalent cause of death in the world. Early detection is paramount for suitable diagnosis and effective treatment of different kinds of cancers, but this is limited to the accuracy and sensitivity of available diagnostic imaging methods. Breast cancer is the most widely diagnosed cancer among women across the globe with a high percentage of total cancer deaths requiring an intensive, accurate, and sensitive imaging approach. Indeed, it is treatable when detected at an early stage. Hence, the use of state of the art computational approaches has been proposed as a potential alternative approach for the design and development of novel diagnostic imaging methods for breast cancer. Thus, this entry provides a concise overview of past and present conventional diagnostics approaches in breast cancer detection.

Keywords: Breast cancer ; imaging ; Diagnosics

1. Introduction

Cancer is a non-communicable disease characterized by abnormal cell proliferation or cell division, with the ability to spread to other parts of the body [1]. Cancer continues to be a major public health problem and has been labeled as a global threat exacerbated by poor lifestyle choices and environmental factors [2][3]. Generally, cancer is classified according to the affected body part or tissue of origin. The most common cancer diseases include but are not limited to lung cancer, ovarian cancer, prostate cancer, head and neck cancer, breast cancer, etc. [4]. Indeed, breast cancer has been considered as one of the most common cancers diagnosed among women around the world. Breast cancer comprises 18% of the total cases of female cancer and approximately a million new cases are reported in the world every year[5]. Due to the ability of this type of cancer to metastasize to distant organs or lymph nodes, it has been considered to be the leading cause of mortality in females[5][6].

2. Types of Biomedical Imaging

2.1. Mammography

Mammography is an excellent method used in primary breast imaging. It is used for early detection of abnormalities in the breast, especially those suspicious for breast cancer before it becomes apparent clinically, by using low-dose X-ray imaging to generate the images of the breast [7][8]. According to the United States of America preventive services task force (USPSTF), this type of breast imaging has been helpful in the earlier and better treatment for women over 40 years of age and has decreased breast cancer mortality by at least 30% [9]. Although this imaging approach remains the key for early breast cancer detection and screening, the overall accuracy of the test remains low and second-line accurate imaging techniques are required in some instances to lessen the number of unnecessary excisional biopsies [10][11].

Screening mammography is credited with the examination of an asymptomatic woman and decreases the risk of breast cancer-related death [12][13]. Conventional mammography has limitations in specificity and sensitivity, especially in dense breasts. The sensitivity of this type of imaging in breast cancer diagnostics is about 50 to 85%, depending on the density of the breast. Meanwhile, the sensitivity is below 50% in the dense breast due to tissue superposition; this is a major reason for the false-positive result, which leads to additional imagining and cost and false-negative results due to masking of true lesions [14][15][16].

In the breast, the normal internal mammary lymph node chain is usually below 5 mm in diameter. Metastases to this chain cannot be easily detected by mammography or ultrasonography clinical examination because they are normally covered by cartilaginous and bony structures of the chest wall [17][18]. The use of mammography in the detection of recurrent breast cancer is a challenging task due to changes in the architecture of the breast, mainly in fibrosis and scarring secondary to radiotherapy and surgery, resulting in difficulties to interpret mammograms. Breast compression is another major

challenge faced by this modality due to accompanied pain which could lead to delayed diagnosis. Hence, considering all of the aforementioned mammography limitations, there is a call for alternative and more accurate methods that can resolve the imaging of dense breasts [15][16].

