Status and Progress of Multimodal Ultrasound Diagnosis of Triple-negative Breast Cancer

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Abstract: *Breast cancer is a highly heterogeneous cancer that is exceptionally harmful to women. It is generally divided by immunohistochemistry into four primary molecular subtypes: triple-negative (TN), human epidermal growth factor receptor 2 (HER2) overexpression, luminal A, and luminal B. Different breast cancer molecular subtypes exhibit diverse biological traits, clinical symptoms, therapeutic responses, and prognoses. Among them, triple-negative breast cancer (TNBC) is a highly malignant subtype with no particular treatment modalities and an inferior prognosis. As diverse ultrasonographies can offer complementing information on various features of breast cancer, multimodal ultrasonography provides a more reliable method for predicting TNBC than conventional ultrasound alone. This article reviews the research status and progress of multimodal ultrasound diagnostic techniques such as traditional ultrasound combined with sonoelastography (SE), contrast ultrasonography (CEUS), three-dimensional ultrasound (3D-US) and superb microvascular imaging (SMI) in predicting triple-negative breast cancer. It aims to use ultrasound diagnosis technology to predict TNBC and provide a reference for guiding clinical treatment and enhancing prognosis.*

Keywords: Triple-negative breast cancer, Multimodal ultrasound, Diagnosis

1. Introduction

Breast cancer is the most common malignancy in women, surpassing lung cancer[1]. It is also the second leading cause of cancer-related deaths in women, and its prevalence is still increasing, according to Cancer Statistics 2023 [2], which estimates that 31% of new cancer cases in women will be breast cancer. Breast cancer is a highly heterogeneous malignant tumor with differences in pathology, biological behavior, clinical manifestations, treatment response, and prognosis [3-7]. Timely and early diagnosis is essential to the choice of treatment and patient outcomes because delayed diagnosis and treatment are the primary reasons for high breast cancer mortality [8]. Due to the high cost and poor availability of polygenic molecular assays, molecular subtypes of breast cancer, including luminal A/B, HER2 overexpression, and triple-negative form, are usually determined clinically by immunohistochemistry (IHC) by examining the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), and proliferation index (Ki67)[9]. About 15%–20% of breast cancer cases are triple-negative breast cancer (TNBC), a unique subtype with a high degree of malignancy, fast proliferation, and a poor prognosis for ER, PR, and HER2 negativity[10, 11]. Ultrasound is frequently used in detecting and screening breast cancer since it is a secure, non-invasive, and affordable imaging technique. Breast lesions, both benign and malignant breast lesions, can be more accurately diagnosed using multimodal ultrasonography[12-16]. TNBC frequently exhibits the characteristics of benign tumors on conventional ultrasound imaging, even though various molecular subtypes of breast cancer might exhibit diverse appearances on sonogram[s] [17]. Therefore, routine ultrasound examination of TNBC is prone to misdiagnosis, which can impact both treatment and prognosis. Therefore, early recognition is essential to improve the prognosis of TNBC. The study of predicting molecular subtypes of breast cancer is expanding along with the continual development of new ultrasound technologies, such as contrast-enhanced ultrasound (CEUS), sonoelastography (SE), three-dimensional ultrasound (3D-US), Superb Microvascular Imaging (SMI), etc. However, TNBC, as the most malignant subtype of breast cancer, is easily misdiagnosed, so the diagnostic efficiency of ultrasound on TNBC still needs to be improved. Based on this, this article reviews the research status and progress of TNBC breast cancer in multimodal ultrasound manifestations, aiming to propose the common presentations of triple-negative breast cancer in ultrasound examination based on the literature

review to improve the diagnostic efficiency of ultrasound for TNBC, to achieve early detection, early diagnosis, and early treatment, as well as to improve prognosis.

2. Routine Ultrasound Features of TNBC

2.1 Two-dimensional grayscale ultrasound (2D-US)

Two-dimensional grayscale ultrasound (2D-US) is the basis for judging the benign and malignant breast mass; by evaluating the morphology, border, echo, posterior echo, and microcalcification of the breast mass, we can understand the breast mass. Previous studies have found that TNBC's performance on 2D-US differs from other breast cancer subtypes and has specific characteristics.

