

The Role of Contrast Enhanced Axillary Ultrasonography in Early Breast Cancer Patients

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ABSTRACT

The most important prognostic factor for the patients with breast cancer are metastases to axillary lymph nodes (ALNs). Preoperative ultrasound (US) combined with fine needle aspiration biopsy (US-FNAB) has been proved to be the most reliable method to detect nonpalpable axillary metastases in patients with breast cancer. Our study was aimed to examine the value of US contrast agent (CA) SonoVue in the US examination of the axilla for the detection of axillary lymph node (ALN) metastases in breast cancer patients. Therefore, two studies were performed. The first study included 27/70 patients with breast cancer who had an indeterminate result of the standard US examination of the axilla (L/T < 1.2 or MCT > 3 mm or predominantly non-hilar vessel signal) and underwent US examination with CA. In the second study, 26 breast cancer patients underwent standard axillary US examination performed independently by two skilled operators. The patients with indeterminate or malignant ALN underwent US-guided fine needle aspiration biopsy (US-FNAB). For macrometastases, the sensitivity, specificity, NPV and PPV of US-FNAB were 91%, 93%, 100% and 100%, respectively. The reproducibility of the standard US examination (the second study) was 85% (22/26 patients), and for the metastases larger than 5 mm, it was 100%. Moreover, our second study proved that the same results as with CA can be achieved by two skilled operators performing a standard US examination. The sensitivity of both operators was 92%. In the case of metastases larger than 5 mm, the reproducibility was 100%. Micrometastases remain a problem also in the hands of very experienced operators even if using CA.

Key words: breast cancer, axillary lymph node, ultrasound, the contrast agent, the reproducibility

Introduction

The most important prognostic factor for the patients with breast cancer are metastases to axillary lymph nodes (ALNs)¹. Over the last 15 years, sentinel lymph node (SLN) biopsy has been used as an alternative to the routine axillary lymph node dissection (ALND) as a standard method for staging the patients with breast cancer^{2,3}. ALND is indicated only in the patients with metastatic deposits in the SLN. This, however, resulted in a high number of second operations in the patients with metastatic deposits in the SLN. Thus, an additional reliable preoperative staging of the ALNs can identify the patients who should directly undergo ALND, sparing them the second surgical procedure. Preoperative ultrasound (US) combined with fine needle aspiration biopsy (US-FNAB) emerged as the most reliable method to detect nonpalpable axillary metastases in the patients with

breast cancer^{4,6-8}. As demonstrated in our previous study, it can spare approximately 20 percent of breast cancer patients or almost half of patients with metastases in ALNs one surgical procedures⁴. However, the sensitivity and specificity of the procedure is operator and equipment dependent⁴⁻⁶. Baseline gray-scale and color Doppler US examinations have limited accuracy in the characterization of ALNs in breast cancer patients^{7,8}, because benign and malignant lesions may have similar echo patterns and vascular architectures. Examination by applying a contrast agent (CA) together with the usage of contrast-specific US modes is contrast enhanced US (CEUS) which facilitates to overcome the limitations of baseline gray-scale and color Doppler US examinations. CEUS was proved to have an improved diagnostic performance in different organs⁹⁻¹¹. Sulfur hexafluoride-filled micro-

bubble CA is a second generation of CA. This agent has a strong and long nonlinear harmonic response when it is insonated with low acoustic power^{10,11}.

The aim of the first study was to examine the additional value of using CA SonoVue for the detection of ALN metastases.

The aim of the second study was to find out the reproducibility of the standard US examination of the axilla when performed by different operators.

Materials and Methods

From September 2006 to January 2007, seventy consecutive female patients aged 26–73 (mean age was 55 years) with histologically proved breast cancer and non-palpable ALNs underwent standard preoperative US examination of the axilla. In both studies, US machine (Aplio HV, Toshiba, Otawara, Japan) with a 7–12 MHz 38-mm linear transducer was used.

On gray-scale US, the size of each ALN visible by US was measured by using the longitudinal (L) and transverse (T) axis dimensions to obtain longitudinal-transverse axis ratio (L/T). If central echoic hilus was detected, the maximum cortex thickness (MCT) of lymph node was measured.

