Ultrasound in Med. & Biol., Vol. ■, No. ■, pp. 1–9, 2017
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0301-5629/$ - see front matter

http://dx.doi.org/10.1016/j.ultrasmedbio.2017.03.019

● *Original Contribution*

SONOGRAPHIC PHENOTYPES OF MOLECULAR SUBTYPES OF INVASIVE DUCTAL CANCER IN AUTOMATED 3-D BREAST ULTRASOUND

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(*Received* 10 *November* 2016; *revised* 27 *January* 2017; *in final form* 27 *March* 2017)

Abstract—Our aim was to investigate whether Breast Imaging Reporting and Data System—Ultrasound (BI-RADS-US) lexicon descriptors can be used as imaging biomarkers to differentiate molecular subtypes (MS) of invasive ductal carcinoma (IDC) in automated breast ultrasound (ABUS). We included 125 IDCs diagnosed between 2010 and 2014 and imaged with ABUS at two institutes retrospectively. IDCs were classified as luminal A or B, HER2 enriched or triple negative based on reports of histopathologic analysis of surgical specimens. Two breast radiologists characterized all IDCs using the BI-RADS-US lexicon and specific ABUS features. Univariate and multivariate analyses were performed. A multinomial logistic regression model was built to predict the MSs from the imaging characteristics. BI-RADS-US descriptor margins and the retraction phenomenon are significantly associated with MSs (both $p < 0.001$) in both univariate and multivariate analysis. Posterior acoustic features and spiculation pattern severity were only significantly associated in univariate analysis ($p < 0.001$). Luminal A IDCs tend to have more prominent retraction patterns than luminal B IDCs. HER2-enriched and triple-negative IDCs present significantly less retraction than the luminal subtypes. The mean accuracy of MS prediction was 0.406. Overall, several BI-RADS-US descriptors and the coronal retraction phenomenon and spiculation pattern are associated with MSs, but prediction of MSs on ABUS is limited. (E-mail: jan.vanzelst@radboudumc.nl) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Breast neoplasms, Imaging, Ultrasonography, Diagnosis, Cancer, molecular subtypes.**

INTRODUCTION

From gene expression profiling, it is clear that breast cancer is a heterogeneous disease (Perou et al. 2000; Sorlie et al. 2003; van't Veer et al. 2002). Four clinically relevant molecular subtypes (MSs) (luminal A, luminal B, HER2-enriched and triple-negative cancers) have been identified with very different prognoses (Wirapati et al. 2008). These MSs vary in estrogen and progesterone receptor expression, human epidermal growth factor receptor 2 (HER2) status and proliferation indexes such as Ki-67 and the mitotic activity index (MAI) (Aleskandarany et al. 2012). Apart from the prognostic significance, medical treatment of breast cancers is increasingly being tailored to this molecular subclassification (Ha et al. 2015; Grimm et al. 2015). Currently, the MS of a breast cancer can only be determined by surgical resection specimen analysis. Tissue samples obtained by core needle biopsy (CNB) or vacuum-assisted biopsy (VAB) during the diagnostic workup produce the earliest available material for this classification (Bufi et al. 2014; Ha et al. 2015; Mazurowski et al. 2014; Miyake et al. 2014). However, biopsies are vulnerable to sampling error, and this may negatively affect the treatment decision, especially in the era of increasing use of primary systemic therapy over primary surgery (Dekker et al. 2013; Greer et al. 2013; McMahon et al. 1992; Shah et al. 2003). In addition, these sampling errors can significantly increase health care costs of breast cancer diagnosis when repeated testing on hormonal receptors and HER2 status is needed (Chen et al. 2012; Li et al. 2012; Rakha et al. 2014; VandenBussche et al. 2015; Wolff et al. 2013). Breast cancer imaging is readily available in many breast cancer patients from routine

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Conflict of interest disclosure: N. Karssemeijer is a shareholder in Qview Medical Inc. and Matakina Ltd. and is CEO and co-founder of Screenpoint Medical Inc. R. Mann is a speaker for Siemens.

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workup or screening. Thus, determination of imaging phenotypes for prediction or confirmation of the MS might be a non-invasive, low-cost tool in better breast cancer diagnosis and treatment planning.

The use of breast ultrasound (US) has been established in the clinical workup of breast lesions. Automated 3-D breast ultrasound (ABUS) systems are a relatively novel extension of this technique. In contrast to handheld US devices, ABUS obtains 3-D volumes of the entire breast and, hence, allows evaluation of breast lesions in multiple planes. In addition, ABUS enables temporal comparison and batch reading of ultrasound examinations. Hence, the availability of ABUS in clinical practice is increasing.

