Performance of imaging exams in screening and diagnosis of breast cancer

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Abstract

Breast cancer imposes a significant burden on our society. According to the 2020 data from the International Agency for Research on Cancer (IARC), approximately 2.3 million women in 185 countries were diagnosed with breast cancer, and 685,000 women lost their lives to the disease. Medical imaging is essential for the timely detection and the precise staging of breast cancer, playing a crucial role in cancer management. Although there have been notable advancements in medical imaging, there is no single imaging technique that can comprehensively identify and characterize all breast abnormalities. Hence, a combined modality approach may still be required in certain cases. This review offers a comprehensive analysis of the imaging techniques used in breast cancer diagnosis, assessing their efficacy, strengths, weaknesses and clinical utility. In order to collect relevant articles on breast cancer detection methods, an extensive search was carried out across databases, including PubMed, Elsevier and Google Scholar.
Keywords: *neoplasm, breast, ultrasound, imaging technology, mammography, magnetic resonance imaging*

Rezumat

Cancerul de sân reprezintă o povară semnificativă asupra societății. Conform datelor din 2020 furnizate de Agenția Internațională pentru Cercetarea Cancerului (IARC), aproximativ 2,3 milioane de femei din 185 de țări au fost diagnosticate cu cancer de sân, iar 685000 de femei și-au pierdut viața din cauza acestei boli. Identificarea precoce și stabilirea corectă a stadiului sunt fundamentale pentru gestionarea cancerului de sân, iar imagistica medicală joacă un rol esențial în acest proces. Deși au existat progrese remarcabile în domeniul imagisticii medicale, este încă valabil faptul că nicio tehnică de imagistică nu poate identifica și caracteriza în mod exhaustiv toate anomalii sânului. Prin urmare, în anumite cazuri este necesară o abordare combinată a modalităților. Acest articol oferă o analiză cuprinzătoare a tehnicilor imagistice utilizate în diagnosticul cancerului de sân, evaluând eficacitatea lor, punctele forte, punctele slabe și utilitatea clinică. Pentru a căuta articole relevante despre metodele imagistice de detectare a cancerului de sân, s-au utilizat baze de date precum PubMed, Elsevier și Google Scholar.
Cuvinte-cheie: *neoplasm, sân, ultrasonografie, tehnologie imagistică, mamografie, imagistică prin rezonanță magnetică*

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Introduction

Breast cancer holds great importance as a public health issue, threatening the physical and mental well-being of women worldwide. According to the recent GLOBOCAN 2020 data released by the International Agency for Research on Cancer (IARC), in 2020 an estimated 2.3 million females across 185 countries were diagnosed with breast cancer, representing 24.5% of all cancer cases worldwide, ranking first for incidence and mortality in the majority of the world countries(29). An estimated 685,000 women died from breast cancer in 2020, representing approximately 16% of all cancer deaths in the world or one in every six cancer deaths in the world(29). The future burden of breast cancer is expected to escalate significantly, with estimates indicating over 3 million new cases and 1 million deaths by the year 2040(3).

In the realm of breast cancer care, medical imaging plays a vital role. It aids in the detection and staging of the disease, it facilitates therapy monitoring, and it enables post-therapeutic follow-up examinations. Imaging is a tool that allows early-stage cancer detection which is the main factor in reducing breast cancer death rates(36). In the light of escalating of breast cancer incidence across all age groups worldwide(30), there is a need to adopt imaging modalities that enable the detection of the disease at younger ages.

The imaging techniques provide the clear visualization of the morphology and location of tumor tissues, offering valuable clinical information to healthcare professionals. The primary imaging techniques used in breast cancer diagnosis and evaluation are mammography (MG), ultrasound (US) and magnetic resonance imaging (MRI). While significant advancements have been made in medical imaging, it remains true that no single imaging modality can effectively identify and characterize all breast abnormalities. Therefore, at times, a combined modality approach will continue to be necessary to ensure the comprehensive and accurate assessment of breast conditions. In addition, there are various other medical imaging techniques, such as tomosynthesis, elastography, photoacoustics and optical imaging, that have received relatively less attention due to their inherent challenges and complexities.