2.2. Tomosynthesis

Due to the limitations of mammography, breast tomosynthesis was introduced to the clinic because of its ability to produce three-dimensional information at a lower dose and its relative cost-effectiveness. Consequently, there has been an upsurge in interest in tomosynthesis. The Food and Drug Administration (FDA) has approved some products that are now in use and on the market [19]. This technique involves using X-ray projection images acquired over an arc to generate image slices for a partially 3D image [20]. Tomosynthesis allows for the generation of an arbitrary number of in-focus planes retrospectively from a series of radiograph projections obtained in a single motion of the X-ray tube [21]. Notably, a combination of tomosynthesis and digital mammography increases the brightness of invasive cancers while at the same time decreasing the likelihood of false-positive data [20]. Tomosynthesis has been applied to several clinical tasks, including dental imaging, angiography, breast imaging, bone imaging, and chest imaging [19]. In breast cancer, tomosynthesis increases the sensitivity of mammography, which could enhance the early detection of breast cancer due to the improved lesion margin conspicuity [21]. This is very beneficial to breast cancer patients, especially those with radiographically dense breasts. However, Poplack et al. [22] showed that breast tomosynthesis has a comparable or superior image when compared with diagnostic film-screen mammography in 89% of recruited subjects. More recently, this was supported by another study where one-view stand-alone digital breast tomosynthesis (DBT) detected more breast cancer than digital mammogram (DM) [23]. This suggests that the use of one-view DBT alone could be feasible in breast cancer screening. Although the acquisition procedures of tomosynthesis mimic standard mammography, the X-ray tube of tomosynthesis takes several low-dose exposures as it travels within a limited arc of motion unlike conventional mammography [22]. Sechopoulos [24] has written an excellent review of all aspects of tomosynthesis, including doses and reconstruction processes. When the overall dose used for visualization is constant, the quality of the image improves with a wider angular range [25]. However, the quality of image degenerates once the maximum is attained at a particular number of projections.

2.3. Ultrasound Imaging

Ultrasound (US) imaging diagnostics, otherwise known as sonography or ultrasound scanning, is a painless and safe approach. US makes use of 1 to 10 MHz sound waves to produce pictures that reveal the movement and structure of the breast, and other soft tissue [26][27]. It can also reveal the movements of blood and other materials within the blood vessels and body [27]. It is a cross-sectional technique that uses a small probe, known as a transducer, and gel that is directly placed on the breast/skin; it displays the tissues without overlap [27][28][29]. The high-frequency soundwaves travel from the probe via the gel into the body, and the probe receives the sounds that bounce back, which in turn produces an image on a computer. This type of imaging technique does not make use of radiation because it captures images in real-time [27][28][29].

In recent times, the development of high-resolution US technique has greatly improved the diagnosis of breast cancer because, in the past, US was thought to only be suitable for the diagnosis of cysts [30][31]. It has been shown to enhance the differential diagnosis of both benign and malignant lesions during guided interventional and local preoperative staging diagnosis. Due to the higher sensitivity of this type of imaging technique, it has been adopted as a complementary technique to mammography with limited sensitivity to identify early, node-negative cancer in dense breasts [32][33].

However, the use of US imaging techniques is diminishing due to the time and skill required to detect small tumors with hand-held imaging, and non-palpable cancers. The implementation of this imaging technique in breast cancer diagnostics has been hampered by limited numbers of qualified personnel and lack of uniformity in the results; this has caused low specificity that can lead to the generation of high numbers of false-positive results [34]. This assertion is corroborated by findings of some previous studies which revealed that US can identify and detect the presence of carcinoma in dense breasts. Some other studies have shown low detection of cancerous cells in dense breasts, but have proposed the addition of this imaging method to negate mammography which seems to have limited cost-efficiency and is controversial for women with dense breasts without any other major risk factors. In addition, due to the high scattering ability of the soundwaves at bone and air interfaces, various parts of the body are invisible, which limits the effectiveness of depth imaging in most organs to about 10 cm [35][36].

2.4. Dedicated Breast Computed Tomography

Dedicated breast computed tomography (DBCT) is a recently used and fastest-growing imaging technique that allows for true isotropic and provides three-dimensional (3D) information which can be reconstructed or rebuilt into several imaging planes. Although DBCT is comparable to breast magnetic resonance imaging (MRI), the process involved can be carried out without breast compression, and is not limited by breast implants or the density of the breast [37][38][39]. The radiation dose in this type of imaging technique is similar to that of a conventional two-view mammogram [38]. Boone et al. [40] investigated the feasibility of low dose radiation on the image quality of DBCT. The findings from their average glandular dose for 80-kVp breast CT study, when compared to two-view mammography, revealed that the breast CT dose for thicker breasts is approximately one-third lower than that of two-view mammography. For a typical breast of 5 cm 50% glandular, it was discovered that the maximum dose of mammography in 1 mm^3 voxel is far greater (20.0 mGy) than that of breast CT with 5.4 mGy. It was further stated that the CT images for 8 cm cadaveric breasts have an average glandular dose of 6.32 mGy, which is superior to the estimated dose of 5.06 mGy for the craniocaudal view, with an average glandular dose of 10.1 mGy for standard two-view mammography of the same specimen [40]. The invention, improvement, and development of DBCT with dedicated scanners with novel technology has been documented in the literature by Sarno et al. [41]. Studies further reported the development of low radiation dose scanners with improved spatial resolution and rapid image acquisition times, which is aimed at addressing the issue of imaging dense breasts and painful breast compression [37][38][39].

