Initial experience of axillary lymph nodes enhancement in ultrasound after the injection of contrast media in women with breast cancer

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Purpose

The detection of metastatic lymph nodes in the axilla of women with breast cancer is of fundamental importance in oncologic staging, since it directly influences not only the patient's prognosis, but also the selection of the appropriate therapy. Furthermore, this information is crucial for the surgeon, in order to organize the surgery plan. Ultrasound of axillary lymph nodes may improve preoperative staging and treatment staging, thereby ensuring better patient compliance (1). However, high resolution grey scale ultrasound and Colour/Power Doppler can only depict morphological features and coarse vascularity respectively, which often are not enough to reliably answer if there is any lymph node affected by the disease. Contrast enhanced ultrasound (CEUS) overcomes this drawback, by making it possible to examine lymph node microcirculation (2). This information is quite important, as increased vascularity has been described as a characteristic feature of malignancy.

As CEUS is a non-invasive procedure, it is well tolerated by patients and may potentially replace biopsy, which is an invasive and expensive procedure and therefore, should be avoided if possible. Furthermore, CEUS may enable better identification of likely positive lymph nodes for sampling and thus the selection of patients who would benefit from axillary node dissection (3).

The purpose of this study was to evaluate the pattern of enhancement in axillary lymph nodes using CEUS, so as to differentiate benign from infiltrated nodes, in women with breast cancer.
Methods and Materials

The 29 women included in this study were recruited after the diagnosis of breast cancer. Prior to surgery, they were examined with CEUS in order to recognize any potentially infiltrated lymph node in the ipsilateral to the affected breast axilla. During the study, 30 lymph nodes were evaluated.

The sonographic criteria for selecting indeterminate, suspicious or metastatic-appearing lymph nodes were: a) increased thickening and/or lobulation of the hypoechoic lymph node cortex compared with other ipsilateral or contralateral lymph nodes, b) eccentric lobulation of the hypoechoic lymph node cortex with compression of the adjacent hilar fat, c) complete disappearance of the hilar fat, which was replaced by hypoechoic cortex and d) round lymph node shape (4).

All women gave their written informed consent after the procedure of the study has been explained to them in detail. The study was approved by the hospital’s Research Ethics Committee. Furthermore, the ultrasound department where the procedure took place is adequately equipped, so as to encounter with any side effects that may appear.

The ultrasound examination was performed with a Logiq 9 System ultrasound machine, using the Coded Contrast Imaging Technique and TAD (TruAgent Detection) Imaging Techniques with Low mechanical index (MI 011-017), PO4% (Power output). A 10L linear probe 10L with a frequency range of 5-12 MHz has been used.

During the procedure, women first underwent high resolution grey scale ultrasound (B-mode) to the ipsilateral to the breast lesion axilla, in order to determine the lymph node’s morphological features. A Colour/Power Doppler study followed, which depicted their coarse vascularity. The lymph node bearing the more suspicious features according to the criteria mentioned before was selected as the one going to be examined. The position of the probe was selected so that the most vascularized area of the lymph node was visualized. The study continued with the intravenous bolus administration of 5 ml of the ultrasound contrast media based on sulphur hexagluoride. An intravenous injection of 10 ml of sterile solution followed. The lymph node’s enhancement was recorded during the first 2 minutes after the bolus injection of contrast media.

In the meanwhile, women remained under inspection for a mean time of 30 minutes, after contrast media administration, so as to ensure that no side effect would appear (5).

At surgery, the sentinel lymph node was removed in all women and if it was infiltrated, the patient underwent an axillary lymph node dissection.

The acquired images were analysed according to the lymph nodes’ pattern of enhancement. The assessment criteria included homogeneous or heterogeneous lymph node enhancement, centrifugal or centripetal enhancement, as well as late or early wash-
in and wash-out enhancement. The excluded results were correlated with the histological findings.

Statistical analysis was performed with IBM SPSS 19. Sensitivity and specificity of contrast-enhanced ultrasound were calculated. Differences between sensitivities and specificities before and after contrast media injection were assessed with McNemar's test. Continuous variables are presented as mean (standard deviation, SD), while categorical variables are presented as percentages.
Results

Mean age of women was 57.6 years (SD=13). The evaluated nodes had mean longitudinal diameter 1.78 cm (SD=0.49) and mean transverse diameter 0.73 cm (SD=0.26).