In this review, we provide an overview of the primary imaging techniques applied in breast cancer diagnosis. We evaluate their performance, we highlight their advantages and disadvantages, and we discuss their relevance in clinical practice. To gather pertinent articles on breast cancer detection methods, an extensive search was conducted using databases such as PubMed, Elsevier and Google Scholar. The search utilized the keyword "breast cancer", along with specific terms such as "nuclear imaging", "mammography", "ultrasound", "MRI", "optical imaging", and "tomosynthesis". This inclusive approach aimed to capture a wide range of literature on various imaging modalities employed for breast cancer detection. To ensure the most current and pertinent information, only articles published within the last 20 years were selected

Mammography

A mammography is a medical procedure that involves compressing the breast tissue between two plates and using low-energy X-rays to create two-dimensional images of the breast tissue in the standard craniocaudal and mediolateral oblique views(5).

Randomized controlled trials have provided evidence that screening mammography can lead to a significant reduction of approximately 30% in breast cancer mortality(16). The findings detected during a mammogram can include the identification of masses, asymmetrical calcifications, and areas of the breast that exhibit deformities or irregularities. Also, mammography has its limitations, particularly in cases with dense breast tissue. However, mammography has a sensitivity of approximately 70%(16). To ensure a standardized terminology for describing mammographic findings, the American College of Radiology developed the Breast Imaging Reporting and Data System (BI-RADS)(16).

The traditional screen-film mammography has been for a long time regarded as the gold standard for breast cancer screening(26).

Now, the new preferred imaging modality is digital mammography which has overall diagnostic accuracy similar to film mammography, but it is more accurate in women under the age of 50 years old, in those with radiographically dense breasts, and in premenopausal or perimenopausal women(39). An important randomized study assigned 25,263 women (from 45 to 69 years old) to digital or film screen mammography. The results revealed that digital mammography allowed a higher detection rate than film mammography, but the difference did not have a statistical significance, and the detection rate was nearly equal in the age group of 45-49 years old(41). Other benefits of using digital mammography over film mammography are represented by the reduced dose radiation, a high image quality, telemedicine and digital archiving(15). A 2021 meta-analysis of 29 articles, with a total of 16,583,743 screening examinations comparing digital mammography to film mammography regarding cancer detection rates, cancer interval rates and cancer recall rates, concluded that, although the replacement of film mammography with digital mammography led to an increase in cancer detection and to increased recall rates, this did not translate into a reduction in the interval cancer rate(13). This suggests that the shift, adopted in many countries, to digital mammography in the screening for breast cancer did not result in improved health outcomes for women(13). When digital mammography is accessible, it has the potential to detect a slightly higher number of breast cancers in individuals under the age of 50. Nevertheless, film mammography continues to be a suitable screening method for all patients.

While the primary benefit of mammography screening is the reduction of breast cancer-related deaths, overdiagnosis is considered the main harm associated with this screening method(31).

Research indicates that women between the ages of 50 and 69 years old who undergo biennial screening for breast cancer in Europe have an estimated risk of experiencing a false positive mammogram of approximately 20%, with a risk of biopsy of 3%(19). In the United States of America, the risk of false positive results from mammograms is notably higher, with a 10-year false positive rate of 30%. Additionally, it is estimated that approximately 50% of all women will encounter a false positive mammogram at some point in their lives(22). In addition to the financial implications, false positive test results pose challenges such as negative impacts on psychological well-being(28) and alterations in health behavior, along with a decrease in trust towards the healthcare system as a result for women who receive them(10). Women who receive false positive findings during screening may experience psychological distress for a minimum duration of three years(10). A Danish cohort study with 12 to 14 years of follow-up focused on the long-term psychological effects resulting from false positive screening mammography came to the conclusion that women are still affected by their false positive result after 12 to 14 years(18).

There are valid and numerous concerns regarding the potential radiation risk associated with mammography, particularly considering that the breast is a highly radiosensitive organ. The radiation dose and the corresponding risk associated with a single mammography examination vary based on factors such as age, breast density, and breast thickness(12). A 2022 review of the medical literature regarding radiation associated to screening mammography concluded that over a screening lifetime from 40 to 74 years old, the mean glandular dose used (2.5-3 mGy) potentially leads to 65 induced cancers and to eight deaths per 100,000 women, but this risk, compared to the potential mortality reduction achievable with screening mammography, is small(20). Overdiagnosis is a problem less discussed, and it represents the detection of a disease that would not have caused morbidity or mortality if it had not been found. In theory, overdiagnosis can happen when a tumor lacks the potential to progress to a clinical stage or even regresses, or when a woman passes away from other causes before breast cancer becomes clinically apparent[31]. Overdiagnosis can result in certain patients undergoing treatment for a cancer that would not have caused harm if left undetected. This can lead to adverse effects, both medically and psychologically, without any reduction in mortality rates.