Tumors of the TNBC subtype are much larger than those of other subtypes, according to Liu Hui et al. [18]. A further study by Wu Tong et al. found that common ultrasound findings in TNBC include circumscribed and microlobulated margins, lack of calcification, and a high incidence of post-echo enhancement and apparent hypoecho[19, 20]. Similar findings were obtained by Sheng Changrui et al., who found that TNBC masses are primarily regular, with microlobes and distinct boundaries, frequently show posterior echo enhancement but do not include internal microcalcification[21]. The findings of Yang Qi et al. further support the notion that TNBC has a higher propensity for post-acoustic enhancement[22]. The researchers offered two explanations for the enhancement of posterior echo: first, it might be related to the mass necrosis formed inside the tumor, which decreases ultrasonic attenuation[23]; second, about 56% of TNBCs displayed a syncytial growth pattern, which is less layered than the trabecular pattern, promoting ultrasound propagation.

Additionally, several studies indicate that TNBC is more prevalent than other breast cancer subtypes regarding the lack of calcification, suggesting a relationship between TNBC and the absence of calcification[21, 24-26]. Inconsistent with the findings of Wu Tong et al.[19, 27], Wang Kangjian et al.'s study showed that the proportion of noticeable hypoechoic lesions in tumors of the TN subtype was 23.91%, indicating that the proportion of obvious hypoecho in TNBC was higher than that in non-TNBC[28]. While only 65.31% of non-TNBC lesions lacked posterior acoustic features, Wang Kangjian et al. found that 73.91% of TNBC lesions typically lacked these aspects. This contrasts with the previous study, which found that the posterior acoustic features in TNBC lesions were often absent [28]. Another study, which indicated that TNBC is unlikely to exhibit posterior acoustic attenuating, found no statistically significant difference between the TNBC group and the non-TNBC group regarding the proportion of post-acoustic echo alterations[26]. Li Jiawei et al.'s analysis of data from 104 cases of TNBC and 456 examples of non-TNBC revealed additional confirmation of the independent ultrasonic characteristics of TNBC, including regular shape, absence of needle-like/angular edges, posterior acoustic enhancement, and lack of calcification[17].

2.2 Color doppler flow imaging (CDFI)

The mainstay of non-invasive methods for evaluating the vascular system of breast lesions is color Doppler flow imaging (CDFI). Most studies employed Adler's classification[29] to measure breast cancer blood richness using CDFI, with grade 0-I being identified as less blood flow and grade II-III as rich blood flow. Previous studies have demonstrated that in TNBC, the blood flow detected by CDFI is mainly grade 0-I [18, 19]; that is, the blood flow of TNBC is less. Similarly, in the study of Wang Kangjian et al., 21.74% of TNBC lesions showed avascular blood flow[28]. In contrast, there were only 2 cases of hypoperfusion in non-TNBC lesions. Overall, TNBC lesions have a higher incidence of anovascular type. However, the researchers suggested that TNBC has a lot of blood flow in two recent investigations that were published in 2023[30, 31]. According to Kurt S A et al., TNBC was dominated by grade II-III blood flow (27/29, 93.1%)[31].

In summary, for TNBC, common findings in conventional ultrasound images include large tumor size, distinct boundaries, regular morphology (with microlobulated structure), absence of microcalcification, and marked hypoecho. TNBC is more likely than other subtypes to have no posterior characteristics and posterior acoustic enhancement, while rear-echo attenuation is less frequent. TNBC was more frequently present when there was little or no blood flow, according to CDFI.

3. Ultrasound Elastography Features of TNBC

Strain elastography (SE), shear wave elastography (SWE), and acoustic radiation force impulse (ARFI) are three types of ultrasound elastography that provide details on the tissue stiffness of breast masses and aid in the diagnosis of breast cancer. Better resolution decreased observer-to-observer variability, and less stress concentration and pre-imaging area slippage are all advantages of ARFI imaging. SWE features low operator reliance, no stress concentration, and good observer consistency[32]. Additionally, SWE and ARFI have good character, making them popular tools for researching the elasticity data of various molecular subtypes of breast cancer.

