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Research progress on ultrasound medicine in diagnosis and evaluation of chemotherapy effect of breast cancer

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Abstract. Breast cancer has the highest incidence rate among cancers in the world and is the main cause of death among female cancer patients around the world. The progress of ultrasound technology has continuously improved the ability to identify the shape and microvessels of breast masses. It plays an important role in the differentiation of benign and malignant breast masses and is the main auxiliary diagnostic method for breast cancer. The widespread implementation of neoadjuvant chemotherapy for breast cancer has improved the survival rate of patients. Evaluating the efficacy after chemotherapy and adjusting chemotherapy strategies as needed can help improve the prognosis of patients. Ultrasound can conduct multi-parameter measurements of breast tumor hardness, blood flow velocity and vascular distribution, which can be applied to evaluate the efficacy of neoadjuvant chemotherapy for breast cancer. This article reviewed the application and research progress of multi-modal ultrasound in the diagnosis and evaluation of chemotherapy efficacy of breast cancer.

Keywords: breast cancer; ultrasonography; diagnosis; neoadjuvant chemotherapy.

1. Introduction

Breast cancer is the most common cancer, Since the mid-20th century, the incidence rate of female breast cancer has slowly increased by about 0.5% every year[1]. In recent years, more than 2 million women have been diagnosed with breast cancer every year around the world, leading to more than 520000 deaths[2], which is the leading cause of death among female cancer patients worldwide. The detection of early cancer is crucial to the successful outcome of breast cancer screening[3], the results of Breast cancer diagnosis rely on the detection of early breast cancer. Mammography has long been the most widely used imaging technology in breast cancer screening and early diagnosis, but it is limited by the density of breast tissue[4]. Furthermore, in resource-limited areas, the use of mammography is also limited due to the high cost of X-ray equipment and the lack of professional radiologists and technical experts[5].

Ultrasonography has become an important imaging tool for the examination and diagnosis of breast masses due to its unique advantages such as no ionizing radiation, real-time imaging, repeatable operation, unconditional restrictions, high resolution, simple operation, low cost, etc. It plays an important role in the development of surgical plans, diagnosis and clinical treatment for breast cancer patients. Among patients with confirmed breast cancer, breast ultrasound plays a vital role in identifying the size and location of tumors and helping surgeons more rationally plan the extent of breast tissue removal during partial mastectomy[6].

The current ultrasound mode includes B-mode ultrasound, color Doppler ultrasound, ultrasonic elastography, contrast-enhanced ultrasound, three-dimensional ultrasound, and artificial intelligence systems combined with ultrasound that have developed rapidly in recent years. At present, the application of single-mode ultrasound imaging is less, and the combination of various ultrasound modes shows great development prospects in clinical diagnosis, that is, multimodal ultrasound.

The appearance of new ultrasound technology provides more convenient, efficient and accurate imaging methods for the diagnosis of breast cancer and the evaluation of curative effect after chemotherapy, which are expected to provide greater help for the early detection of breast cancer and the good prognosis of patients. This article reviewed the roles of different ultrasound modes in the diagnosis and evaluation of neoadjuvant chemotherapy efficacy of breast cancer, to evaluate the advantages and disadvantages of the applications in diagnosis and prognosis of breast cancer of various ultrasound modes, summarized the latest progress of various ultrasound modes in neoadjuvant chemotherapy of breast cancer, and explored the development potential and future development direction of the application of ultrasound in breast cancer.

2. Ultrasonic diagnosis of breast cancer

2.1. Mode Ultrasound

B-mode ultrasound,, also known as two-dimensional ultrasound or grayscale ultrasound, is a single parameter morphological imaging method that displays the characterization of breast lesions[7], It mainly determines the benign or malignant nature of tumors based on the morphological characteristics of the lesions. After the bilateral breast conventional B ultrasonic examination, radiologists can obtain at least two orthogonal images of each breast lesion, namely the transverse and longitudinal planes or the radial and anti-radial planes[8].