Kuzmiak et al. [38] investigated the confidence of radiology experts in the characterization of suspicious breast lesions with a DBCT system compared with the conventional diagnostics of two-dimensional (2D) digital mammography in terms of overall lesion visibility and dose. It was discovered that DBCT is superior in the characterization of the masses and radiologists' visualizations, although it is inferior to calcifications when diagnostic mammography is used. It was further averred that the DBCT application could help eliminate the 2D mammography drawback of overlapping tissue. Their study concluded that the technical challenges in breast imaging remain, but 3D DBCT could have a promising clinical application in breast cancer diagnosis or screening, however, this needs further investigation.

In 2008, Lindfors et al. [37] carried out a comparative study between the DBCT and screen-films mammograms where it was discovered, in the study of the selected group of women, that the visualization of breast lesions with both the DBCT and screen-film mammography is approximately the same. Although, DBCT was reported to be superior in the visualization of the masses, while in the imaging of microcalcification lesions screen-film mammography shows to be better. It was further deduced in their study that women are more comfortable with DBCT screening when compared to screen-film mammography. Hence, it was assumed that DBCT is a potential technology and may be a promising clinical application in diagnostic and screening for breast cancer investigation. Additionally, it was further presumed that DBCT is more accessible and could be a replacement for breast MRI or act as a control technique for tumor ablation procedures or robotic breast biopsy, all of this calls for further studies.

Recently, Shah et al. [39] investigated the characterization of computed tomography (CT). Hounsfield units were used in clinical settings for the purpose of tissue differentiation in a reconstructed CT image in 3D acquisition trajectories on a DBCT system. It was depicted in their statistical study that the approach has a better performance in the saddle orbit, mostly when close to the chest and the nipple areas of dense breast. It was further discovered that the saddle orbit functions significantly well and provides a tighter distribution of Hounsfield unit values in the reconstructed volumes. In addition, the study demonstrated the significance of the application of 3D acquisition for breast CT trajectories and other uses through the establishment of the robustness in Hounsfield unit values in the large reconstructed volumes.

2.5. Magnetic Resonance Imaging

Since the beginning of the third millennium, magnetic resonance imaging (MRI) has developed into a paramount tool in breast cancer screening, diagnosing, staging, and follow-up [41]. This imaging tool has played a vital role in the screening of high-risk breast cancer patients. Breast MRI uses an intravenous contrast agent such as gadolinium, which allows for the visualization of lesions. The sensitivity of this tool in breast cancer has been documented to be over 90% while the specificity is still about 72%; hence, the distinction between benign and malignant lesions is still challenging [41]. Although mammography is the basic imaging tool for breast tumor identification, it has been indicated that MRI has a higher sensitivity for detection of breast cancer, and the breast density does not affect it [42]. In most cases, the sensitivity of mammography in the detection of multiple malignant foci is below 50%. It is important to note that breast MRI is not meant to replace mammography particularly in ductal carcinoma in situ, which is not detectable by MRI but rather by mammography [43]. The MRI screening in women with genetic susceptibility to breast cancer has proved to be beneficial [44][45]. In a prospective cohort study, the sensitivity of MRI in women with a high risk of breast cancer but who were asymptomatic was between 93–100%, the 10-year survival was 95.3% [45]. Similarly, the sensitivity of MRI in contralateral