3.1 Shear wave elastography (SWE)

SWE creates real-time, quantitative shear wave velocity images using acoustic radiation. The speed of shear wave propagation is proportional to Young's modulus (kPa), a measure of tissue shear resistance currently used to measure lesion elasticity quantitatively and is highly reproducible.

Chang J M et al.' [33] analysis of the stiffness of 337 invasive breast cancer cases and 64 TN cases revealed an independent relationship between tumor hardness as measured by SWE and the aggressive subtype of breast cancer. According to Chang J M et al.'s research, of the four subtypes of tumors, TN tumors had the highest mean stiffness value (Emean) (165.8 kPa±48.5), which was significantly more significant than the value for er-positive tumors (136.9 kPa±57.2, P 0.0001). Similarly, TNBC had a larger Emean in both 3D and 2D SWE in the study by Kang H J et al. [34]. However, the outcomes of multivariate analysis were not statistically significant. However, the research results limited to stage T1 (≤2 cm) breast cancer revealed that TNBC was an independent factor linked to greater Emean in both 3D and 2D SWE. All signs point to TNBC having a higher Emean in SWE, meaning its tissue is more rigid. The maximum lesion hardness (Emax), minimum lesion hardness (Emin), mean lesion hardness (Emean), standard deviation (SD), and ratio to normal gland (Eratio) were all compared between the TNBC group (42 instances) and the non-TNBC group (120 cases) in a 2021 study [21]. Emean, Emax, and Eratio values in the TNBC group were much lower than those in the non-TNBC group, and these differences were statistically significant (P <0.05), according to the results[21]. According to a study, TNBC appears primarily red on elastography, and the lesion morphology is regular and heterogeneous. TNBC has a lower hardness than other aggressive breast cancers. In addition, TNBC lesions are softer than the surrounding fat[35].

However, it has been reported that the molecular subtype of the tumor is not independently associated with tumor stiffness[36, 37]. Retrospective examination of 166 instances of breast cancer by Youk J H et al.[36] revealed that TN tumor subtypes were connected to Emean using univariate logistic regression analysis. The immunohistochemical features of the tumor were not independently linked with Emean, according to multivariate logistic regression. Similar findings were made by Ganau S et al. [37], who prospectively examined 216 cases of aggressive breast cancer in 190 women with histological confirmation and assessed the relationship between SWE Emax and Emean and tumor subtype. They discovered no statistically significant connection between elastic parameters and molecular subtypes.

3.2 Acoustic radiation force impulse (ARFI)

By using brief, intense acoustic pulses to show the longitudinal displacement of tissue components, the Acoustic Radiation Force Impulse (ARFI) qualitatively creates a static map of the relative stiffness of tissue inside a small box. Virtual touch tissue imaging (VTI) and virtual touch tissue quantification (VTQ) identify tissue elasticity.

TNBC had the highest mean shear wave velocity (SWVmean) (7.36 m/s ±1.83) compared to other aggressive breast cancers, and the qualitative VTI score measurement was also higher than that of ER+ tumors and HER2+ tumors, according to Wan Jing et al.[38], who evaluated the mean tumor hardness of 234 breast cancers with ARFI. High VTI score, ambiguous VTI boundary, and SWV ≥3.51 m/s were reported to be substantially linked with TNBC by Pu Huan et al.[39]. In contrast, Chen Weiping et al. [40] in 2021 said that the SWV maximum (SWVmax), minimum (SWVmin), and mean (SWVmean) in the TNBC group were significantly lower than those in the HER2+ breast cancer group (p<0.001) in VTQ imaging. This study included 28 TNBC patients and 32 patients with HER2+ breast cancer. Similar findings were found in Cheng Chunxia et al.'s study [41], where SWVmin was discovered to be an independent influencing factor of TNBC (OR=1.682), and the results of the VTI examination revealed that SWV max, SWVmean, and SWVmin in the TNBC group were lower than those in the non-TNBC