The advantages of B-mode ultrasound application include no generation of ionizing radiation, real-time imaging, repeatable operation, high resolution, unrestricted conditions, non-invasive, and relative sensitivity to dense breasts, etc[7]. It is particularly effective in distinguishing between solid breast masses and fluid filled cystic lesions[11],, supplementary ultrasound screening for women with uneven or extremely dense breasts can reduce the mortality of breast cancer to 0.36/1000 women with dense breasts compared to mammography alone, It is worth noting that the application drawbacks of B-mode ultrasound include operator-dependence[12], inability to visualize the whole breast, close correlation between diagnostic results and the professional skills of doctors, and low possibility of standardization of diagnostic results, with the main limitation being its low positive predictive value and the large number of false-positive results that may lead to unnecessary biopsies or short-term follow-ups[13].

2.2. Color Doppler Ultrasound

Color Doppler ultrasound can visualize blood vessels, display the vascularity of masses, and initially identify tumor capillaries by displaying the distribution of tumor blood vessels, blood flow rate, etc. After obtaining information on the distribution of blood vessels, it is possible to further characterize breast lesions, and improve the diagnostic accuracy of ultrasound in identifying benign masses and malignant tumors, so that color Doppler ultrasound has become the main auxiliary imaging tool for the diagnosis of breast cancer[8].

Color Doppler ultrasonography is a noninvasive, safe, widely used, and relatively inexpensive vascular imaging method that can be repeated and has been widely used to detect neovascular changes caused by malignant tumors[15]. Choi[8] et al. have shown that the combination of color Doppler ultrasound and B-mode ultrasound can greatly improve the diagnostic performance of breast tumors. However, color Doppler ultrasound can only detect large vessels with diameters of 100-200 um, only sensitive to fast blood flow, and is incapable of structural analysis of the microvasculature, resulting in highly fragmented and plaque-like images of the underlying vessels and is not suitable for distinguishing local recurrence and fibrosis in lesions[16].

2.3. Elastography Ultrasound Imaging

Elastography ultrasound imaging(EUS) can be used to assess the biomechanical properties of soft tissues, provide mechanical information about breast tissues, and improve the specificity of breast ultrasound diagnosis, which has been widely used in breast cancer diagnosis and screening[14]. EUS includes strain elastography and shear wave elastography, strain elastography is used to assess the deformation of an injury that occurs when the injury is subjected to compression[21],and shear wave elastography utilizes an acoustic force impulse (ARFI) to generate shear waves perpendicular to the ARFI pulse, which is a quantitative imaging method that allows elasticity values to be obtained directly.

EUS allows real-time quantitative measurement of breast tissue stiffness and qualitative identification in the form of elastic chromatograms, which significantly improves the specificity of conventional B-mode ultrasound in identifying benign and malignant breast masses while maintaining high sensitivity, and reduces unnecessary biopsies[1]. However, compared with B-mode ultrasound imaging, EUS is more operator-dependent, including probe position, applied pressure, and compression frequency. In addition, EUS needs to calculate tissue displacement based on the ultrasound echo signals, and the accuracy of the displacement calculation is also strongly affected by signal attenuation, which leads to a reduction in its sensitivity for diagnosing lesions in deeper tissues, and significant degradation of the image quality of this part[18].

2.4. Contrast-Enhanced Ultrasound

Contrast-enhanced ultrasound(CEUS) refers to the injection of Ultrasound Contrast Agents(UCAs) into a vein or localized tissue that travels along the lymphatic or blood vessels, thus serves as a tracking and labeling agent. UCAs are expected to be the new generation of tracers due to their fast metabolism in the body, low toxicity, no radiation, ability to show lymphatic vessels and lymph nodes in real-time, and assistance in determining the benign or malignant nature of tumors. Similar to the role of contrast agents in computed tomography (CT) and magnetic resonance imaging (MRI), tissues containing UCAs have an increased contrast with surrounding tissues in ultrasound imaging[22], thus improving the detection of tumor microvasculature by CEUS[16]. CEUS has evolved in breast imaging applications, with the use of microbubble contrast agents and refinement of acquisition techniques greatly enhancing the signals from the breast lesion site, allowing for a more accurate assessment of the microvascular distribution and blood perfusion status of assessed breast tumors[23]. With the use of high-frequency probes, the spatial resolution of ultrasonographic imaging has increased, allowing more image detail to be obtained for the morphologic evaluation of lesions[24].