The tumoral vessels were imaged by color Doppler US using slow-flow settings (pulse repetition frequencies of 800–1,500 Hz, wall filters of 40–50 Hz and high levels of color vs. echo priority and color persistence) for optimal visualization of slow blood flows. For each ALN, the distribution of vessels was defined as hilar (central, benign) and nonhilar (peripheral or mixed or malignant).

According to literature⁴, malignant ALNs were defined as follows: L/T < 1.2 and MCT > 3 mm and predominantly nonhilar vessel signal (Figure 1); in those, US-FNAB with a 21-G needle was performed. Benign ALNs had L/T > 1.2 and MCT < 3 mm and predominantly hilar vessel signal. If ALNs met only one criteria of malignancy, the results obtained by baseline gray-scale and



Fig. 2. US indeterminate ALN.

color Doppler US examination were considered as indeterminate (Figure 2).

The first study was performed on 27 patients with indeterminate result of CEUS. Before CA (SonoVue (Bracco, Milan, Italy) injection, a technique of low mechanical index was applied to observe non linear harmonic answer. After the preparation of CA (sulfur hexafluoride) by shaking 2.4 mL (5 mg/mL) of it, CA was injected by a 21-G needle for 5–10 seconds, followed by 10-mL normal saline flush. Microbubbles were observed for 200 seconds. All patients received only one bolus. When more than one ALNs were considered indeterminate on previous baseline gray-scale and color Doppler US, only the largest ALN was examined by CEUS.

Malignant CEUS characteristics were nonenhanced ALNs or parts of it because of deposits (Figure 3).

In all patients with malignant CEUS characteristics additional US-FNAB of non enhanced part of lymph node was performed.

In the second study aimed to test the interobserver reproducibility from February 2007 to April 2007 addi-



Fig. 1. US malignant ALN with peripheral type of vascularisation.

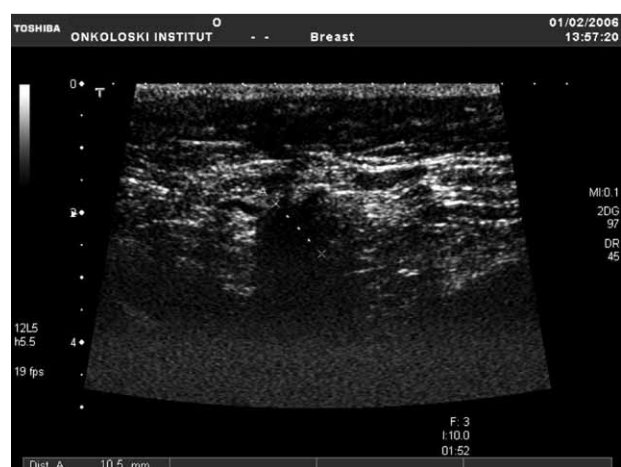


Fig. 3. US malignant ALN on CEUS.

tional 26 consecutive patients aged 31–73 (mean age was 52 years) with histologically proven breast cancer and nonpalpable ALNs underwent standard axillary US examination performed independently by two skilled operators. When the result of the US was considered by one or both observers as indeterminate or malignant, FNAB was performed.

Informed consent was obtained from the patients of both studies after the nature of the procedure had been explained to them.

The patients with cytologically proved malignant cells proceeded directly to ALND without SNB.

US and US-FNAB results were compared with final histopathological results of ALNs and the sensitivity, specificity, PPV and NPV were calculated.

Results

The first study

Preoperative US revealed an indeterminate result in 27/70 patients who were all referred to CEUS. CEUS was successfully performed in all 27 patients and revealed 10 positive and 17 negative results. FNAB confirmed ALN metastases in 9/27 patients who all proceeded directly to ALND. All others underwent SLN biopsy which revealed ALN metastases in additional 4 patients, in three of them only micrometastases (≤ 2 mm). The mean size of metastases was 7 mm (range 1–15). The mean size of breast cancer was 1.4 cm.