The current guidelines for breast cancer screening in the United States and Europe exhibit some degree of variability. The Society of Breast Imaging, the American College of Radiology, and the National Comprehensive Cancer Network advise that women at an average risk for breast cancer should undergo annual screening mammography starting at the age of 40 years old[16]. As a result of differing assessments of the advantages and disadvantages of screening, the American College of Obstetricians and Gynecologists (ACOG) recommends that women with an average risk of breast cancer should undergo screening mammography every one or two years and that the decision should be made through an informed and shared decision-making process with the patient, that involves a thorough discussion of the advantages and disadvantages of both annual and biennial screening[11,32].

The European Society for Medical Oncology (ESMO) – the Europe's leading medical oncology society – recommends mammography screening every two years, as studies have shown that this interval provides the greatest reduction in the mortality benefit for individuals aged 50-69 years old[40]. Also, ESMO acknowledges that the available evidence supporting the effectiveness of mammography screening in women aged 40-49 years old is limited. The recent breast cancer screening report from the International Agency for Research on Cancer also reached the same conclusion[27].

Contrast-enhanced mammography (CEM) is an innovative technique that uses iodinated contrast materials to visualize the blood vessels in the breast, similar to how MRI works. It is an emerging method that helps in detecting breast neovascularity more effectively[24]. Angiogenic vessels frequently exhibit contrast material leakage, causing the diffusion of contrast within tumor tissue, resulting in an iodine-enhanced image which enables the visualization of a malignant tumor even in the presence of dense breast tissue[24]. CEM has the advantage of demonstrating both anatomic changes and local changes in breast perfusion, presumably caused by tumor angiogenesis, whereas digital mammography and digital breast tomosynthesis (DBT) rely on anatomic changes in the breast caused by breast cancer. CEM has a higher sensitivity, of 93-100%, compared to mammography, which has a sensitivity of 71.5-93%. Additionally, CEM increases the specificity from 42% to 87.7%[16].

CEM has the potential to serve as a comprehensive screening tool, particularly for women with dense breast tissue[7]. CEM is also indicated in evaluating the extent of disease with newly diagnosed cancer, as well as monitoring the response to neoadjuvant chemotherapy[7].

The disadvantage of this contrast examination is that, approximately, the iodinated contrast is injected intravenously, and the sensitivity reactions can occur at the same rate as with computed tomography (CT) examinations[16].

Digital breast tomosynthesis (DBT), also known as three-dimensional (3D) mammography, has gained significant popularity in the field of breast imaging, being widely utilized in both screening and diagnostic scenarios[14]. DBT involves capturing a sequence of low-dose mammograms from different angles. These two-dimensional images are then processed using computer algorithms to reconstruct 3D images of the breasts[37]. DBT slightly increases the radiation dose by an average of 20%, but it also enhances cancer detection by approximately 15-30%[17]. Additionally, it reduces recall rates by 15-20% by minimizing overlapping shadows that can resemble breast cancer[17].

One study found that the use of DBT resulted in higher rates of false positive screening results[8]. When digital breast tomosynthesis is combined with digital mammography, it has been observed to detect 90% more cases of cancer in a population that had previously undergone screening with digital mammography alone[38]. Remarkably, this increased cancer detection is achieved while maintaining similar recall rates and exposing the patients to twice the usual radiation dose[38]. Current data do not indicate a significant decrease in interval cancers among women screened with digital breast tomosynthesis as compared to digital mammography[21].

Digital breast tomosynthesis has proven to be highly beneficial for women with mixed to dense breast tissue. However, it does not offer significant advantages for women with extremely dense breast tissue[16]. DBT has the potential to address the main limitation of traditional two-dimensional mammography, which is the masking effect caused by overlapping fibroglandular breast tissue. By doing so, it enhances the diagnostic accuracy by distinguishing between benign and malignant features and improving the visibility of lesions, especially in dense breasts[16].

Digital breast tomosynthesis has received approval for both screening and diagnosis in multiple countries. However, there are certain challenges associated with using DBT as a screening tool, such as the need for additional reading time, IT storage and connectivity requirements, concerns about overdiagnosis, and considerations regarding cost-effectiveness[17].