Compared with static breast ultrasound images, CEUS depicts and provides more detailed information about the tumor blood supply, which has higher sensitivity and specificity in identifying benign and malignant breast masses[22], and reduces the number of unnecessary biopsies[7], therefore, improved diagnostic accuracy is not only beneficial to the patient but also reduces the cost of the examination. The examination time for CEUS is relatively long because of the necessity of injecting intravenous contrast agents, in addition, CEUS images require kinetic evaluation of the images using specific software[7] and diagnosis by experienced radiologists through observation and grading, however, due to the subjectivity of visual observation and the lack of a standard grading scheme for breast tumors, radiologists have subjectivity in their diagnosis[25].

2.5. Three-Dimensional Ultrasound

Three-dimensional ultrasound(3D ultrasound) is the latest development in breast ultrasound imaging, an effective tool for evaluating the morphology of breast masses, and can provide information that B-mode ultrasound cannot provide, such as morphologic features in the coronal plane and the overall appearance of the vascular distribution of the mass. Three-dimensional ultrasound has shown significant promise in differentiating benign and malignant breast lesions and has played an important role in image-guided biopsies and neoadjuvant chemotherapy treatments[26]. Three dimensional ultrasound diagnostic modes include three-dimensional power Doppler ultrasound, three-dimensional contrast-enhanced ultrasound, three-dimensional automatic breast ultrasound, etc., which can obtain more precise ultrasound images and more convenient diagnostic methods. The combinations of various ultrasound diagnostic modes and traditional ultrasound are widely used in the clinical diagnosis of breast cancer.

2.5.1. 3D Power Doppler Ultrasound

3D power Doppler ultrasound is used to assess the vascular distribution of a volume or organ, and the three indices, vascularization index(VI), flow index (FI), and vascularization flow index (VFI), correlate with the total and relative amount of power Doppler information at the detector site and reflect the number of vessels within the volume of interest (VI), the intensity of flow at the time of the 3D sweep(FI), and both blood flow and vascularization (VFI)[27].

3D power Doppler ultrasound is more capable of detecting the vascular distribution of solid breast masses compared with conventional Doppler ultrasound and can characterize the vascular structure and tissue vascular distribution in areas of slow blood flow and poor blood flow in greater detail. However, for some breast tumors with different ultrasound characteristics, the diagnosis may remain unclear due to differences in histologic type, histologic grading, and tissue composition within the tumor[29].

2.5.2. 3D Contrast-Enhanced Ultrasound

3D contrast-enhanced ultrasound is a technique that combines ultrasonography with the stereoscopic vision of 3D ultrasound and provides unique spatial visualization in three vertical planes, allowing contrast images to be viewed from any angle of the three vertical planes, as well as three-dimensional reconstruction of detected organ images, which helps the diagnostic physician to get a comprehensive view of the overall perfusion of the lesion[30].

3D technology is more reproducible than two-dimensional technology, and 3D contrast-enhanced ultrasound can automatically scan according to the desired angle, obtain the volume data of the examined area, and reconstruct the three-dimensional model by tomography, while 3D contrast-enhanced ultrasound can integrate the information of multiple two-dimensional ultrasonography images to display the images of the detected area from different angles, which has been widely used for breast imaging in clinical practice[30]. 3D contrast-enhanced ultrasound is a new technology with promising clinical applications. However, the operation and post-processing techniques of 3D contrast-enhanced ultrasound systems today still depend mainly on the operator's experience[30], and thus more researchers are needed to conduct further experiments and studies on the intelligence of 3D contrast-enhanced ultrasound technology.

2.5.3. 3D Automated Breast Ultrasound

Mammography is considered the reference standard for breast cancer screening. However, mammography has significant limitations in patients with dense breast tissue. Dense breast tissue has poor contrast with masses with similar breast X-ray density[31], and contrast check reduces the sensitivity of mammography by covering breast cancer lesions. Automated Breast Ultrasound(ABUS) was approved by the FDA in 2012 as a novel breast cancer screening modality that uses a slice scanning approach to provide a 3D view of the entire breast by performing an automated scan of the whole breast[32]. Vourtsis[34] et al. found in a large sample study of 1886 cases that, in the presence of deformations of structures identified in the coronal reconstruction plane ABUS was superior to handheld breast ultrasound. In addition, ABUS is also useful in identifying non-calcified carcinomas that are masked by dense breast tissue.

