BreastCare

Original Article

Breast Care 2015;10:331–335
DOI: 10.1159/000436958

Published online: July 10, 2015

Contrast-Enhanced Color Doppler Ultrasonography for Preoperative Evaluation of Sentinel Lymph Node in Breast Cancer Patients

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Keywords
Ultrasonography · Contrast enhanced · Sentinel lymph node · Breast cancer

Summary
Background: Sentinel lymph node (SLN) biopsy is the standard of care for breast cancer patients with non-palpable axillary lymph nodes. We evaluated the usefulness of contrast-enhanced ultrasonography in preoperative detection of malignant SLNs. **Methods:** 50 patients with breast cancer (median age: 60 years) underwent a color power Doppler ultrasonography with intravenous contrast (Sonovue®) preoperatively, and findings suggestive of metastatic disease to the SLN were documented. The final histopathological report and the radiological preoperative record were compared. Finally, the sensitivity, specificity and diagnostic accuracy of this evolving diagnostic modality were calculated. **Results:** Contrast-enhanced ultrasound scan identified a negative SLN in the axilla of 27 patients and final histopathology was negative for 30 cases in total, so negative predictive value was calculated as 90% and positive predictive value was 75%. Overall sensitivity was 83.33% and specificity was 84.38%. Moreover, the ability of contrast-enhanced ultrasound to differentiate between SLN status was only statistically significantly correlated with the actual final histopathological report ($p < 0.001$), while successful ultrasound prediction was not correlated with any factor. **Conclusions:** SLN status can be evaluated preoperatively using contrast-enhanced color Doppler ultrasonography with high accuracy.

Introduction

Axillary lymph node (ALN) status is the most important prognostic factor for the management of breast cancer patients in the absence of metastatic disease; thus, for some time ALN dissection (ALND) was the standard of care in these patients [1]. However, screening programs and increased awareness on the disease tend to identify more breast cancer patients at an earlier stage in which ALN is negative. Moreover, standard ALND is often accompanied by complications such as lymphedema and neuropathy [2], so less morbid alternative techniques needed to be developed to evaluate lymph node (LN) status in breast cancer patients. During the previous decade it was shown that the sentinel LN biopsy (SLNB) technique could safely replace standard ALND for proper clinical axillary staging [3]. Patients were selected for SLNB when the axilla was negative on clinical examination, but the sensitivity of solely clinical examination is only 30–68% because metastatic LNs are often not palpable and reactive LNs may be mistaken for metastases [4, 5]. Currently, several imaging modalities, such as ultrasonography (U/S), computed tomography (CT), magnetic resonance (MRI) and nuclear medicine techniques are used to detect suspicious ALNs and these patients undergo SLNB. Of these techniques, U/S is the most accurate, easily reproducible, low cost and finally most applicable study in the estimation of ALN status [6]. Conventional gray scale U/S does, however, have some limitations and contrast-enhanced U/S (CEUS) seems to improve the accuracy of the method by making an examination of the LN microcirculation possible [7]. On the other hand, SLNB does not come without disadvantages [8], and if preoperative investigations could narrow down the group of patients that need SLNB, it would be a

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great adjunct in the management of these patients. The aim of our study was to evaluate the usefulness of CEUS in detecting SLNs bearing metastatic disease and evaluating the axillary nodal status of breast cancer patients.

Methods

Over a 3-year period, from January 2010 to January 2013, 50 patients with confirmed breast cancer (median age 60 years) with clinically negative ALNs underwent a color power Doppler U/S with intravenous contrast (Sonovue®). Inclusion criteria consisted of: (1) Tru-cut histopathological or fine-needle aspiration cytological confirmation of malignancy of the breast lesion; and (2) clinically negative ALN status, as evaluated by the same experienced breast Surgeon. All women gave their informed written consent after the procedure of the study had been explained to them. The study was approved by the hospital's Research Ethics Committee. The U/S examination was always performed by the same specialized Radiologist, using a 10L linear probe with a frequency range of 5–12 MHz. Patients initially underwent high-resolution gray scale U/S (B-mode) of the axilla ipsilateral to the breast lesion to determine the morphological features of the LNs. The SLN was detected according to anatomical site, and size and suspicious findings, such as increased thickness or asymmetry, decreased echogeneity or an irregular medullar structure, the lack of a hyperechoic hilum and the prevalence of vertical over horizontal diameter, were documented [9]. The second part of the U/S examination included the intravenous (i.v.) bolus administration of 5 ml of the U/S contrast media based on sulphur hexafluoride (Sonovue®). An i.v. injection of 10 ml sterile solution followed. The enhancement of the LNs was recorded during the first 2 min after the bolus injection of contrast. The assessment criteria included homogeneous or heterogeneous LN enhancement, centrifugal or centripetal enhancement, and late or early wash-in and wash-out enhancement. Multiple parameters are used in CEUS and are mostly related to time that the contrast media interferes with the examined node. The rise time, the time to peak, the mean transit time and dynamic vessel pattern are the major useful values [10]. More and smaller vessels are identifiable in LNs after contrast media application and more accurate delineation of vascular architecture becomes possible [11].