None of these women ever mentioned any clinically significant side effect after the contrast media administration and the examination was well tolerated.

An analysis of the pattern enhancement of these lymph nodes followed. Benign lymph nodes appeared to have homogenous and centrifugal enhancement. No unenhanced areas were demonstrated (Fig. 1, 2). Furthermore, their wash-in and wash-out enhancement was late (wash-in time #15 sec).

On the contrary, invaded lymph nodes appeared to have heterogeneous and centripetal enhancement, while demonstrating areas with no enhancement at all, especially the larger ones (Fig. 3, 4, 5). These areas were considered as potentially necrotic regions in the lymph nodes' volume, in accordance with the corresponding features of contrast media enhancement on CT and MRI. An early wash-in and wash-out enhancement completed the malignant pattern of enhancement (wash-in time # 10 sec).

Having obtained all the above information, lymph nodes were characterized as potentially infiltrated or not. US sensitivity before contrast media injection was 50% (6/12), while after contrast media injection was 83.3% (10/12). There was not statistically significant difference between two sensitivities (McNemar's test, \(x^2=2.3, \, \text{df}=1, \, p=0.13\)), but there was clinically significant difference (33.3%). Specificity before and after the injection of contrast media was 83.3% (15/18).
Fig. 1: Colour Doppler of an axillary lymph node to a 37 years old woman, with cancer on her left breast. Lymph node's vascularity is not visualized at all.

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Fig. 2: CEUS of the lymph node of figure 1. The lymph node enhances homogenously and centrifugally. No unenhanced areas are demonstrated, while the wash-in and wash-out enhancement is late (wash-in time # 11 sec). The lymph node characterized as potentially benign and the pathological examination proved its benign nature.

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Fig. 3: Colour Doppler of an axillary lymph node to a 48 years old woman, suffering from breast cancer. Lymph node vascularity is not adequately visualized.

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Fig. 4: Power Doppler of the lymph node of figure 3 is not more illuminating as regards to the lymph node's vascularity.

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**Fig. 5:** CEUS of the lymph node of figure 3. Although this lymph node appears to have benign morphological features, it enhances only partly on CEUS. An early wash-in and wash-out enhancement is in accordance with the malignant pattern of enhancement. This lymph node was pathologically characterized as metastatic.

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Conclusion

The characterization of regional tumour draining lymphatics is important in the management of women with breast tumours. Identification of metastasis-free sentinel lymph nodes may obviate extensive regional node dissection. If node dissection can be avoided, the patient is spared both morbidity, such as persistent arm lymphedema and the long term results of a more extensive operation. At present, 35% of patients who undergo sentinel lymph node excision biopsy require axillary lymph node dissection, because of nodal metastasis (6). However, current methods of staging in breast cancer are depended on operative excision or on biopsy.

As a non-invasive examination, grey-scale standard axillary ultrasonography of enlarged and morphologically abnormal lymph nodes has probably limited value in detecting involved nodes (7). On the other hand, CEUS has been shown to improve the detection of blood flow through small vessels and allows more complete delineation of the vascular anatomy by enhancing the signal intensity from microvessels (8). In metastasis, vascularity may increase as a result of angiogenetic factors in tumour cells, but blood flow may decrease, because of vascular encasement, compression by neoplastic tissue, a high trans-endothelial fluid exchange or a poorly functioning lymphatic circulation. This explains the fact that infiltrated lymph nodes are vascularized with heterogeneous vessel topography. CEUS facilitates an estimation of blood volume alterations in different regions of lymph nodes. Thus, this method can be a useful adjunct to the accurate staging of the disease in patients with breast cancer (9).

In conclusion, the use of contrast media to the evaluation of potentially invaded axillary nodes in women with breast cancer increases the sensitivity of ultrasound examination, which enables the radiologist to express a valid opinion and help the surgeon to the preoperative staging. Additionally, as a non-invasive method, it is better tolerated by the patients and it promises to decrease the number of biopsies in the axilla of women affected by breast cancer. Although there is a controversy in the literature about the real value of CEUS, it seems to be rather important in clinical practice and in decision making.