The ability of 3D ABUS to provide visibility of all breast tissue allows the diagnostician to assess symmetry, bilaterality, and multiplicity of findings, thereby reducing the incidence of false-positive results[31]. The main advantages of ABUS over handheld ultrasound are standardized acquisition, operator-independence, lack of formal training, reproducibility of images, and time-comparison capability[7]. However, viewing ABUS views can be a time-consuming task because ABUS can generate multiple 3D views when examining a breast, creating a three-view atlas[35]. In conclusion, understanding the technical points and misconceptions of ABUS is crucial for breast image interpretation to reduce the false-positive rate of diagnostic results and shorten the image interpretation time[8], as well as to improve the diagnostic rate of breast cancer.

2.6. Artificial Intelligence System Integrated With Breast Ultrasound

In recent years, computer technology has been improving, machine learning and deep learning algorithms have been developed, and deep learning models, convolutional neural networks (CNN) based on SWE parameters, etc. have greatly improved the accuracy and reliability of computer-aided diagnosis. Artificial intelligence techniques are good at recognizing complex patterns in images and quantifying information that is difficult for humans to detect, thus providing assistance in clinical treatment strategies and bringing new opportunities for the development of the healthcare field[36]. .

The application of artificial intelligence to ultrasound-assisted diagnosis is of great significance in reducing the workload of imaging physicians, improving the diagnostic efficiency of breast masses, and reducing diagnostic subjectivity and dependence on operators[25]. However, current AI systems integrated with breast ultrasound still have major limitations, as different ultrasound devices may have different signal processing and image optimization parameters, the developed systems are only applicable to a single model of an ultrasound device, and breast radiologists often refer to the patient's previous imaging to assess the morphological changes of suspicious lesions over time. Future research may focus on enhancing the ability of AI systems to extract relevant information from past ultrasound systems thereby improving diagnostic accuracy[11]. In addition, it is difficult to differentiate between the four types of malignant tumors, benign tumors, adenopathies, and inflammatory masses based on the size of the mass alone, both by working experienced diagnosticians and by AI systems combined with breast ultrasound[36], therefore, more in-depth studies are needed to improve the accuracy of AI systems in differentiating between the types of masses in the future.

Table 1. Advantages and limitations of various ultrasound diagnostic methods for breast cancer

Type of Ultrasound		Advantages	Limitations
B-mode Ultrasound		Real-time imaging, high resolution[10], reproducible, no ionizing radiation, noninvasive, sensitive to dense breasts[9]	Operator-dependent, not able to visualize the whole breast[12]
Color Doppler ultrasound		Noninvasive, safe, inexpensive, reproducible[15]	Inability to perform structural analysis of small diameter microvessels[16]
Elastography Ultrasound Imaging		Higher sensitivity and specificity[21], reduction of unnecessary biopsies[19]	Operator-dependent, low sensitivity for diagnosis of deep tissue lesions[18]
Contrast-enhanced Ultrasound		Strong ability to detect microvessels[16], high spatial resolution[24], high specificity, Provision of detailed blood supply information for tumors[22], reduction of unnecessary biopsies[7]	Long inspection time, reliance on specific analysis software[7]
Three-Dimensional Ultrasound	3D Power Doppler Ultrasound	Sensitive for detecting solid breast masses, low-velocity, low-volume blood flow[29]	Uncertainty in the diagnosis of breast tumors with varying ultrasound characteristics[29]
	3D Contrast-Enhanced Ultrasound	Reproducible, three-dimensional spatial visualization[30]	Dependence on operator experience[30]
	3D Automated Breast Ultrasound	Standardized acquisition, operator-independent, no formal training required, image reproducibility[32],ability to compare over time[9]	Time-consuming image interpretation[35]
Artificial Intelligence System Integrated With Breast Ultrasound		Reduces physician workload and improves diagnostic efficiency[36],reduces diagnostic subjectivity and operator dependence[25]	Accuracy of differentiation of mass types needs to be improved[36]

3. Ultrasound Differentiation of Benign And Malignant Breast Lesions

Ultrasound, with its non-invasive, non-ionizing radiation, portability, high sensitivity and specificity for cancer, ability to guide biopsies in real-time, and cost-effectiveness, is now widely used in all phases of breast cancer diagnosis and treatment, including screening, diagnosis of dense breasts, and prognosis during chemotherapy. Ultrasound imaging works on the principle that high-frequency ultrasound enters the body, and different types of soft tissues in the body have different echoes due to their different densities, resulting in reflection and scattering to further visualize various anatomical areas in the body[38].