The CEUS procedure was always performed the afternoon before the scheduled operation. The proposed SLN skin site was marked with non-washable ink, and information of exact location (depth from skin, maximum diameter, proximity to muscle) were provided to the surgeon.

All patients underwent SLNB intraoperatively, using blue-dye identification. Methylene blue (2 ml) was injected subdermally into the upper outer border of the areola and 5 min later an axillary skin incision was made and dissection was carried out for SLN excision. If the frozen sections of the SLN were positive, a typical ALND was performed.

The recorded and analyzed parameters included age, primary tumor size (maximum histopathological diameter in cm), LN status (according to TNM/AJCC 7th ed. classification), final histopathological report regarding involvement of the SLN, SLN size (maximum histopathological diameter in cm), tumor grade, estrogen hormone receptor (ER) expression status (positive or negative), human epidermal growth factor receptor (HER-2) expression status (positive or negative), histological tumor type (ductal vs. non-ductal) and CEUS prediction of SLN involvement. If CEUS and final histopathology coincided, 1 extra parameter was calculated and analyzed regarding successful CEUS prediction.

Statistical analysis was conducted using IBM SPSS Statistics v.20 software (IBM Corp, USA). Since not all variables demonstrated normal distribution or equal probabilities, bivariate analysis was conducted using appropriate non-parametric tests (Spearman correlation, Chi square, Mann-Whitney U test, Fischer's exact test or Independent Sample Median Test accordingly) and multivariate analysis was conducted using logistic regression (forward LR methodology with an accepted significance of $p < 0.05$).

Table 1. Specific tumor characteristics

	n	%
Tumor grade		
I	9	18.0
II	31	62.0
III	10	20.0
ER status		
Negative	9	18.0
Positive	41	82.0
HER2 status		
Negative	33	66.0
Positive	17	34.0

ER = estrogen receptor

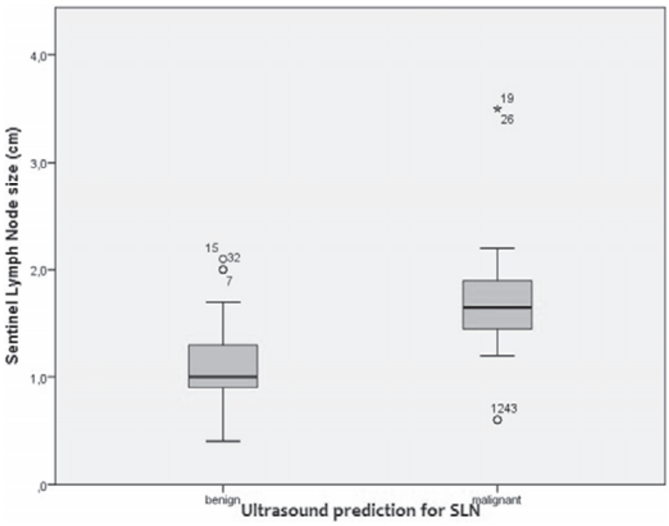

Fig. 1. Contrast-enhanced ultraultrasonography (CEUS) according to sentinel lymph node (SLN) size.

Results

Fifty female patients (median age 60 years, range 37–87 years) with confirmed breast cancer diagnosis were studied preoperatively. The histopathological diagnosis of the primary tumor was ductal infiltrating breast cancer in 45 (90%) patients and non-ductal in 5 (10%). Of the patients with non-ductal breast cancer, 2 had mucinous infiltrating carcinoma, 1 papillary carcinoma and 2 lobular infiltrating carcinoma. The median size of the primary breast carcinoma was 2.1 cm (range 0.1–6.0 cm). LN status in the final histopathological report was: N0 for 32 (64%) patients with LN negative disease; N1 for 10 (20%) patients with 1–3 infiltrated LNs; N2 in 7 (14%) patients with 4–9 LN involvement; and N3 for 1 (2%) patient with more than 10 LNs positive and subclavian node site involvement. SLN median size was 1.3 cm (range 0.4–3.5 cm). Tumor grade and ER and HER2 status are presented in table 1.