breast tumor detection was documented to be 91%, and specificity was 88% [46]. In women with a known BRCA1/2 mutation, MRI surveillance detected breast cancer at early stages; encouragingly, there was no distant recurrence after 8.4 years follow-up since diagnosis [46]. This tool can be used in identifying the size and degree of the tumor towards achieving better surgery procedures. Nevertheless, the use of MRI before surgery continues to be controversial with extensive variations in the outcome; however, it helps in planning conservation in patients that respond to chemotherapy where feasible [41]. Despite the high sensitivity of this imaging tool in breast cancer, the cost involved in MRI makes it difficult to be employed in the general population. Conclusively, the invention and development of new imaging techniques such as diffusion-weighted imaging offer an added advantage in breast cancer management.

2.6. Diffusion-Weighted Imaging

Since the early years of the 21st century, diffusion-weighted imaging (DWI) has been at the forefront of cancer imaging attaining widespread recognition due to its ability in the diagnosis of stroke [47][48]. DWI is a noninvasive MRI technique that relies on the principle of random molecular motion of free water in tissues (Brownian movement). With the development of stronger diffusion gradients and application in whole-body imaging, DWI has attracted attention in oncology [49]. In breast cancer, Sinha et al. [50] demonstrated that DWI is reliable in a clinical setting with an echo-planar sequence and possesses potential in breast lesion characterization as either benign or malignant using apparent diffusion coefficient (ADC) values. Generally, breast lesions classified as malignant have a high-cellular level with limited water diffusion and lower ADC values when compared to benign lesions [51]. An earlier clinical study that recruited women with breast lesions stated that ADC values and the tumor biological aggressiveness correlate; hence, ADC is a promising factor in the evaluation and analysis of the degree of the malignancy [52]. In most clinical settings, DWI is interpreted in combination with dynamic contrast-enhanced (DCE)-MRI to increase the specificity. However, more recently, lesions in the breast (31 = malignant; 13 = benign) were analyzed using quantitative diffusion-weighted sequence on 3T MRI with b-values of 500 and 1000 s/mm^2 [53]. The ADC cut-off value for benign and malignant lesions was set to 1.21 × 10^{-3} mm^2/s for b = 500 s/mm^2 and 1.22 × 10^{-3} mm^2/s for b = 1000 s/mm^2, respectively. The sensitivity of DCE-MRI was 100% with a specificity of 66.7%, when DCE-MRI was combined with b = 1000 s/mm^2, 100% specificity was attained and sensitivity of 90.6%; there was no significant difference between the ADC and prognostic factors [53]. Non-contrast (NC)-MRI can be an alternative for DCE-MRI for breast cancer diagnosis, though its inferior lesion conspicuity and lower inter-reader agreement should be considered [54]. This study and many more have documented explanatory results for DWI as a tool for diagnosing breast lesion and aids the orthodox breast MRI procedures. Several pitfalls, which include but are not limited to motion artifacts, ADC value accuracy, image quality, and signal-to-noise ratio, are associated with DWI [55][56]. These challenges are bothersome and lay emphasis on the need to incorporate computer science into breast cancer diagnosis, for example, robotics could significantly decrease time in DWI MRI and create improved breast cancer detection.

2.7. Computed Tomography

CT scan is a method that exposes the pictures of cross-sections or 2D slices of the body's organs via a connected computer [55][56]. The use of a contrast solution (iodine), injected into the body via the arm, dramatically improves and aids in the visualization of the cancerous cells in organs. In 2003, the use of CT for breast cancer imaging was proposed by Suga et al. [57], after a surgical issue in patients, to obtain interstitial lymphography that can map and present sentinel lymph nodes of the breast. The use of CT in breast cancer has some advantages, which includes patient comfort and fast scanning time. However, CT has not been widely used in breast cancers due to the risks involved in radiation exposure and poor quality of the image produced.

Due to the dynamic technique of CT, it can be used in the detection and characterization of breast tumors, investigation of neoadjuvant chemotherapy effects, and local staging of cancerous cells in the breast. In 2015, Foo et al. [58]employed this imaging scan method to evaluate the staging of cancer cells in newly diagnosed breast cancer patients that are in a locally advanced stage. It was revealed that a limited number of patients involved in this study had some pelvic significance with relation to a patient who had peritoneal cancer with widespread metastasis, and a patient with a presumed gene carrier of a concurrent primary ovarian malignancy. It was further stated that 50% of all pelvic results required additional radiological examinations.