In recent years, ultrasound technology has developed rapidly, including B-mode ultrasound, color Doppler ultrasound, contrast-enhanced ultrasound, three-dimensional ultrasound, automated breast ultrasound, and elastography ultrasound imaging, which have maximized the sensitivity and specificity of conventional ultrasound for breast tissue[37].

3.1. Color Doppler Ultrasound

Color Doppler ultrasound, an imaging modality that describes the mean intravascular frequency shift induced by the Doppler effect of flowing blood cells, is an important complementary tool for assessing the distribution of diseased vessels. The vasculature in malignant tumors varies greatly from that in normal tissue or benign tumors, low oxygen levels in early-appearing tumors stimulate the release of vascular endothelial growth factor (VEGF), which induces neovascularization and stimulates tumor growth, whereas the additional demand for oxygen by growing tumor cells leads to vascular leakage and the formation of fragile and curved vessels. In most benign cases, tumor growth is controlled by mechanisms similar to those of normal tissues, leading to the formation of organized and non-curved vascular shapes[17], and on ultrasound images, the presence of irregular branching vascular distributions and a large number of peripheral vasculature is highly suspicious for malignant lesions of breast tumors[39]. Malignant tumors tend to show excessive, irregular and abundant vascularity with more than one vascular pole; therefore, the typical color Doppler signs of malignant tumors are central, penetrating, branching and disorganized vascularity within the tumor [40].

3.2. Elastography Ultrasound Imaging

Elastography ultrasound imaging provides information about tissue biomarkers such as elasticity, viscosity, and tissue nonlinearity[41], and the technique is capable of detecting changes in the elasticity of soft tissues caused by a specific pathological process. Malignant breast masses tend to be stiffer than benign lesions, and therefore the stiffer the lesion, the higher the probability of a diagnosis of malignancy[39]. The ratio of lesion size from strain elastography to lesion size from B-mode ultrasound, known as the E/B ratio, can be used to predict the benign or malignant nature of breast masses, with a ratio of less than 1 suggesting a benign mass and a ratio of greater than 1 suggesting a malignant mass, and the ratio has a sensitivity of up to 100% for prediction[21]. Elastography ultrasound imaging is used to qualitatively assess tumor stiffness by analyzing color scale images or quantitatively by determining the mean and maximum elasticity values (kPa) and the ratio of maximum elasticity to adipose tissue, with images that are red for stiffness and blue for soft tissue, with colors closer to red and higher elasticity values or ratios indicating malignant lesions[42].

3.3. Contrast-enhanced Ultrasound

Due to the high density and chaotic distribution of blood vessels in breast tumors, the CEUS technique can reflect the shape characteristics of the tumor and can provide detailed information about the blood supply of the tumor, providing valuable information for the diagnosis of breast tumors[41]. During CEUS examination, firstly, the contrast agent is injected into the tumor area of the patient, and secondly, the radiologist observes the brightness changes of the tumor area through CEUS images, and the brightness changes of the CEUS frames reveal the blood supply of the tumor[41]. Malignant tumors grow faster and metabolize more than benign tumors because of their rich blood flow, contrast retention indicates poor venous return due to disturbed vascular distribution within the tumor, thus the irregular shape shown on the CEUS image is the rich and disorganized blood flow in the malignant tumor and its infiltration into the surrounding breast tissues[42], thus if the tumor diameter in the CEUS image is larger than the tumor diameter in the ultrasound image, the there is a higher risk that the tumor is malignant[41].

3.4. Three-Dimensional Ultrasound

In 3D ultrasound, the common type of breast cancer presents as an irregular sea urchin-like mass with jagged edges extending to the entire periphery of the mass, whereas fibroadenomas are smooth in structure and surrounded by a continuous hypoechoic rim. Among the morphological features of breast cancer in 3D ultrasound, the convergence pattern on the coronal plane is highly characteristic of malignant masses, and this pattern is also unique to 3D technology[43]. In addition, the combined use of 3D ultrasound and 3D power Doppler ultrasound will identify a breast mass as a malignant tumor when it presents with features such as irregular shape, abnormal orientation, unclear margins, heterogeneous echostructure, absence of acoustic transmission, retracted or star-shaped, and disorganized vascular structure[29].