group. The differences were statistically significant (all P<0.05). Different from the previous studies, WU Fang et al.[42] used VTIQ technology to observe the elastic characteristics of the marginal band, central region, and surrounding tissues of 101 breast cancer masses and measured their SWVmax. The results showed that the triple-negative type was mostly homogeneous, the elastic characteristics of the Luminal type were mainly marginal dominance, and the human epidermal growth factor receptor 2 (HER-2) overexpression type was primarily the central dominant type (P<0.05). In addition, the authors also found significant differences in SWVmax in the marginal zone of tumors of each molecular subtype, with triple-negative (n=13) <HER-2 overexpression (n=18) < Luminal B (n=59) < Luminal A (n=11) (P<0.05). According to many studies, the average elastic hardness of tumors is influenced by parameters such as palpable anomalies, tumor size, lymphovascular invasion, and histological grade [36, 43, 44]. Chang J M et al. reported that tumor size and histological grade were independent influencing factors of the mean stiffness of tumors.[33], as well as Denis M et al.[45]. This implies that removing potential sources of confusion within subgroups will aid in establishing a more precise correlation between tumor subtypes and mean elasticity values.

In conclusion, the research findings on the elastic characteristics of SWE and ARFI of TNBC still need to be determined. Tum size, lymphovascular invasion, and histological grade may influence them. To determine the molecular subtype of breast cancer, several studies have discovered that the elastic characteristic of the tumor periphery is more valuable than the center region. The research on the elastic properties of TNBC needs to be confirmed by numerous prospective and multicenter investigations; however, as there are currently few studies in this field, special attention should be paid to controlling for differences across groups to increase the reliability of the findings.

4. CEUS Features of TNBC

Contrast-enhanced ultrasound (CEUS) is a commonly used adjuvant diagnostic technique for breast cancer, using pure blood pool imaging to visualize small blood vessels and microvessels inside tumors. Contrast agents with microbubbles are used to increase vascular signaling on ultrasonography, which improves the assessment of the presence and morphology of breast tumor microvessels[46]. Several studies have shown that TNBC exhibits high enhancement, morphological regularity, and clear boundaries in CEUS images, and the enhanced range is not significantly expanded [47-49]. However, a study[50] also discovered that TNBC had additional characteristics on CEUS images, such as evident internal filling defects and perforated arteries, compared to non-TNBCs, and the vascular architecture was primarily branching. Recent research by Cheng Chunxia et al.[41], support earlier findings. On CEUS and sonoelastography, they compared the performance of TNBC and non-TNBC, and they discovered that TNBC frequently displayed distinct boundaries after enhancement, internal filling defects, and an uneven distribution of contrast media, whereas enlargement was uncommon. Additionally, it was discovered that internal filling defects after enhancement and clear boundaries were independent influencing factors impacting TNBC (OR=3.087 and 2.119, P<0.05).

The differences in CEUS quantitative parameters across breast tumors with various molecular types, on the other hand, have been the subject of investigation in recent years. In a retrospective analysis of the qualitative and quantitative differences between TNBC and non-TNBC ultrasound in 2016, Zhang Y et al.[51] the TNBC group frequently showed distinct borders (66.7%) and hyper-enhancement perfusion (73.3%). The peak intensity (PI) of the TNBC group was often higher than that of the non-TNBC group, and the sharpness of the most vital half-point of perfusion was usually lower than that of the non-TNBC group, according to the study of quantitative data. According to Zuo Wensi et al.'s research [48], luminal epithelial breast cancer's PI was lower than that of TNBC and HER-2 overexpressed breast cancer. These findings have some predictive relevance for TNBC and HER-2 overexpressed breast cancer. However, for several molecular kinds of breast cancer lesions, there was no statistically significant difference between metrics like time to peak (TTP), mean transit time (MTT), area under the curve (AUC), and wash-in slope (WIS) (P > 0.05). Similar findings were made by Liang Xingyu et al. [52] in their study, which discovered that there was no significant difference between TNBC's perfusion parameters. Additionally, they state that enhanced border clarity can achieve 90.5% sensitivity, 80.0% specificity, and 91.9% diagnostic accuracy for identifying TNBC. In contrast, there were differences in AUC, TTP, and PI amongst the four subtypes in the study of Wen Baojie et al.[53]. (P < 0.05). Remarkably, the H2 subtype's AUC (535.7 ±222.0, P = 0.007) and the TN subtype's (496.6± 254.7, P = 0.019) were both noticeably higher than the LA subtype's (305.1 ±188.4). Furthermore, the LA subtype's PI (4.7 ±2.3) was considerably lower than those of the LB subtype (6.6 ± 2.3, P = 0.027), H2 subtype (7.4 ±2.2, P = 0.005), and TN subtype (6.9 ± 2.6, P = 0.014). These study results demonstrate that TNBC has much greater PI and AUC than LA subtype breast cancer, allowing for easier differentiation between the two subtypes.