Although the CT scan technique in breast cancer examinations may not replace the conventional mammography routine, based on improvements carried out in some studies [59][60], it can be used to overcome several limitations associated with mammography such as detection of cancers in premenopausal, dysplastic, and dense breasts. The mean glandular dose of 8.2 ± 1.2 mGy has also been documented for different types of breast shapes and sizes [61]. As documented by Park et al. [60], in prone positions, low-dose perfusion CT is possible for imaging with regards to the quantification of tumor vascularity and radiation doses. CT can be used in the detection of unsuspected very small cancers in the breast that

cannot be identified or seen by physical examinations or conventional mammography. It is useful in definitive diagnostic evaluation in a situation where physical examinations and mammography are inconclusive, and it can also be helpful in recognition of precancerous and high-risk lesions. More so, CT can be used in the discrimination of tumor tissue from normal tissue in breast cancer patients without the use of a contrast medium.

2.8. Near-Infrared (NIR) Fluorescence

During human surgery, X-ray fluoroscopy and ultrasound have been used widely. However, during X-ray fluoroscopy, patients and caregivers are exposed to ionizing radiation; in an ultrasound, only a thin surgical field-of-view is seen and requires direct contact with tissue, in this case, breast. Interestingly, none of the methods can be amended by target contrast agents to guide imaging during oncologic surgery due to the number of procedures required[62][63]. Thus, near-infrared (NIR) light, with a wavelength range of about 700 to 900 nm, has offered diverse significant advantages over some widely used tools including relatively high penetration of photon in and out of living tissue (breast) due to the reduction in the rate of absorbance and scatter. Owing to lower tissue autofluorescence, NIR has a higher signal-to-background ratio [63][64]. This technique has a great potential to interrogate deep tissues (breast) for molecular-based imaging. The NIR light is visible to the human eyes when conjugated with NIR excitable fluorophore or dyes. These are chemical compounds which convert light generated from one NIR wavelength into the NIR light of diverse wavelength. It has been recommended that the mapping of sentinel lymph nodes (SLN) is a standard approach for the management of breast cancer and care staging of the axilla [63].

NIR fluorescence imaging, which uses indocyanine green (ICG), has been shown to improve the procedure of the SLN mapping by facilitating percutaneous incisions and identifying the intraoperative ability of lymphatic channels and SLNs [63][64]. The safety and accuracy of NIR fluorescence imaging applications for identifying SLNs in patients suffering from breast cancer were demonstrated by Verbeek et al. [65]. The use of the Mini-FLARE camera system and 1.6 mL of 0.5 mM ICG showed the excellent identification of the SLN in patients with breast cancer. Although, the technique which should be used as the gold standard in future analyses, was raised as a question [65]. In a similar study by Mieog et al. [65], the clinical translation of a novel NIR fluorescence imaging system and the optimal ratio of ICG to the human serum albumin (HSA) dose for mapping of SLN in breast cancer was described. It was stated that 400 and 800 μM is the optimal dose of the injection ratio of ICG:HSA and this can be chosen based on the preferences of local preparation. For instance, a dose of 500 μM was depicted to be the most convenient in the United States due to the minimal requirement in the manipulation of albumin volumes. Other studies that have employed this approach in mapping SLNs in breast cancer patients include Sevick-Muraca et al.[66] which demonstrated the prospective feasibility in the use of the minimal dose of ICG in noninvasive optical imaging of lymph nodes in the breast cancer patients undergoing SLNs mapping. In 2008, Altınoğlu et al. [67]. demonstrated the synthesis and bioresorbable use of calcium phosphate nanoparticles (CPNPs) which incorporated the molecule of the NIR emitted fluorophore and ICG. In their study, the in vivo and ex vivo studies demonstrated the potentiality of the NIR CPNPs in diagnostic imaging of early breast solid tumors. Although, the result from their ex situ imaging of deep tissue showed that the depths of NIR CPNPs in porcine muscle tissue is 3 cm. Poellinger et al. [68] employed the use of NIR fluorescence imaging with the late and early enhancement of ICG, which corresponds to extravascular and vascular phases of contrast agent enhancement to distinguish between malignant and benign breast lesions as well as to detect breast cancer. Ke et al. [69] assessed the specificity of continuous-wave NIR fluorescence imaging by an intensified charge-coupled device (CDD) camera on a novel epidermal growth factor (EGF)-Cy5.5 to detect EGF receptors in breast cancer xenografts.