CEUS prediction was positive for malignancy SLN in 20 patients (40%) and negative in 30 (60%). Bivariate analysis demonstrated a statistically significant correlation ($p < 0.001$) between

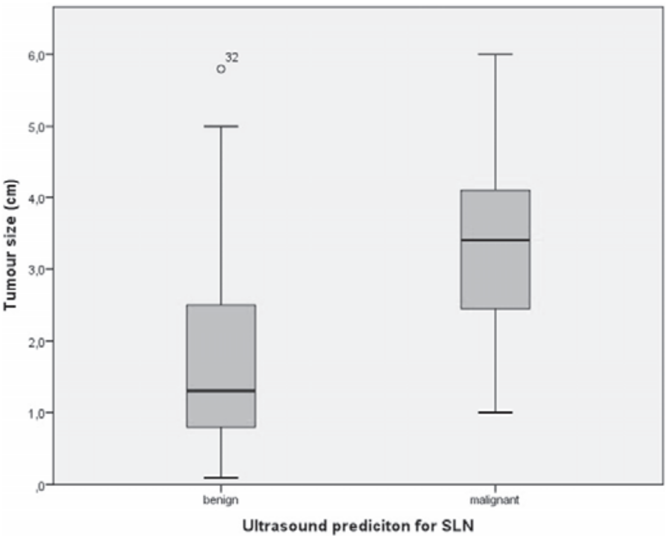

Fig. 2. CEUS prediction results according to primary tumor size.

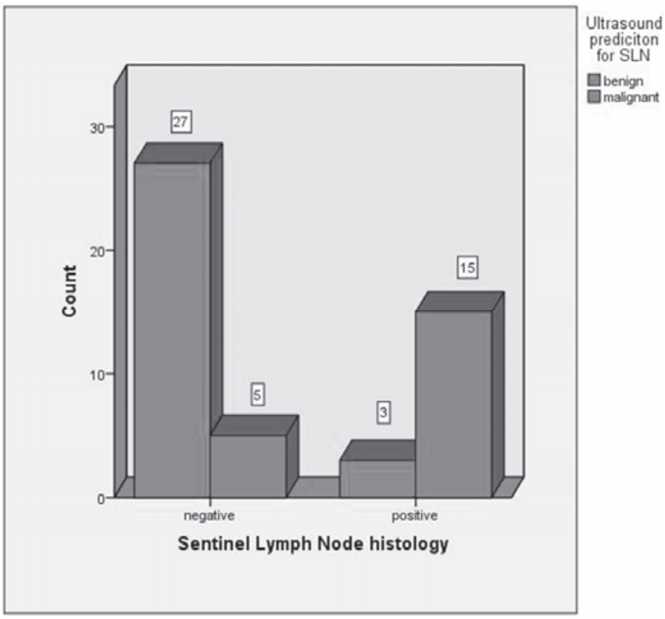

Fig. 3. CEUS preoperative diagnosis and final SLN histopathological report.

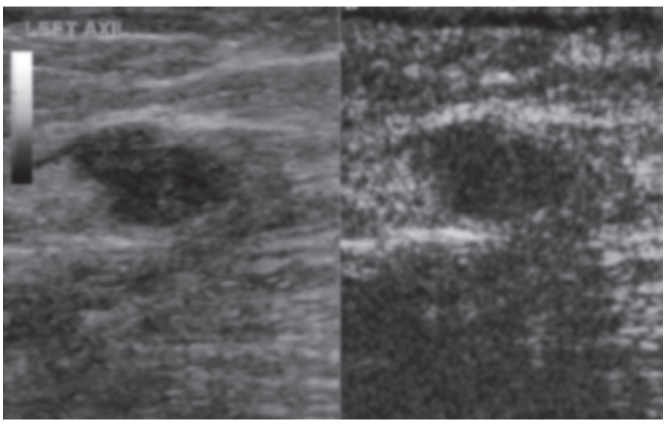
Fig. 4. Conventional gray-scale U/S and CEUS of positive SLN.

CEUS prediction and SLN maximum diameter size (fig. 1). Another result of the bivariate analysis was a statistically significant correlation ($p < 0.001$) between breast tumor size and the CEUS prediction preoperatively (fig. 2). Multivariate analysis showed that the CEUS outcome was only correlated with the actual final histopathological report on the SLN ($p < 0.001$). Multivariate analysis did not detect any correlation between successful CEUS prediction and other parameters.

Figure 3 presents details of the CEUS findings compared to histopathological outcome. Negative predictive value was calculated as 90%, positive predictive value was 75%; sensitivity was 83.33% and specificity 84.38%. Overall CEUS was accurate in 42 cases (84%) and erroneous in 8 cases (16%).

All cases with 3 or more positive LNs were detected preoperatively with CEUS. We observed that uninvolved nodes enhanced strongly and homogeneously, with a late wash-in and wash-out enhancement. On the other hand, involved nodes enhanced heterogeneously, with an early wash-in and wash-out enhancement (fig. 4). No adverse reaction to the contrast media was reported.

