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Imaging features of automated breast volume scanner: Correlation with molecular subtypes of breast cancer

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ABSTRACT

Objectives: To investigate the correlation between the imaging features obtained by an automated breast volume scanner (ABVS) and molecular subtypes of breast cancer.
Methods: We examined 303 malignant breast tumours by ABVS for specific imaging features and by immunohistochemical analysis to determine the molecular subtype. ABVS imaging features, including retraction phenomenon, shape, margins, echogenicity, post-acoustic features, echogenic halo, and calcifications were analysed by univariate and multivariate logistic regression analyses to determine the significant predictive factors of the molecular subtypes.
Results: By univariate logistic regression analysis, the predictive factors of the Luminal-A subtype (n = 128) were retraction phenomenon (odds ratio [OR] = 10.188), post-acoustic shadowing (OR = 5.112), and echogenic halo (OR = 3.263, $P < 0.001$). The predictive factors of the Human-epidermal-growth-factor-receptor-2-amplified subtype (n = 39) were calcifications (OR = 6.210), absence of retraction phenomenon (OR = 4.375), non-mass lesions (OR = 4.286, $P < 0.001$), absence of echogenic halo (OR = 3.851, $P = 0.035$), and post-acoustic enhancement (OR = 3.641, $P = 0.008$). The predictors for the Triple-Negative subtype (n = 47) were absence of retraction phenomenon (OR = 5.884), post-acoustic enhancement (OR = 5.255, $P < 0.001$), absence of echogenic halo (OR = 4.138, $P = 0.002$), and absence of calcifications (OR = 3.363, $P = 0.001$). Predictors for the Luminal-B subtype (n = 89) had a relatively lower association (OR $\leq$ 2.328). By multivariate logistic regression analysis, retraction phenomenon was the strongest independent predictor for the Luminal-A subtype (OR = 9.063, $P<0.001$) when present and for the Triple-Negative subtype (OR = 4.875, $P<0.001$) when absent.
Conclusions: ABVS imaging features, especially retraction phenomenon, have a strong correlation with the molecular subtypes, expanding the scope of ultrasound in identifying breast cancer subtypes with confidence.

1. Introduction

Breast cancer is the most common malignancy in women worldwide and is a leading cause of cancer death among women [1]. Breast cancer is a heterogeneous disease, resulting in varied therapeutic responses and outcomes. Over the past two decades, molecular subtypes of breast cancer have been identified, extending our understanding of the heterogeneity of this disease and aiding significantly in treatment selection, prognosis prediction, and disease-course monitoring [2–5]. The four main subtypes are Luminal A (LA), Luminal B (LB), Human epidermal growth factor receptor 2-amplified (HER2), and Triple Negative (TN). Generally, the LA subtype, the most common one, responds well to endocrine therapy and has the best prognosis of the four subtypes, while LB patients can benefit from neoadjuvant chemotherapy. The HER2 subtype behaves more aggressively but can have a good outcome when treated with trastuzumab. The TN subtype has a poor clinical outcome but a greater likelihood of complete response to neoadjuvant chemotherapy [4–7]. Hence, the ability to identify different molecular subtypes of breast cancer preoperatively can be of great significance in clinical practice. Although core needle biopsy is the

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gold standard for pathological assessment [8], it is invasive and may not be an option in certain circumstances. Accordingly, a simple and noninvasive method of diagnosis is needed.

Previous studies have reported that conventional ultrasonography (US), a convenient and safe method for diagnosing breast lesions, has the potential to identify molecular subtypes. Several features that can be identified by US, such as post-acoustic features, echogenic halo, calcifications, and margins, have proven to be valuable in differentiating the subtypes [6,9–12]. However, the application of such noninvasive method to pathologic diagnoses is not yet practical clinically and needs more studies to confirm. Besides, conventional US is operator-dependent and, therefore, suffers from a lack of reproducibility, which may lead to inconsistencies between studies. What's more, no single feature characterises the different molecular subtypes satisfactorily [12], the more accurate the diagnostic results are expected to be, the more predictive features are needed.

Automated breast volume scanner (ABVS) is a new three-dimensional (3D) US imaging system that can perform multiplanar reconstruction. With the advantages of automatic scanning and digital storage, ABVS is less operator-dependent than conventional US and, thus, highly reproducible [13]. Although previous studies showed equivalent diagnostic accuracy of ABVS compared with conventional US in differentiating benign and malignant breast lesions, ABVS is a promising modality owing to its advantages of operator-independence and more diagnostic information provided by the reconstructed coronal planes [14,15]. More importantly, retraction phenomenon, a feature that can only be detected on coronal planes, has proved to be a characteristic of breast malignancy with a high specificity (98.3%–100%) [14–16]. Although several studies using 3D US have explored the correlation between this special feature and certain histopathological characteristics of breast cancer [17,18], to our knowledge, no published study has reported its application in differentiating molecular subtypes of breast cancer. Accordingly, this study aims to explore how retraction phenomenon and other ABVS imaging features correlate with the molecular subtypes of breast cancer to find more predictive US features and increase the possibility of noninvasive pathologic diagnoses of breast cancer.