2.9. Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) is a medical imaging tool based on tomographic reconstruction protocols and routinely used in a clinical decision in cancer [70], coronary artery disease, left ventricular dysfunction [71], and Parkinson disease [72]. In fact, it is the most used tool in myocardial ischemia assessment. SPECT aims at getting a perfect 3D radioactivity distribution resulting from the uptake of a radiotracer in humans. One or more photons are released in random directions when a SPECT radioisotope decays [73]. However, collimators are used to focus the angle of the emitted photons that reach the detector because conventional lenses cannot restrict high-energy photons, and only 0.02% of the decay events is measured [73]. SPECT, coupled with CT, can be used when conventional images are complex to interpret, for example, suspicion of contamination [74]. Clinically, SPECT/CT provides more value in anatomical localization of sentinel nodes. This highlights a relevant role for this tool in the surgical approach and may improve staging [75]. The sentinel lymph node biopsy is a well-known procedure used in evaluating the status of the axillary lymph node in patients with early stages of breast cancer [76]. Markedly, SPECT/CT improved visualization from 84% to 92% in patients, but it only showed sentinel nodes in 11 out of 22 breast cancer patients (50%) with non-visualization on planar imaging [75]. Similarly, Lerman et al. [77] documented that the addition of SPECT/CT to lymphoscintigraphy enhances sentinel node

identification in breast cancer patients who are overweight. Notably, SPECT/CT identified hot nodes in 91% of patients and sentinel nodes in 29 of 49 patients (59%) who were negative on planar imaging (planar lymphoscintigraphy) [77]. Hence, this technique is of high relevance in overweight breast cancer patients because intraoperative techniques have failed in the identification of draining nodes. Another SPECT/CT evaluation study demonstrated a sentinel node in 91.1% of breast cancer patients, and localization was more precise on SPECT/CT fusion images than on the planar views [78]. Mann et al. [79] documented that the use of dedicated SPECT identifies regions of interest at a global lower-level threshold within dense breast tissue without any negative effects, which in turn betters patient care. Additionally, dedicated breast positron emission tomography (PET)/CT can accurately visualize uncompressed breast suspected lesions in 3D [79]. However, this scanner was unable to generate a full quantitative image. Recently, Tornai et al. [80] developed a fully 3D CT in a hybrid SPECT/CT breast imaging system that facilitated complex trajectories, which improved the quality of the image when compared with simple circular breast CT acquisitions. The SPECT-subsystem allows viewing of the chest wall for pendant breast imaging [80]. Recently, it was shown that the hybrid SPECT/CT provides precise anatomical data that enables clear assessment of patients contaminated with radionuclide during the procedure [74]. Such precise data can assist surgeons towards a better surgical plan. Non-visualization of sentinel nodes, unexpected lymphatic drainage, and complicated planar imaging interpretation are challenges faced by these imaging techniques. However, this can be amended by incorporating AI, such as deep learning and machine learning algorithms, with currently available breast cancer imaging tools. Overall, such combinations will improve breast cancer diagnosis, predict treatment outcome and ultimately, improve the patient quality of life. The dose in the dedicated SPECT-CT system using both the geometric and anthropomorphic phantoms showed that the average doses absorbed in 100% fibroglandular-equivalent was 4.5 ± 0.4 mGy, while 100% adipose-equivalent tissues was 3.8 ± 0.2 mGy. More so, the dose measured in a cadaver breast using a radiochromic film in the same study yielded an average dose of 4.3 ± 0.3 mGY and 4.2 ± 0.3 mGy along two orthogonal planes [81].

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