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● *Original Contribution*

CONTRAST-ENHANCED ULTRASOUND-GUIDED FINE-NEEDLE ASPIRATION FOR SENTINEL LYMPH NODE BIOPSY IN EARLY-STAGE BREAST CANCER

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Abstract—The purpose of this study was to assess whether translymphatic contrast-enhanced ultrasound (CEUS) combined with fine-needle aspiration (FNA) can be used pre-operatively to assess the status of axillary lymph nodes in early-stage breast cancer patients. Furthermore, we wanted to determine whether this less invasive method could potentially be a pre-operative surgical strategy. One hundred sixty-four sentinel lymph nodes (SLNs) were detected by CEUS after intradermal injection of microbubbles in 126 cases. One hundred twenty of 126 cases (95.24%) were accurately diagnosed with the SLN-FNA method. All 6 false-negative cases were due to micrometastasis or macrometastasis. There were no false-positive results after CEUS-guided FNA biopsy based on post-operative histopathological results. In conclusion, translymphatic CEUS combined with SLN-FNA is a less traumatic approach that has high accuracy in the pre-operative evaluation of axillary lymph node status. It might have the potential to be as reliable an indicator for axillary lymph node dissection as SLN biopsy. (E-mail: szdssun@163.com)

Key Words: **Sentinel lymph node, Sentinel lymph node biopsy, Early-stage breast cancer, Fine-needle aspiration cytology, Contrast-enhanced ultrasound.**

INTRODUCTION

Breast cancer is one of the most common malignancies and the leading cause of cancer-related deaths among women worldwide. According to the National Central Cancer Registry of China, in 2011 the incidence of breast cancer was high among Chinese women, at 37.86 cases per 100,000 women, which was greater than the rate for any other cancer among females in that year (Chen et al. 2015; Zhou et al. 2015). The proportion of early breast cancer (EBC) cases continues to increase because of popularized secondary prevention strategies. Hence, greater emphasis should be placed on the comprehensive treatment of EBC, especially the development of individualized and minimally invasive standard treatments.

Axillary lymph node (ALN) status is a major predictor of survival of breast cancer patients and is of great significance in the development of treatment plans and prognosis assessment (Carter et al. 1989; Cianfrocca and Goldstein 2004; Fisher et al. 1993). The sentinel lymph node (SLN) is the first lymph node that receives lymphatic drainage from the tumor and, anatomically, refers to the first lymph node that receives lymphatic drainage of an organ or tissue (Huang et al. 2012; Kuenen-Boumeester et al. 2003). Sentinel lymph node biopsy (SLNB) is recommended for staging of ALN metastases by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) as a preferred procedure compared with traditional ALN dissection (ALND) (Gradishar et al. 2015; Lyman et al. 2005), because the latter carries a greater risk of complications, such as lateral upper limb pain, numbness, edema and movement disorders (Kuehn et al. 2000; Leidenius et al. 2005).

Sentinel lymph node biopsy is a common method for SLN exploration and has the highest accuracy compared with other methods (Lyman et al. 2005). It is difficult to predict whether SLNs are metastatic before resection and intra-operative pathologic diagnosis, which would inevitably prolong the surgery. Moreover, possible false-negative

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intra-operative diagnosis of a frozen section could lead to inappropriate treatment (Geertsema et al. 2010; Hoen et al. 2016; Wong et al. 2015).

Translymphatic contrast-enhanced ultrasound (CEUS) detection of SLNs has garnered much attention in recent years because of the effectiveness of this modality for mapping SLNs (Gkegkes and Iavazzo 2015; Sever et al. 2009). Therefore, the aim of the present study was to determine whether translymphatic CEUS combined with fine-needle aspiration (FNA) is useful for pre-operative diagnosis of ALN metastases in EBC.