3.5. Three-Dimensional Automated Breast Ultrasound

3D ABUS uses a high-frequency transducer to provide a large field of view, and in clinical exams, it is often necessary to acquire images from three to five different directions to cover the entire breast, with each ABUS volume comprising hundreds of 2D slices. 3D automated breast ultrasound helps to detect breast lesions and differentiate between malignant and benign lesions, and to predict the extent of breast lesion[37]. Benign lesions on ABUS coronal images show the presence of an echogenic wall, which Vourtsis[34] et al. termed the "white wall" sign, which corresponds to the acoustic enhancement found on HHUS, and therefore lesions with "white wall" features shown on ABUS are mainly diagnosed as benign lesions, including simple cysts, fibroadenomas, papillomas, etc.[34]. The coronal image of ABUS shows the entire breast from the skin and nipple-areola complex to the chest wall, and depicts the radial organization of the mammary ducts, the distribution of the mass, i.e., the blackness or cavities, and the burrs of the linear projections of the echoes emanating from the centroid or the lumps are called "retraction phenomena", which is highly associated with cancer but may also be radial or surgical scars[31]. Therefore, when a stellate lesion with hyperproliferative retraction of connective tissue appears as a sign of the "retraction phenomenon" on the coronal image of ABUS, malignancy is suspected[34].

3.6. Artificial Intelligence System Integrated With Breast Ultrasound

Recent advances in Artificial Intelligence (AI) algorithms have contributed to a more accurate and objective description of ultrasound images, which can be used to comprehensively assess the size, intensity, texture, and other less obvious features of breast tumors[25]. Tumor classification is one of the fundamental tasks in computer-aided diagnosis (CAD) systems, benign tumors usually have smooth, round and oval borders, while most malignant tumors have irregular and sharp shapes[35]. Deep learning-based CAD systems have achieved widespread success in the field of breast cancer diagnosis, and many of the models have achieved excellent performance in clinical trials, such as ME-CNN, SaNet, MSGRAP, DL-CNN-FCRN, and COAM[41] etc. Shen[11] et al. developed an AI system that was trained and validated on large-scale datasets by increasing the dataset, enhancing the joint collaboration between the system and radiologists, and replacing image-level or pixel-level labels with a weakly-supervised learning paradigm[11] in order to ensure that the system works better in clinical practice, and it is able to reduce the number of false-positive diagnoses and benign biopsies. Moon[10] et al. proposed a CAD system to diagnose benign and malignant breast tumors in ultrasound using raw tumor images, segmented tumor images, tumor masks, and fused images. It was shown that the CAD system based on CNN architecture can incorporate a wide range of tumor features, and it can provide accurate results for tumor diagnosis of breast cancer patients.

Both inflammatory and adenopathic masses are benign tumors, but current AI systems integrated with breast ultrasound have limited diagnostic capabilities for both masses[44], therefore, new opportunities presented by the development of AI in breast ultrasound are expected to be able to improve the efficiency of breast ultrasound examinations as well as the diagnostic accuracy of breast images for the greater well-being of patients.

4. Evaluation of The Efficacy of Neoadjuvant Chemotherapy For Breast Cancer

Neoadjuvant chemotherapy (NAC) for breast cancer, which aims to shrink breast tumors, eradicate axillary lymph node metastases, and provide the option of breast-conserving surgery rather than mastectomy, has been validated in many clinical trials and studies in terms of increasing overall survival and improving quality of life improvement[43]. According to the current guidelines of the National Comprehensive Cancer Network (NCCN), neoadjuvant chemotherapy is not only indicated for locally advanced breast cancer but is also an effective treatment for patients with surgically treatable early breast cancer[47]. Current methods of neoadjuvant chemotherapy for breast cancer include MRI, CT, PET/CT, ultrasound, and artificial intelligence imaging techniques combined with these methods.

4.1. Serological Indicators

Serological indices have the advantages of easy material extraction, low physical trauma, and repeatable monitoring, and effective serological indices are very useful for assessing the efficacy of NAC. Changes in the levels of VEGF and CTCs can be used to assess the efficacy of neoadjuvant chemotherapy, and the high expression of VEGF provides the vascular and lymphatic systems required for CTCs shedding[48]. However, serological indices in assessing the efficacy of NAC are mostly revealed after several cycles, which is time-consuming and does not allow for visualization of the tumor and obtaining specific information about the shape, size, and blood supply of the tumor, so the use of serological indices alone in evaluating the efficacy of NAC has limitations.