Several reports indicate that sonographic imaging features from the Breast Imaging Reporting and Data System for US (BI-RADS-US) lexicon are associated with histologic subtype, grade and hormone and HER2 receptor status of breast cancer in handheld ultrasound examinations (Au-Yong et al. 2009; Lamb et al. 2000; Wojcinski et al. 2012). However, the imaging biomarkers for differentiation of MS (Brenton et al. 2005) in ABUS examinations have not been explored. Therefore, the purpose of our study was to investigate whether BI-RADS-US lexicon descriptors and specific ABUS features can be used as imaging biomarkers for non-invasive determination of the MS of breast cancers in ABUS.

METHODS

The use of ABUS examinations in this retrospective study was approved by the institutions' local ethics committees, and the need for informed consent was waived.

ABUS examination

All ABUS scans were acquired with an ACUSON S2000 Automated Breast Volume Scanner (ABVS) (Siemens, Erlangen, Germany). All ABUS examinations were performed by trained technicians. The ABVS acquires 318 transverse 0.5-mm-thick B-mode ultrasound slices with a mechanically driven linear array (14 L5BV) 5- to 14-MHz transducer. These scans form a 3-D volume of 15.4 × 16.8 cm with an depth adjustable up to 6 cm. ABVS systems use pre-defined settings that technicians can select based on a woman's breast cup size (A–D+). Each cup size setting has a specific frequency and focus depth. Technicians were instructed to select the pre-sets that ensure that the pectoral muscle and underlying ribs are seen and the fibroglandular breast tissue is in the focal zone. Radiologists subsequently evaluate the ABUS images on a dedicated multiplanar

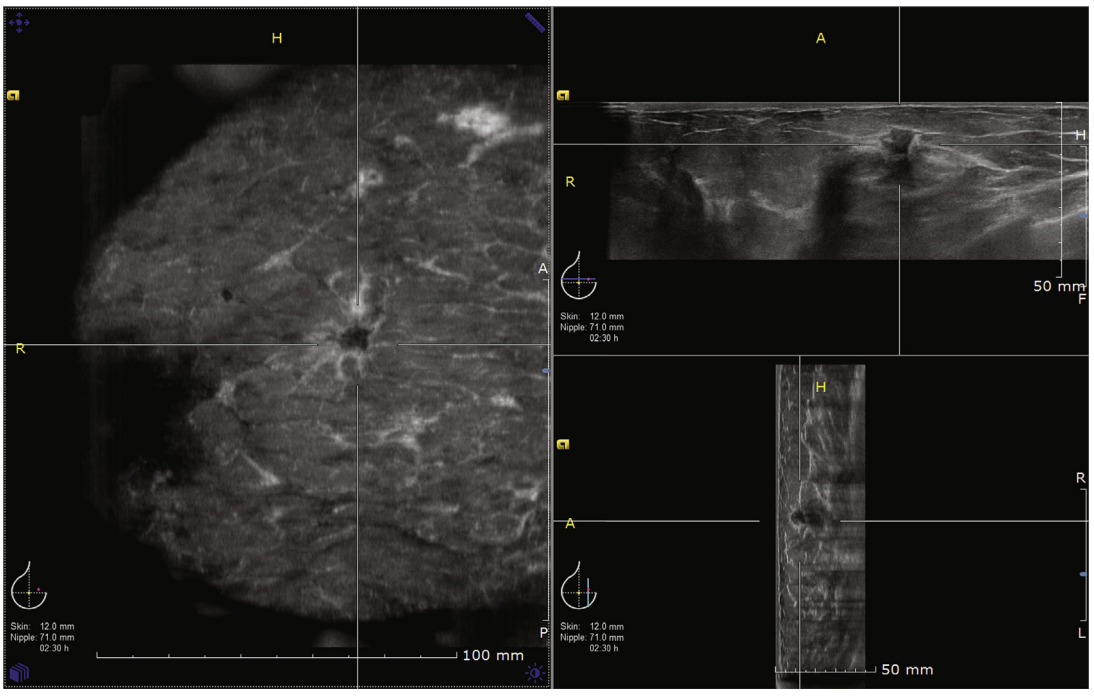

Fig. 1. Example of a luminal A invasive ductal cancer on automated breast ultrasound on a standard multiplanar hanging workstation (left plane: coronal reconstruction, top right plane: transverse acquisitions, bottom right plane: sagittal reconstructions). This invasive ductal cancer is an irregularly shaped, non-parallel oriented, non-circumscribed and hypoechoic lesion that presents with posterior acoustic shadowing and a strong retraction pattern on the coronal plane.

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