METHODS

Clinical data

The study cohort was limited to core needle biopsy (CNB)-confirmed breast cancer inpatients treated at Peking University Shenzhen Hospital from January 2016 to June 2017 who met the following inclusion criteria: (i) breast cancer stage T0–2 scheduled for surgical resection; and (ii) no suspected ALN involvement by clinical palpation and gray-scale ultrasonography, or suspected lymph node with negative FNA/CNB results. A suspected ALN met the criteria of a mean long/short diameter ratio <2.0, eccentric cortex and thickness >3 mm and a thin medulla with no hilum (Alvarez et al. 2006; Choi et al. 2009; Feu et al. 1997). Exclusion criteria included tumors with distant metastases, previous neo-adjuvant chemotherapy or radiotherapy, history of breast tumor excision in the outer upper quadrant, axillary surgery, pregnancy, age <18 y and any other contraindication to CEUS. The protocol for this prospective study was approved by the Institutional Ethics Committee of Peking University Shenzhen Hospital, and informed consent was obtained from each patient.

Instruments, contrast agents and imaging methods

Traditional gray-scale ultrasound detection of a tumor in the breast or axillary region was performed using the MyLab Twice system (Esaote SpA, Genoa, Italy) or the Reasonal 7 system (Mindray Medical International Co., Ltd., China) before translymphatic CEUS. Contrast agents were injected intradermally into the outer upper quadrant near the areola. Gray-scale harmonic imaging was performed using a linear array probe (LA5-10) at a consistent low mechanical index of 0.07 with 2 mL of Sonovue suspension (Bracco Imaging SpA, Naples, Italy) prepared by suspending 59 mg of powder in 5 mL of normal saline and vigorously shaking for 15 s. The injection site in the axilla was gently massaged to promote movement of the contrast agent into the LNs. An ultrasonic probe was used to follow the enhanced lymphatic vessels to the axilla, and the first enhanced lymph node was regarded as the SLN for use as a FNA target. The axillary skin was marked for intra-operative identification. Related ultrasonography and translymphatic CEUS, including injection of contrast agents, were performed by an experienced senior doctor.

FNA procedure and cytologic specimen processing

Cytologic specimens collected with a 22G puncture needle (Hakko, Osaka, Japan) were used during FNA biopsy for SLNs under routine disinfection conditions. Multipoint samples of each SLN were obtained. Significant thickened cortices and areas of inhomogeneity were sufficiently sampled. Specimens were smeared on glass slices within 10 s, soaked in 95% alcohol for more than 15 min and then stained with hematoxylin and eosin. Negative FNA results denoted that no tumor cell was found among all slices of an individual case. Any slice with a tumor cell was defined as FNA positive.

Sentinel lymph node biopsy

Blue dye combined with radionuclide was used for SLNB, which was performed within 48 h after SLN-FNA by two well-trained surgeons during standard breast tumor resection. Patients were injected with ^{99m}Tc-labeled sulfur colloid (Guangzhou Atomic Hightech Co., Guangdong, China) into the subcutaneous tissue near the areola 6 to 18 h pre-operatively. The injection volume was 3–5 mCi. The Gamma Detection System (Neoprobe 2000, Dublin, OH, USA) was used pre-operatively to detect the distribution of hot spots in the axilla, and the gamma count of the injected site was recorded. During the operation, 1 mL of 1% methylene blue (Jiangsu Jumpcan Pharmaceutical Co., Taixing, Jiangsu, China) was subcutaneously injected near the areola. Five to 15 min later, SLNB began. The surgeon found and removed the first blue-stained lymph node through one or more blue-stained lymph tubes during the axillary incision. Finally, the surgeon detected the entire axillary area, searched for the entire ALN radioactive peak and separated those lymph nodes with a radiation intensity greater than the lowest radioactivity of the blue-stained lymph nodes or higher than 10% of the radioactivity peak. The aforementioned LNs were regarded as SLNs (Chao et al. 2016; Chinese Anti-cancer Association for Breast Cancer 2015). The excised SLNs were then frozen for fast pathologic examination. All resected SLNs were fixed with 10% formalin for final pathologic examination. Cytologic and pathologic results were separately diagnosed by an experienced cytopathologist and histopathologist. Histologic pathologic results of paraffin-embedded sections were regarded as the gold standard for final diagnosis.

Statistical methods

SPSS Version 17.0 software (IBM, Armonk, NY, USA) was used for all statistical analyses. The following parameters were used to judge axillary metastatic status of the SLN samples collected by FNA: sensitivity,