Discussion

Newly diagnosed breast cancer patients require a staging of their cancer that is as accurate as possible to help physicians to deliver appropriate treatment protocols. Physical examination of the axilla is unreliable, with sensitivity reported to range between 30–68%, even when experienced breast surgeons are involved, and cannot distinguish reactive nodes from malignant ones, while positive nodes are frequently non-palpable [5, 12].

U/S examination is a valuable adjunct to the investigation of ALN status. Benign sonographic features are a predominantly hyperechoic LN due to fat replacement, the presence of a thin homogeneous symmetrical cortical rim around the hyperechoic hilar fat, and symmetric cortical lobulations similar to contralateral ALNs [13]. Suspicious or metastatic nodes may have thickening or eccentric lobulation of the hypoechoic cortical rim, compression or displacement of the fatty hyperechoic hilum, or complete replacement of the hilar fat by hypoechoic tissue [14]. However, sensitivity of gray-scale U/S alone in detection of malignant ALNs is reported to range from 42% to 56% and specificity from 70% to 90% [15].

CEUS has been shown to improve the assessment of blood flow through small vessels and allows a more complete delineation of the vascular anatomy by enhancing the signal intensity deriving from microvasculature [16]. It facilitates the estimation of blood volume variations in different regions of LNs, which is of importance for the radiologist in defining malignant features [17]. Breast cancer is known to have a higher microvessel density than benign lesions. Special CEUS software exists that can analyze the dynamic vascular pattern, giving more information about the possibility of malignancy in a defined mass [18]. However, CEUS cannot easily distinguish malignant from benign reactive nodes. Malignant nodes show more enhancement than benign nodes after contrast material administration and display a heterogeneous pattern of enhancement in their cortex, whereas benign nodes are homogeneously dyed and have centrifugal enhancement [17]. In addition, there is a higher peripheral vessel distribution in malignant nodes, which is emphasized after contrast material administration, and the enhancement lasts for longer periods compared to benign nodes [19, 20]. The diagnostic confidence in SLN characterization is improved using the CEUS [10].

In our study there were 5 cases for which the conventional gray scale U/S was ambiguous for LN characterization, but after i.v. injection of contrast media the CEUS aided the radiologist in preparing the final statement about the node's status.

In the past, preoperatively, sensitivity and specificity of the evaluation of ALNs was increased when U/S was combined with fine-needle aspiration of suspicious nodes, which, however, is an invasive procedure [21, 22].

SLNB is the established standard of care for early breast cancer patients with clinically negative ALNs. Despite SLNB being characterized as a minimally invasive method, morbidity from SLNB is definitely lower than that from ALND, but is still not negligible. For example, the NSABP B-32 trial reported lymphedema after SLNB in the range of 7–9%, and a tingling and residual arm numbness in 7.5% of patients 6 months after surgery [8]. The identification rate and false-negative rates of the SLNBs are within international standards [23]. In addition, the presented results regarding the accuracy of U/S in predicting SLN status are consistent with previous studies on the same field [19, 24].

In the present study, the few factors that were correlated with CEUS outcome on bivariate analysis did not maintain the correlation on multivariate analysis, with the only exception being the actual final SLN histopathology. Moreover, multivariate analysis did not demonstrate significant correlations between successful CEUS prediction and any other parameter. Thus, it can be argued that CEUS outcome is an independent diagnostic predictor of SLN involvement with the aforementioned diagnostic features.

In 3 cases CEUS failed to identify a finally positive SLN. In 2 of these cases histopathology revealed a micrometastasis (diameter < 2 mm), and the last case had a metastatic lobular carcinoma. Given the fact that recent studies question even the role of systematic ALND in positive SLNB [25], it might be argued that micrometastasis cases that are not detected by CEUS might be even clinically insignificant.

Study limitations are: (1) the inability to prove with 100% accuracy that the sonographically examined node was the same as that was removed surgically, despite the effort of preoperative marking; (2) that only few histopathological types of breast cancer were included in the study; and (3) that the CEUS study of the LN was performed in 1 plane, which remained unchanged during the procedure.

In conclusion, the use of contrast media in the evaluation of potentially involved ALNs in women with breast cancer provides a U/S examination with considerable sensitivity, enabling the radiologist to express a reliable opinion and help the surgeon in the preoperative assessment. Additionally, CEUS is a non-invasive method and could possibly decrease the number of axillary biopsies in women with breast cancer. Although controversy still exists in the literature about the actual value of CEUS, this investigation seems to demonstrate rather important and expandable features in the context of clinical practice and decision making.

Disclosure Statement

The authors declare no conflict of interest.

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