4.2. MRI

MRI has higher sensitivity and accuracy in assessing tumor size, and conventional MRI is able to initially measure lesion size and has a high value in determining tumor fibrosis after NAC, as well as making a preliminary imaging diagnosis of the relationship between the tumor and surrounding tissues[48]. Breast MRI is the best method for assessing tumor response to NAC, but MRI examinations are expensive and their use is limited in patients with specific conditions, and magnetic resonance imaging gadolinium-based contrast agent can diffuse from the blood vessels into the adjacent mesenchymal tissues, thereby overestimating the extent of the residual tumor and generating potentially false-negative or false-positive results[43].

4.3. PET/CT

PET/CT has demonstrated higher sensitivity, specificity and accuracy in the assessment of residual lesions, providing important information about the morphological changes in breast lesions and lymph nodes before and after NAC, and playing a key role in assessing the effectiveness of NAC in the treatment of breast cancer[48]. However, PET/CT has limitations such as low spatial resolution, risk of radiation exposure[49], and the examination is more expensive and burdensome for chemotherapy patients, thus its general acceptance among patients is low[47].

4.4. Ultrasound

Ultrasound can provide information on breast tumor size, morphology, and blood supply, and can further reveal internal and peripheral perfusion and determine whether the mass is liquefied and necrotic[49]. Conventional grayscale ultrasound monitors and predicts pathological response by assessing dynamic changes in breast cancer tumor size, providing information about the morphology and internal structure of the tumor and its relationship with surrounding tissues after NAC. However, due to factors such as operator error and choice of cutting surface, conventional ultrasound has a relatively low specificity and accuracy for the assessment of NAC efficacy, and performs in accurately predicting response to neoadjuvant chemotherapy poorly[43].

Ultrasound can be used to evaluate the efficacy of patients' neoadjuvant chemotherapy in a multi-parameter comprehensive manner, so as to provide better clinical guidance and improve patients' prognosis, and it has a broad prospect of application in breast cancer NAC[48]. Currently, the ultrasound modalities applied in breast cancer neoadjuvant chemotherapy include Elastography ultrasound imaging, color Doppler ultrasound, contrast-enhanced ultrasound, and automated breast total volume imaging, etc.

4.4.1. Elastography Ultrasound Imaging

Elastography ultrasound imaging is highly specific and sensitive in the differential diagnosis of benign and malignant lesions and has been widely used to qualitatively and quantitatively assess differences in stiffness or elasticity of breast lesions[48]. Tissue stiffness is an important feature in determining the efficacy of NAC[47], and since high-grade invasive breast cancers may have well-defined borders and lack invasive and progressive features on conventional ultrasound, CEUS can detect differences in tissue stiffness and thus provide an accurate diagnosis of such breast cancers[50]. Average hardness can be used as a preoperative predictor of invasive breast cancer, with less invasive breast cancers tending to be less hard, and invasive breast cancers with lower hardness showing a better response to NAC[50], and after NAC, the state of the tissue within and around the tumor can be altered by the action of drugs, and its hardness will change accordingly[48]. As another key factor, elasticity value has an important role in accurately predicting the response to neoadjuvant chemotherapy, and the relationship between low elasticity values and a good response to neoadjuvant chemotherapy has consistently been able to be demonstrated, with a better overall response to treatment at low elasticity values, and with differences in elasticity values that are significantly associated with the level of TIL for each tumor subtype[45].

Elastography ultrasound imaging has higher sensitivity in evaluating the efficacy of NAC and can provide valuable information for patient prognosis[50], however, it is more demanding for the operator, the quality of the image is susceptible to the patient's status such as respiration, thickness of the fat layer, and peripheral vascular pulsations, and it does not allow for complete sampling of larger masses, etc.[48].