2. Materials and methods

2.1. Patients

This study was approved by the hospital's institutional review board, and informed consents were obtained from all patients. From January 2014 to December 2015, 326 female patients who were diagnosed with breast cancer by surgical pathology were recruited. Preoperative localisation by conventional US was performed for all the patients up to three days before surgery. Subsequently, ABVS examinations were performed on all but 12 patients, who had considerable deformity of the breast or chest. Patients who had received neoadjuvant therapy (n = 8) or who had vague lesions near the areola on ABVS images (n = 6) or lesions with undetermined immunohistochemical results (n = 10) were excluded. After exclusions, 290 female patients (mean age ± standard deviation, 57 ± 12 years; range, 28–88 years) with 303 tumours were enrolled in this study.

2.2. Conventional US localisation and ABVS examinations

The localisation of breast lesions was performed by an experienced technologist using an Acuson S2000 ultrasound unit (Siemens Medical Solutions, Mountain View, CA, USA) equipped with an 18L6 (6–18 MHz bandwidth) linear array transducer. Lesions were marked on the skin surface with patients in the supine position and arms perpendicular to the body, imitating the surgical position. Subsequently, ABVS examinations were performed by the same technologist using an ABVS system integrated with the Acuson S2000. The technical aspects of the ABVS imaging system have previously been described in detail [16]. Patients laid in either a supine or a lateral position according to the location of the marked lesions. Appropriate pressure was exerted on the scanner to maximally cover the breast. Scanning orientations included anterior-posterior, lateral, medial, or other non-standardized orientations. One to four scanning cycles were performed for each breast to cover all the marked lesions. After acquisition, the data were transmitted to a 3D ABVS workstation and reconstructed in multiple orientations.

2.3. Histopathological analysis

The estrogen-receptor (ER), progesterone-receptor (PR), human epidermal growth factor receptor 2 (HER-2), and Ki-67 statuses of all patients were determined by immunohistochemical analysis as part of the routine pathologic assessment for clinical management. ER and PR statuses were defined as positive when more than 1% of the tumour cells showed positive nuclear staining for either ER or PR, respectively [19]. HER-2 status was graded as 0, 1+, 2+, and 3+ and was considered negative when the grade was 0 or 1+, positive when 3+, and borderline when 2+. Fluorescence in situ hybridisation was performed on all HER-2 2+ tumours to make a final determination on status. The HER-2 gene was considered amplified if the gene-to-chromosome ratio was more than 2.0 [20]. Histological grade was classified as 1, 2, or 3 according to the Elston and Ellis grading system. For the purpose of this study, grades 1 and 2 were considered lower grade, whereas grade 3 was considered higher grade [18]. Tumour size was determined by the maximum diameter measured on fresh specimens after surgical resection. Molecular subtypes were categorised according to the St. Gallen Consensus 2011 [21], as follows:

1 LA subtype: ER and/or PR positive (hormone-receptor [HR] positive), HER-2 negative, and Ki-67 < 14%;
2 LB subtype: HR positive, HER-2 negative, and Ki–67 ≥ 14%; or HR positive and HER-2 positive;
3 HER2 subtype: HR negative and HER-2 positive; and
4 TN subtype: HR and HER-2 negative.

2.4. Image review and data analysis

Two radiologists who were blinded to the patients' previous imaging data and clinical information reviewed the volume data on an ABVS workstation. They had 7 and 10 years of experience in conventional breast US, and both had more than 1.5 years of experience in ABVS-image interpretation. The lesion type was classified as mass or non-mass. Non-mass lesions were defined as lesions that showed focal heterogeneity distinct from normal breast parenchyma with minimal or no mass effect. Conversely, mass lesions were defined as space-occupying lesions in three orthogonal projections. Retraction phenomenon, a convergence tendency of surrounding tissues towards a breast lesion, was evaluated on the coronal planes as described in detail in our previous study [16]. Other ABVS imaging features were analysed synthetically on three orthogonal planes (axial, coronal, and sagittal) according to the Breast Imaging-Reporting and Data System (BI-RADS) lexicon, including shape (oval, round, or irregular), margins (spiculated, microlobulated, or angular), echogenicity (hypoechoic, isoechoic, hyperechoic, or complex), post-acoustic features (enhancement, shadowing, or no change), echogenic halo, and calcifications. In