The results of CEUS examination and FNAB were true positive in 9 patients who underwent ALND without SLNB. In 14 patients, the results were true negative, those women underwent SLNB. In four patients, the second operation – ALND, was performed because of the false negative results. In 3/4 patients with false negative results of CEUS, micrometastases were proved only histologically, in one patient, a metastasis measuring 7 mm was overlooked. For macrometastases, the sensitivity of examination was 91% and the specificity and NPV were 93% and 100%, respectively. When CEUS was used in combination with US-FNAB, PPV rose to 100%.

The second study

Also in the second study, ALNs were detected by US in the axillae. Of 26 patients, 12 patients who underwent gray-scale and color Doppler US performed blindly by two skilled operators, had metastases in ALNs proved by histology. The mean size of metastases was 13 mm; the size range 2–20 mm. The mean size of breast cancer was 1.9 cm.

Of those 12 patients with histologically proven metastases in ALNs detected preoperatively (92% sensitivity), 11 underwent ALND immediately. In 4 of those patients, only one ALN was affected. In 13 patients, the results of preoperative standard US examination performed blindly by two skilled operators, were true negative. US-FNAB was performed in 13/26 patients, because of indeterminate or malignant appearance of ALNs. In 11/13 pa-

tients, metastatic cells were proved, so those patients proceeded directly to ALND. In 2/13 patients, only inflammatory cells were found; so, they proceeded to SNLB. One was later referred to ALND because of a 6 mm large metastasis. In other 13 patients, FNAB was done; because US examination confirmed benign ALNs, they underwent SNLB. The results of US examination and US-FNAB performed by two skilled operators were reproducible in 22/26 patients (85%). In four patients, the results of US examinations were suspicious for the first operator who performed US-FNAB and proved metastases in ALNs only in two patients. The ALNs of the same four patients were assessed by the second operator as benign; so FNAB was not done. The first operator had 92% sensitivity, 100% specificity, 100% PPV and 93% NPV. For the second, the sensitivity was only 75%. The metastases in ALNs that were assessed differently by the two operators were smaller than 5 mm. The reproducibility for larger metastases was 100%.

Discussion

The major drawback of SLNB which successfully replaced ALND is the need for a second operation in case of a positive result.

It is well established that the preoperative US together with US-FNAB can reduce the number of SLN procedures. As we demonstrated in our previous study, it can spare approximately 20 percent of breast cancer patients or almost half of patients with metastases in the ALNs one surgical procedure⁴. In this study, we assessed the possibility of further reducing the number of unnecessary second operation by increasing the sensitivity of preoperative US by CEUS. During the past decade, a number of US CA that consist of encapsulated gas microbubbles have been developed to enhance the intensity of US signal^{12–16}. The first CA Albunex (Molecular Biosystems, San Diego, Calif) was used in echocardiography. The second CA, the galactose-based Levovist (Schering, Berlin, Germany), which is now available in a number of European countries, has been proved to enhance the US signal intensity in the vessels throughout the body, but it has a very short half-life. Sono Vue can circulate for several minutes after intravenous injection; this allows sufficient time to examine specific anatomic areas of interest. However, to date, CA was used mostly in the examination of the liver. To the best of our knowledge, CEUS of ALNs in breast cancer patients have been described only in one work¹⁷. There are many reasons for this: firstly, with the application of CA, a non invasive US examination becomes invasive; it is more time consuming for the patients as well as operator and is also much more expensive. The operator must be skilled in axillary US and CA procedures. It should be taken into account that nonlinear harmonic answer to CA response is higher in abdominal examinations because abdominal probes are more suitable to accept such answers than linear probes¹⁷.

In our study, the preoperative CEUS in combination with US-FNAB detected 9/13 ALN metastases. It proved

to be a very sensitive method (93%) in the examination of patients with macrometastases, but not of those with micrometastases. So the added value of CEUS is at best questionable since it is sensitive only in the detection of macrometastases. In the group of patients with macrometastases, a standard preoperative axillary US examination itself has a sensitivity of more than 80%⁴.

