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● *Clinical Note*

CLINICOPATHOLOGICAL AND ULTRASONIC FEATURES OF TRIPLE-NEGATIVE BREAST CANCERS: A COMPARISON WITH HORMONE RECEPTOR-POSITIVE/ HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2-NEGATIVE BREAST CANCERS

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Abstract—The purpose of this study was to analyze the clinicopathological and ultrasound characteristics of triple-negative breast cancers (TNBCs) and compare these findings with those for hormone receptor-positive (HR-positive)/human epidermal growth factor receptor-2-negative (HER-2-negative) tumors. Seventy-five TNBCs and 135 HR-positive/HER-2-negative breast cancers were reviewed. Data from conventional ultrasound, Doppler vascularity and elastography were included in the analysis. TNBCs had a higher histologic grade and Ki-67 level. On ultrasound, TNBCs often appeared as microlobulated, markedly hypo-echoic masses with an abrupt interface boundary, posterior acoustic enhancement, absence of calcifications and more characteristics of surrounding tissue. Results from multivariate regression analysis revealed that margin, posterior acoustic features and surrounding tissue features of tumors were independent predictive factors in differentiating TNBCs from HR-positive/HER-2-negative tumors. Our results suggest that a thorough evaluation of sonographic findings might be useful in discriminating between TNBCs and HR-positive/HER-2-negative tumors, which may provide accurate evidence for clinical early diagnosis. (E-mail: jwtian2004@163.com)

Key Words: **Triple-negative breast cancer, Estrogen receptor, Progesterone receptor, Ultrasound, Diagnosis.**

INTRODUCTION

Breast cancer remains a major public health issue. It represents the most frequently diagnosed cancer in women throughout the world, and its incidence is rapidly rising in most countries. With a mortality rate of some 458,000 people per year, the impact of breast cancer on women's health in both developed and developing countries can be appreciated (Ferlay et al. 2010). Therefore, early diagnosis and treatment of breast cancer are extremely important. Perou et al. (2000) defined the molecular subtypes of breast cancer, which were distinguished on the basis of expression of three different biomarkers, including estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2). Currently, this immunohistochemistry (IHC)-based molecular classification is closely related to prognosis of breast cancer and provides a standard method for choosing the most effective treatments in breast cancer patients. ER signaling is necessary for the proliferation of cancer cells (Russo and Russo 2006), which are responsive to endocrine therapies, such as tamoxifen. Expression of ER is associated with better disease-free survival and overall survival. PR is regulated by estrogen in mammary tissues and breast cancer cells (Petz et al. 2004), and PR-positive status reflects complete estrogen signaling pathways. Several prior studies (Ravdin et al. 1992) have found that elevated PR levels are significantly correlated with increased probability of response to endocrine therapy in patients with ER-positive tumors. Therefore, ER- and PR-positive (HR-positive) tumors have a better prognosis and long-term survival.

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Among breast cancer subtypes, triple-negative breast cancer (TNBC), in which tumors are negative for ER, PR and HER-2, have a higher rate of distant metastases, especially a higher initial incidence of brain metastases (Dent et al. 2007). TNBCs are usually characterized by onset in young women and dense breast tissues (Tan et al. 2009), and there currently exist no proven effective target therapies and endocrine therapies for TNBCs. Accordingly, this subtype is associated with an increased risk of recurrence and poor prognosis. Thus, accurate identification of the imaging characteristics of TNBCs is particularly critical for its diagnosis, treatment and prognosis. There exist comparisons of imaging findings for TNBCs and non-TNBCs (Choi et al. 2011; Li et al. 2016); however, few studies have included a comprehensive comparison of the ultrasonic features of TNBCs with those of HR-positive/HER-2-negative breast cancers (Boisserie-Lacroix et al. 2013).

The aims of our study were to (i) evaluate the clinicopathological and ultrasonic characteristics of TNBCs using information obtained from conventional ultrasound, Doppler vascularity and elastography in Chinese women, and (ii) compare these findings with those for a group of HR-positive (ER-positive/PR-positive) /HER-2-negative breast cancer patients.

METHODS

Patients

The breast ultrasound images were taken from our prospectively maintained breast tumor database on 230 consecutive patients from January 2012 to June 2016, including 82 women diagnosed with TNBCs and 148 women with HR-positive/HER-2-negative tumors. The exclusion criteria were as follows: (i) receipt of neoadjuvant chemotherapy before ultrasound examination, (ii) special-type tumors (*e.g.,* lymphoma, sarcoma) and (iii) lack of surgical, pathologic and immunopathological data. After these conditions were eliminated, 73 patients with TNBCs (TN group) and 127 patients with HR-positive tumors (HR-positive group) were included in the study. In the TN group, there were 75 lesions in 73 patients: 71 patients with one lesion each and two patients with two lesions each. Within the HR-positive group, there were 135 lesions in 127 patients: 121 patients with one lesion, 4 patients with two lesions and two patients with three lesions. Because this was a retrospective study and all patient information was anonymous, written informed consent was not obtained. The data were obtained from the medical record database of the Second and Third Affiliated Hospitals of Harbin Medical University for both groups. Use of these retrospective materials was approved by the ethics committee of Harbin Medical University.

Breast ultrasound examination

Two professional sonographers, each with 4 y of experience, performed whole-breast ultrasound on all 200 patients, with identical image scanning and storage standards used for all cases. Ultrasound was performed using a 5- to 12-MHz linear-array transducer with a Hitachi Vision 900 system (Hitachi Medical System, Tokyo, Japan) ultrasound unit. During the real-time examination, static images and cine clips were obtained from more than two different standardized longitudinal and transverse views of the target masses, and the maximum diameter of each mass was then measured. Additionally, the color Doppler setting was adjusted according to instructions for the Adler grading method (Adler et al. 1990). Static images and cine clips displaying the most abundant flow signals of lesions were obtained, and the velocity within the largest-diameter vessel was then measured. Ultrasound strain elastography was also performed in this study. Images were obtained by applying repetitive light pressure on the skin superior to the breast lesion two or three times per second, with the probe positioned perpendicular to the skin when applying pressure. All records were saved in a separate folder and added to our database for subsequent evaluation. Ultrasound images were initially evaluated by two ultrasound experts, each with more than 5 y of experience with breast disease diagnosis, and review of images and recording of information were implemented in accordance with uniform standards. In ambiguous cases, a third expert was consulted to achieve a consensus that would enable an objective result. Both experts were blinded to the histopathological results.

Clinicopathological characteristics

Clinicopathological characteristics included age, tumor location, pathologic type, histologic grade, immunohistochemical markers (ER, PR, HER-2, Ki-67) and axillary nodal metastasis. Tumor locations were classified according to their quadrant location (upper-outer, upper-inner, lower-outer or lower-inner quadrant). Histologically, invasive ductal carcinomas were classified as grade 1 (low), grade 2 (moderate) or grade 3 (high). In this study, grades of 1 and 2 were defined as low grade, and grade 3 was considered high grade. ER and PR positivity was defined as the presence of ≥1% positively stained nuclei in 10 high-power fields (Hammond et al. 2010). HER-2 status was graded as 0, 1 + , 2 + or 3 + based on the criteria provided by Dako (Glostrup), with tumor scores of 0 and 1 + considered negative (Abdollahi and Etemadi 2016). Ki-67 expression was graded as low (<10%) or high (≥10%) (Keam et al. 2011).

Ultrasound features

Conventional ultrasound features were retrospectively analyzed based on Breast Imaging Reporting and