Although DBT improves the detection of all types of invasive cancers, it is currently unclear which are the long-term implications for breast cancer mortality[14]. Additional data are crucial in order to comprehend the complete impact of digital breast tomosynthesis and to establish its position within the ever-evolving field of breast cancer care.

Ultrasound

With its enhanced resolution and quick image processing, ultrasound (US) is predominantly utilized as a supplementary tool rather than a primary diagnostic method, serving as a follow-up examination to clarify equivocal findings[15].

It is commonly employed in cases where patients present with clinical symptoms, aiding in the further analysis of

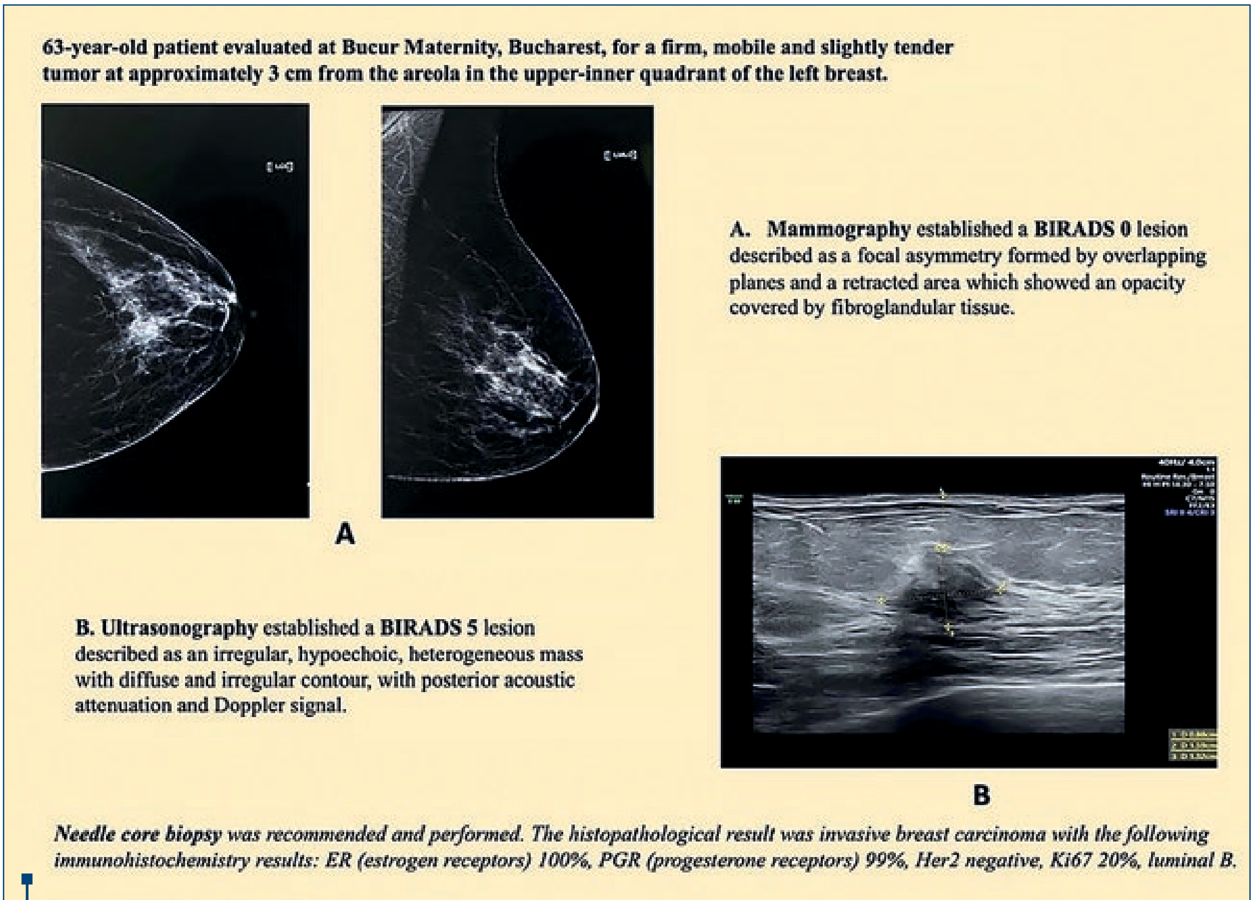

Figure 1. *Ultrasound and mammography working together in diagnosing breast lesions (a case from the "Bucur" Maternity)*

mammography results. Sensitivity increases to 97.3% and specificity increases to 76.1% by adding ultrasound imaging to conventional breast cancer screening methods(9).