In summary, TNBC frequently exhibited high enhancement, regular morphology, and clear boundaries in CEUS images. The enhanced range was not significantly expanded, and internal filling defects and perforating vessels were visible. Among them, the clear edge after enhancement has an excellent diagnostic value for TNBC. In addition, the CEUS manifestations of TNBC and HER-2 overexpressed breast cancer were similar, and both PI and AUC were significantly higher than LA subtypes. TNBC may be distinguished from several molecular subtypes of breast cancer using CEUS.

5. Superb Microvascular Imaging (SMI) Features of TNBC

Superb Microvascular Imaging (SMI) is a new ultrasound medical technology specifically designed to display images of microvessels. It employs adaptive algorithms to suppress clutter signals, reduce motion artifacts, and maintain the encoding of low blood flow velocities to provide more accurate blood flow imaging without using contrast agents. Previous studies have shown that benign and malignant breast lesions differ in using SMI to measure breast lesions' vascular index (VI), and malignant lesions have higher VI values than benign lesions[54, 55]. Diagnostic accuracy for breast masses can be increased by combining VI values with traditional B-mode ultrasonography[13, 56, 57]. Studies that explored the connection between SMI and molecular subtypes of breast cancer have also been conducted in recent years[31, 58].

In 225 cases with mass-type aggressive breast cancer, Zhang Xiaoyan et al.'s study[58] analyzed the relationship between primary tumor VI and molecular subtypes in SMI tests. They discovered that the TNBC could be predicted with a sensitivity of 30.0%, specificity of 90.3%, and an AUC of 0.60 when the VI cut-off was set at 16.4%. Overall, they think VI and the molecular subtype of aggressive breast cancer are related, however, its predictive role is limited. The latest study by Kurt S A et al.[31] analyzed the microvascular structure and VI values of 210 breast cancers using SMI. They proposed a new morphological model to assess the microvascular system and compared VI and the model's effectiveness in predicting molecular subtypes of breast cancer. This model divides microvascular structures into six types: type I, no signal; type II, permeable; type III, rim-shaped; type IV, pointed/linear/regional; type V, wheel-like; type VI, irregular signal. The results showed no significant difference between VI and IHC subtypes. In contrast, this new microvascular classification model is more valuable in predicting molecular subtypes of breast cancer, particularly in HER2 overexpression and TNBC subtypes, dominated by wheel-like signals. Rim-shaped, permeable, and regional types are more common in luminal breast cancer.

In conclusion, the current study shows that SMI has a specific role in predicting TNBC, and the predictive value of VI value is limited. Still, the microvascular classification model detected by SMI proposes a novel approach for predicting the molecular subtype of breast cancer. However, currently, there are few studies on the correlation between SMI and molecular subtypes of breast cancer, and much more study is required to explore the ultrasound performance of TNBC on SMI in the future.

6. 3D-US Features of TNBC

6.1 Automated breast volume scanner (ABVS)

Automated breast volume scanner (ABVS) systems are 3D ultrasound imaging systems that can be automatically scanned, multi-plane reconstructed, and digitally stored. The advantages include less reliance on the operator, good repeatability, and reconstructable coronal surfaces, which offer more diagnostic details than traditional ultrasound.

Zheng Fengyang et al.[59] TNBC has some particular predictors by studying and analyzing the ABVS imaging characteristics of 303 breast cancers, including 47 cases of TNBC. These predictors included no retraction (OR = 5.884), posterior acoustic enhancement (OR = 5.255, P < 0.001), no echoic halo (OR = 4.138, P = 0.002), and no calcification (OR = 3.363, P = 0.001). In particular, the study also discovered that in the triple-negative subtype, retraction was the strongest independent predictor in its absence (OR = 4.875, P < 0.001). In addition, several other studies[40, 60, 61] have yielded the same results, with TNBC rarely showing retraction on the coronal plane. In addition, according to Chen Weiping et al.[40]. On ultrasound, TNBC is more likely to exhibit posterior echo enhancement, morphological regularity (round/oval), and smooth edges. More specifically, morphological regularity was an independent predictor of TNBC (p = 0.04, odds ratio [OR] = 4.479).