In our previous study, performed on 165 patients, the reported sensitivity was already 84%, specificity 91%, PPV 97% and NPV 62%⁴. The reasons for lower sensitivity at that time were most probably less experiences and older equipment (Power Vision 8000 model SSA-390 A; Toshiba; Otawara, Japan). For superficial tissue, the spatial resolution of high frequency probes is well known^{5,6}. In the present study, examinations were performed on a new machine (Aplio HU 80, Toshiba, Otawara, Japan); therefore, the visibility of ALNs increased from 54% (in the previous study) to 100%, and consequently, the sensitivity and NPV also rose to more than 90%.

Moreover, our second present study of the reproducibility of the preoperative US, proved that the same results as with CEUS can be achieved by two skilled operators performing a standard US examination. The sensitiv-

ity of both operators was 92% (11/12). Moreover, this was in fact the sensitivity of one very experienced senior operator. The other operator had a sensitivity of 75%. However, in the case of metastases larger than 5 mm, the reproducibility was 100%. Micrometastases remain a problem even if dealt with by very experienced operators or by additional CEUS examination as was also proved in the study by Rizzato and Chersevani¹⁷. Unfortunately, this is the case also in USPIO-enhanced MR examination because of partial volume effect¹⁹. On the other hand there are only about 10% of patients with micrometastases in ALNs, and the prognostic value of micrometastases is not known at the moment¹⁸.

In conclusions, it seems that standard preoperative US examination of the axilla by an experienced operator is a very sensitive method in breast cancer patients with macrometastases in ALN. In this group of patients, which represents the great majority of patients with early breast cancer, there is no added value of additional CEUS examination. In the minority of patients with micrometastases neither of the two methods is sensitive at all.

The standard preoperative axillary US procedure is reproducible in 85% of patients.

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ULOGA KONTRASTNOG POTPAZUŠNOG ULTRAZVUKA KOD PACIJENTICA S RANIM RAKOM DOJKE

SAŽETAK

Najvažniji prognostički faktor za pacijentice s rakom dojke su metastaze na potpazušnim limfnim čvorovima (ALN). Predoperativni ultrazvuk (US) u kombinaciji sa biopsijom uz pomoć citološke punkcije (US-FNAB) pokazao se kao najpouzdanija metoda otkrivanja neopipljivih potpazušnih metastaza u pacijentica s rakom dojke. Cilj naše studije je bio ispitati vrijednost kontrastnog agenta ultrazvuka (CA) SonoVue tijekom ultrazvučnog pregleda potpazušnog područja u cilju otkrivanja metastaza potpazušnih limfnih čvorova kod pacijentica s rakom dojke. Stoga smo proveli dva istraživanja. Prvo istraživanje uključivalo je 27/70 pacijentica s rakom dojke koje su imale neodređene rezultate nakon standardnog ultrazvuka potpazušja ($L/T < 1,2$ ili $MCT > 3$ mm ili dominantni znak nehilarnih krvnih žila) i koje su, nakon toga, podvrgnute kontrastnom ultrazvuku. U drugom istraživanju, 26 pacijentica s rakom dojke podvrgnute su

standardnom potpazušnom ultrazvuku kojeg su izvela dva neovisna stručna operatera. Pacijentice s neodređenim ili malignim potpazušnim limfnim čvorovima podvrgnute su ultrazvučno vođenoj biopsiji citološkom punkcijom. U slučaju makrometastaza, osjetljivost operatera bila je 91%, specifičnost 93%, NPV citološkom punkcijom 100% i PPV citološkom punkcijom 100%. Produktivnost pregleda standardnim ultrazvukom (drugo istraživanje) bila je 85% (22/26 pacijenata), a za metastaze veće od 5 mm bila je 100%. Štoviše, naše drugo istraživanje dokazalo je da se mogu dobiti isti rezultati sa dva stručna operatera koji pregledavaju standardnim ultrazvukom kao i sa kontrastnim ultrazvukom. Osjetljivost oba operatera bila je 92%. U slučajevima metastaza većih od 5 mm, produktivnost je bila 100%. Mikrometastaze ostaju problem i vrlo stručnim operaterima, čak i kada koriste kontrastni ultrazvuk.