Ultrasound has higher sensitivity than mammography until the age of 45 years old, and is the preferred initial test for women under 30 or for those who are pregnant or lactating(7).

It also helps to determine whether a soft tissue mass is solid or cystic and to differentiate benign from malignant masses(16). Ultrasound is often recommended as an additional screening method, especially for women with dense breasts, as it can be more effective in detecting abnormalities that may not be easily seen on mammography or digital breast tomosynthesis(34) (Figure 1).

Ultrasound has the advantage of not using ionizing radiation, which makes it a safer imaging option compared to other methods. US has advantages such as its portability, lower cost than mammography, and versatility. It is the perfect imaging tool for biopsy(1). Ultrasound-guided core needle biopsy has substantially improved the accuracy of sampling palpable masses, with a miss rate of less than 2% compared to 13% without ultrasound guidance, ensuring a more precise and reliable sampling of tissues for diagnostic purposes(7).

For non-palpable masses, using a 14-gauge core needle biopsy guided by ultrasound is highly effective, providing a definitive result in 93% of cases and having a low false negative rate of 2%(25).

A three-year retrospective review of records of female patients with nipple discharge concludes that ultrasound is a valuable tool for evaluating pathologic nipple discharge in women, and it should be considered as part of the standard diagnostic evaluation, as the US sensitivity in these cases is 56-80%, compared to 15-32% for mammography(4).

Ultrasound is an invaluable tool for diagnosing cancer as well as for assessing the involvement of axillary lymph nodes. It helps in confirming the axillary nodal involvement by detecting indicators such as abnormal rounded shape, loss of echogenicity in the hilum, cortex thickening beyond 3 mm, or irregular and lobulated cortex. These reliable ultrasound findings assist in accurately staging the disease(16).

Ultrasound technology has seen several advancements, such as the introduction of 3D ultrasound, color Doppler, power Doppler, automated breast ultrasound (ABUS), and sonoelastography. These innovations have enhanced the capabilities of ultrasound in various ways, allowing for more detailed imaging, improved blood flow assessment, automated scanning of the breast, and the evaluation of tissue elasticity. These advancements have significantly contributed to the effectiveness and accuracy of ultrasound in diagnosing and monitoring various medical conditions. Nanoparticles in ultrasound challenges the low specificity of US for cancer detection, being used as a contrast agent for both cancer detection and treatment[1]. Another promising technique, optoacoustic ultrasound, also referred to as optoacoustic tomography or photoacoustic imaging, enables the visualization of blood vessels and the detection of tumor-driven angiogenesis[34]. This imaging modality involves the use of laser light pulses to illuminate the tissue, which in turn generates photoacoustic signals through the detection of returning acoustic stress waves, providing valuable insights into tumor vasculature and aid in the early detection of cancer[34].

Ultrasound is not a substitute for mammography screening, but plays an important role in breast cancer diagnosis. It has its limitations, such as assessing chest wall invasion due to the posterior shadowing which obscures evaluation. Also, ultrasound is not the preferred imaging tool when it comes to assessing silicone breast implant integrity, where the chosen method is magnetic resonance imaging[7].

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a valuable tool for breast imaging that utilizes magnets and radio waves to generate images. To accurately diagnose or rule out cancer, the administration of a contrast material (CM) containing gadolinium through intravenous injection is necessary. This contrast material enhances the visibility of certain structures and helps in the detection of abnormalities within the breast. MRI is a safe imaging technique that does not expose the patient to potentially harmful radiation[33]. However, it is important to be aware of other precautions, contraindications and potential side effects, including those related to the use of contrast material. It is crucial to consider these factors to ensure the well-being and safety of the patient during the MRI procedure. Contraindications for MRI imaging techniques are represented by claustrophobia not controlled by premedication, metal or medical devices, prior moderate or severe gadolinium contrast reaction. Also, gadolinium's safety is not well established in pregnancy[7]. For silicone implant evaluation, non-contrast exam is preferred[7]. In addition, it is important to take into account the costs associated with breast MRI, which are higher compared to mammography and ultrasound.