4.4.2. Color Doppler Ultrasound

Changes in the number of blood vessels have been shown to be an independent factor reflecting tumor response to treatment, and Pavlov[51] et al. showed that color Doppler power ultrasound studies of the tumor vascular bed showed a decrease in the number of tumor blood vessels after the first cycle of chemotherapy in the vast majority of cases, and that all of the tumors that were more responsive to treatment demonstrated a decrease in tumor vascularization[51]. In most patients presenting with tumors, tumor vascular flow velocities are high, and Doppler flow velocities tend to be faster in larger tumors, but there is no significant correlation between maximal flow velocities and tumor size[52]. Tumor oxygenation is inextricably linked to the state of its vascular bed, and antitumor therapy affects tumor cells and stroma, including the microvasculature; therefore, color Doppler ultrasound can be used to indirectly assess tumor sensitivity to drugs based on the response of the tumor vascular bed[51]. Current studies have shown that color Doppler is an independent predictor of response to chemotherapy in locally advanced breast cancer, and the gold standard for assessing response to chemotherapy in breast cancer is histological changes in the form of histiocyte hyperplasia, stromal fibrosis, calcification, and lymphocyte infiltration, and since histopathological response is assessed in postoperative specimens, color Doppler ultrasound is a suitable tool for preoperative evaluation of breast cancer.

During NAC, changes in tumor microvasculature usually precede morphological alterations, and NAC has the ability to affect the blood supply to tumor cells, leading to cell death and altering the velocity and resistance to blood flow in and around the lesion; a decrease in the distribution of blood vessels within the tumor during NAC indicates a good response, whereas an increase or no change in the distribution of blood vessels suggests a lack of response[48]. Color Doppler imaging has a low sensitivity for detecting tumor microvasculature, only displaying blood flow signals with diameters greater than 0.2 mm and relatively high flow velocities, and this constraint limits its sensitivity in displaying tumor microvasculature, which may lead to an inadequate assessment of the blood supply to the breast cancer; therefore, color Doppler ultrasound is still limited in its overall ability to assess NAC efficacy ability to assess the efficacy of NAC remains limited[48].

4.4.3. Contrast-Enhanced Ultrasound

CEUS is a quantitative kinetic imaging modality that provides time-intensity profiles before and after NAC treatment and helps to understand the complexity of breast tumor angiogenesis[46]. The spatial distribution of tumor blood vessels is unbalanced. The microvessels density around the tumor is higher than that in the central region, and the necrosis and cyst regions are lower than that in the central region, that is, the heterogeneity of tumor blood vessels. The heterogeneity of tumors leads to the regional distribution difference of CEUS characteristics of breast cancer. The large and abundant nutrient vessels within the tumor provide nutrients, while tumor angiogenesis and new tumor tissue formation often infiltrate surrounding normal tissues at the edge of the lesion. Prior to NAC, the vasculature of the malignant lesion is abundant, twisted, and prone to form arteriovenous fistulas, and the tumors are more enhanced. Effective NAC provides the tumors with nutritive vasculature and reduce the number of new vessels[46]. The study by Saracco[54] et al. found that due to the anti-vascular effect of chemotherapy, the concentration of VGF was reduced, and CEUS after chemotherapy showed a significant slowdown in the rate of intravascular contrast perfusion in breast cancer, which can play an important role in evaluating the early response of invasive breast cancer to NAC. However, CEUS has some limitations in presenting results for tumors with less vascular distribution or deeper location, and cannot well display the characteristics of their microvascular structure and microcirculation[48].

5. Summary and Outlook

B-mode ultrasound, 3D ultrasound, elastography ultrasound imaging, color Doppler ultrasound, and contrast-enhanced ultrasound each have their own advantages, while the combination of each ultrasound modality is the main development trend of ultrasound, but which combination of ultrasound is better needs to be verified and explored in more clinical trials. Artificial intelligence systems that combine with breast ultrasound are emerging, and they show greater promise in achieving a convenient, efficient, and accurate diagnosis of breast tumors. Although various ultrasound modalities show great potential for development in the field of neoadjuvant chemotherapy for breast cancer, the various imaging modalities currently under study have certain limitations and still do not meet the clinical needs, and the future development of ultrasound combined with AI should take safety, convenience, real-time, visualization, and affordability as the primary development goals, and it is believed that shortly, the integration of the various ultrasound modalities and AI will be even closer. The closer integration of each ultrasound modality with artificial intelligence, ultrasound medicine will play a more important value in breast cancer diagnosis with higher efficiency and accuracy, and become the main tool for the evaluation of the efficacy of neoadjuvant chemotherapy for breast cancer.

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