The performance of TNBC on ABVS is comparable to that of conventional ultrasound, and ABVS

provides another crucial piece of information, namely that TNBC rarely exhibits retraction on the coronal plane. In short, in addition to showing conventional ultrasound signs, ABVS can also detect the retraction of the coronal plane that cannot be demonstrated by traditional ultrasound.

6.2 Three-dimensional power doppler ultrasound (3D-PDUS)

Quantitative measurement of vascular features by three-dimensional power doppler ultrasound (3d-PDUS) is a new and refined method for evaluating tumor vascular status. The ability to detect low-velocity blood flow signals at the microvascular level is significantly more sensitive than CDFI[62].

In the Chang Y C et al. study[63], researchers compared 3d-PDUS vascular characteristics of 102 breast cancers, including number of vascular trees (NV), most extended path length (LPL), total vessel length (TVL), number of bifurcations (NB), distance metric (DM), inflection count metric (ICM), vessel diameter (VD), and vessel-to-volume ratio (VVR). The findings demonstrated that except VD, TNBC and her2-overexpressed vascular characteristics were significantly higher than luminal types. However, the difference in all vascular features between the HER2-overexpressed and TN groups was insignificant. This study's previously mentioned 3d-PDUS vascular characteristics could not distinguish between TNBC and HER2-overexpressed breast cancer.

6.3 Three-dimensional color power angiography (3D-CPA)

Three-dimensional color power angiography (3D-CPA) is a newer technique combining 3D grayscale ultrasound and energy Doppler technology, which has high sensitivity and no angle dependence for detecting small, low-velocity blood flow and detailed information about blood flow in and around the tumor.

QI Bing et al. [64] conducted a 3D-US study on 120 breast cancer cases with different molecular types. The results showed that the 3D grayscale of TNBC was similar to conventional ultrasounds, usually offering a lump with regular boundaries and precise edges and slightly enhanced posterior echo. In 3D-CPA, breast cancers with different molecular types had significant differences in 3D-US blood flow volume parameters such as mean gray (MG), mean power (MP), ratio (R), and vascularization flow index (VFI) ($P<0.05$). In addition, TNBC was the lowest expressed in MG, MP, R, and VFI, while HER-2 overexpressed breast cancer was the highest expressed on these indicators. Among them, the level of MG reflects the heterogeneity of the internal echo of the mass, and the lower the MG, the lower the heterogeneity of its internal echo, that is, the more uniform and consistent. The most deficient MG of TNBC represents that its internal echo is uniform and consistent, similar to the rear echo enhancement seen by TNBC on conventional ultrasound, which can be explained by more TN-type tumor cells and fewer interstitial components. In addition, the MP, R, and VFI values all reflect the blood perfusion inside the tumor. The results of this study show that TNBC is not rich in blood flow, whereas HER-2 overexpression breast cancer presents with highly heterogeneous internal echoes and profuse blood flow.

In summary, in 3D-US, ABVS can reconstruct the coronal plane, and the absence of the coronal retraction phenomenon has excellent value in predicting TNBC. According to the available research, there is no significant difference between the characteristics of 3d-PDUS vessels of TNBC and HER2-enriched type, but both are noticeably higher than that of the luminal type. TNBC had the lowest MG, meaning its internal echo was homogeneous and consistent. It also had the lowest MP, R, and VFI values, which suggested less blood perfusion, according to 3D-CPA. However, there aren't many on the correlation between 3d-PDUS, 3D-CPA, and molecular subtypes of breast cancer, and further multicenter and large-sample studies are still required.

7. Summary and Outlook

TNBC has specific ultrasound characteristics, and different ultrasound diagnostic technologies have unique advantages and disadvantages. The use of conventional ultrasound combined with multimodal ultrasound diagnosis technology can help improve the diagnostic performance of TNBC, which is of great significance for improving the prognosis of this population.

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