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● *Original Contribution*

AXILLARY LYMPH NODE SONOGRAPHIC FEATURES AND BREAST TUMOR CHARACTERISTICS AS PREDICTORS OF MALIGNANCY: A NOMOGRAM TO PREDICT RISK

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Abstract—The purpose of this study was to build a mathematical model to predict the probability of axillary lymph node metastasis based on the ultrasonographic features of axillary lymph nodes and the tumor characteristics. We included 74 patients (75 axillae) with invasive breast cancer who underwent axillary ultrasonography ipsilateral to the tumor and fine-needle aspiration of one selected lymph node. Lymph node pathology results from sentinel lymph node biopsy or surgical dissection were correlated with lymph node ultrasonographic data and with the cytologic findings of fine-needle aspiration. Our mathematical model of prediction risk of lymph node metastasis included only pre-surgical data from logistic regression analysis: lymph node cortical thickness ($p = 0.005$), pre-surgical tumor size ($p = 0.030$), menopausal status ($p = 0.017$), histologic type ($p = 0.034$) and tumor location ($p = 0.011$). The area under the receiver operating characteristic curve of the model was 0.848, reflecting an excellent discrimination of the model. This nomogram may assist in the choice of the optimal axillary approach. (E-mail: pakissue@gmail.com) © 2017 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Breast cancer, Axillary ultrasound, Lymph node ultrasound features, Breast tumor characteristics, Fine-needle aspiration, Axillary lymph node metastasis, Nomogram, Statistical model.**

INTRODUCTION

The lymph node status of the axilla is one of the most important prognostic factors in breast cancer staging (Carter et al. 1989). Since the 1990s, sentinel lymph node biopsy has been the primary approach to axillary lymph node examination in patients with breast tumors (Giuliano et al. 1994). Lately, with the development of adjuvant therapies, interest has increased in investigating clinical factors that can predict the risk of axillary metastases in breast cancer patients.

Ultrasonography is used in some centers in the initial evaluation of the axilla in breast cancer patients, especially because ultrasonography is a widely accessible method that permits the guidance of biopsies. Many studies have investigated the ultrasonographic findings that may be associated with lymph node metastases (Bedi et al. 2008; Mainiero 2010). Several studies have found that ultrasound-guided fine-needle aspiration (FNA) has adequate sensitivity and accuracy, excellent specificity and a good positive predictive value (PPV) in detecting lymph node metastases (Bonnema et al. 1997; Houssami et al. 2011; Krishnamurthy et al. 2002; Mainiero et al. 2010; Tahir et al. 2008). Koelliker et al. (2008) reported that performing ultrasound-guided FNA in lymph nodes with normal morphology on ultrasonography could increase sensitivity in detecting metastases, particularly in patients with larger tumors.

Recently, a trial by the American College of Surgeons Oncology Group (ACOSOG) Z0011 (Giuliano et al. 2010) reported no benefit in terms of local control, disease-free interval and overall survival in patients with (i) T1 and T2 tumors and (ii) one or two positive sentinel lymph nodes who underwent either axillary lymph node dissection or no further axillary surgery. These findings resulted in a change in the surgical management of the axillary lymph node in many centers across the globe.

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The role of axillary ultrasound in the pre-operative assessment of patients with breast cancer in the post-Z0011 era is still in doubt.

The SOUND (Sentinel Node versus Observation after Axillary Ultrasound) study, an ongoing study in the European Institute of Oncology of Milan (Gentilini and Veronesi 2012), is testing negative ultrasound or negative fine-needle aspiration of a single doubtful axillary lymph node in patients with tumors <2 cm to address whether it is possible to avoid axillary surgery in patients without clinical and ultrasound suspicion of axillary involvement. This study will likely provide new information on axillary ultrasonography in the staging of patients with breast cancer.

The objective of our study was to build a mathematical model to predict the probability of axillary lymph node metastasis based on the ultrasonographic features of axillary lymph nodes and the tumor characteristics associated with malignancy in our study. Furthermore, we evaluated the value of ultrasonography and FNA in our population. Our secondary objective was to analyze whether, depending on tumor characteristics, lymph nodes that exhibited no change on ultrasonography could have metastatic involvement.

METHODS

Study design and patient selection

This diagnostic test study was conducted at the Radiology Institute and at the Cancer Institute of São Paulo State, both institutes of the Clinics Hospital, University of São Paulo Medical School [Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - HC-FMUSP], the largest public hospital in Brazil, integrated into Brazil's Unified Health System SUS (Sistema Único de Saúde [SUS]). This study was approved by the institution's ethics committee in December 2011. The study included 74 consecutive patients (75 axillas) diagnosed with invasive breast cancer between April 2012 and April 2014. After signing an informed consent form, all patients underwent ultrasonographic evaluation of the axilla ipsilateral to the tumor and FNA of a lymph node selected by the radiologist.

Patients who had ductal carcinoma *in situ* (DCIS), who had undergone neoadjuvant therapy before the axilla evaluation or who had a personal history of breast cancer were excluded.

Epidemiologic information, such as menopausal status and family history, were collected from electronic medical records, as were physical examination, staging and treatment data. Tumor size at pre-surgical evaluation based on imaging methods, tumor size based on surgical specimen size, tumor location, histologic type, histologic grade, nuclear grade, hormonal receptors and molecular classification were also obtained from the patients' electronic medical records.

Examination technique, characterization and selection of axillary lymph nodes

The evaluation of the axilla and FNA of the axillary lymph nodes were performed by a radiologist specializing in breast radiology with at least 2 y of experience or a radiology resident under the supervision of an experienced breast radiologist. The axilla was evaluated with high-frequency transducers using the GE Voluson 730 Pro (Tiefenbach, Austria), GE Logiq E9 (Wauwatosa, WI, USA) and Ultrasonix Sonix 01 (Burnaby, BC, Canada) ultrasound machines.

Axillary levels I, II and III were examined in two orthogonal axes, from the base of the axilla to the axillary fossa and from the posterior axillary line to the medial region of the pectoral muscles. The axillary levels were defined as follows: level I lymph nodes were lateral and inferior to the pectoralis minor muscle, level II lymph nodes were posterior to the pectoralis minor and level III lymph nodes were medial to the pectoralis minor.

After analysis of the axilla, the radiologist classified the lymph node as normal or suspicious. The following data were collected for lymph nodes: shape (oval, round or lobed), cortical thickening of the lymph node (without thickening, diffuse and symmetric thickening or asymmetric thickening), fatty hilum (preserved, partially obliterated or completely obliterated), dimensions (major and minor axes) and cortical thickness (measured in mm in the thickest portion of the cortex).

The criteria used to define a lymph node as suspicious included diffuse cortical thickening (≥3 mm); asymmetric cortical thickening (any measurement of cortical thickness); partial or complete obliteration of the fatty hilum; and rounded (major axes/minor axes <2) or lobed morphology (Abe et al. 2013; Alvarez et al. 2006; Koelliker et al. 2008; Lee et al. 2013; Mainiero et al. 2010; Vassallo et al. 1992). If one of these features was present, the lymph node was classified as suspicious. No data were collected on lymph node vascularity with Doppler.

Ultrasound-guided FNA was performed on the most suspicious lymph node chosen by the radiologist. For patients whose lymph nodes did not meet the criteria for suspicion, lymph nodes at the base of the axilla and closest to the breast, the most common location of sentinel lymph nodes, were selected for FNA. Only one lymph node was sampled with FNA for each patient.

Fine-needle aspiration technique and cytologic analysis

After local sterilization, a sample from the thickest portion of the lymph node cortex was acquired for