Although it is not commonly used for breast cancer imaging, it has various applications, such as preoperative staging, evaluating the response to neoadjuvant therapy, distinguishing between scar tissue and recurrence, assessing breast implant integrity, or investigating cases of cancer with unknown primary origin[16]. While not frequently employed for breast cancer imaging, MRI is a highly sensitive imaging technique that greatly enhances the effectiveness of screening for high-risk women (20-25%) with a familial increased risk for breast cancer, and of women who are carriers of BRCA1 or BRCA2 mutations[7,23]. The overall sensitivity of breast MRI in detecting breast cancer is estimated to be around 90%[33]. This suggests that approximately 10% of cancers may go undetected. These missed cancers are typically either very small or do not exhibit significant contrast enhancement[33]. The American Cancer Society (ACS) recommends that individuals at high risk should undergo annual screening using MRI imaging[23]. This regular screening is advised to ensure early detection and effective monitoring for high-risk patients. Also, ESMO recommends for high-risk women annual screening using MRI concomitantly or alternating every six months with mammography, starting 10 years younger than the youngest case in the family[40].

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is an advanced imaging method that provides a comprehensive view of breast morphology and enhancement kinetics through the identification of angiogenesis, a tumor-specific characteristic related to the development of new blood vessels[16]. DCE-MRI is widely recognized as the most sensitive method for detecting breast cancer, with a pooled sensitivity of 93.2% and a pooled specificity of 71.1%[42]. These statistics highlight the effectiveness of DCE-MRI in accurately identifying breast cancer while minimizing false positive results. Multiple studies have shown that DCE-MRI is the preferred screening method for women at a high risk of breast cancer when compared to conventional imaging techniques[16]. DCE-MRI has been found to provide superior results in detecting and evaluating breast abnormalities in this specific population. Another indication for DCE-MRI is the staging of multifocal and multicentric breast cancer[6].

Different MRI modalities are also available, such as diffusion-weighted imaging (DWI) and magnetic resonance elastography (MRE). Each technique comes with its advantages and disadvantages. Due to concerns about gadolinium deposition in the brain and the overall burden associated with the requirement for intravenous access[35], there is a rising interest in the development of non-contrast MRI examinations for screening purposes. DWI is a valuable technique that enables the visualization and measurement of the random motion of water molecules within tissue, which is influenced by tissue microstructure and cell density. Importantly, this imaging method eliminates the need for an intravenous contrast agent. In cases of breast cancer, the augmented cell density results in reduced water diffusion, leading to a notable increase in signal intensity on diffusion-weighted images[34]. DW-MRI exhibits lower sensitivity compared to DCE-MRI, but it surpasses mammography and ultrasound in terms of sensitivity, having the potential to be a valuable method for detecting malignancies that may be concealed by mammography[2]. Magnetic resonance elastography is a noninvasive imaging method that allows for the measurement of tissue stiffness or elasticity. Currently, MRE is in the research stage, with ongoing efforts focused on reducing scanning time and enhancing spatial resolution. Other MRI modalities are still in research stages, like magnetic resonance spectroscopy (MRS) or nanoparticles in MRI (Np MRI).

Conclusions

In summary, imaging plays a crucial role in the detection and staging of breast cancer, providing valuable information to guide treatment decisions. According to the existing literature, numerous imaging modalities exhibit varying capabilities and levels of success in visualizing breast tissue. Often, no available screening modality is uniquely ideal. Mammography is the primary method used for screening for breast cancer in average-risk women, whereas for high-risk women, MRI is the chosen imaging technique, often associated to mammography. For dense breast tissue, mammography is not efficient and of great use are US and DCE-MRI. Ultrasound is commonly used to affirm the diagnosis of breast cancer, explore potential additional disease within the breast, and guide interventions through imaging of breast procedures.

Alternative imaging techniques have emerged as promising modalities that aim to address the limitations of conventional imaging methods when it comes to sensitivity and specificity in breast cancer screening and diagnosis. DCE-MRI stands out as the most sensitive imaging modality so far for the detection of breast cancer, exhibiting excellent sensitivity and good specificity. In fact, it proves to be more beneficial than mammography and ultrasound in assessing the extent of the disease and in identifying additional areas of concern, being highly advantageous for the comprehensive evaluation and accurate detection of breast cancer. By leveraging the advantages of various imaging techniques and compensating for their limitations, a comprehensive and accurate breast cancer staging approach can be established by employing different imaging modalities.

In the light of new discoveries in imaging modalities, there is a potential for enhancing the traditional screening and diagnostic protocols for breast cancer. As we move forward, it is expected that primary and additional screening methods will evolve, and it is important to better monitor the effectiveness and performance of emerging screening tools in a timely and meaningful manner. ■

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