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Role of ultrasound in the preoperative staging of patients with breast cancer

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Abstract The aim of this study was to evaluate the ability of axillary ultrasound (US) and US-guided fine-needle aspiration biopsy (FNAB) to detect axillary LN metastases. Between January 2001 and September 2003, axillary US was performed in 165 patients with cytologically or histologically proven breast cancer and clinically non-palpable axillary LNs. In patients with US suspicious LNs, US-guided FNAB was performed and patients with cytologically proven malignant LNs proceeded directly to the ALND. In 49/90 patients with US suspicious LNs, US-guided FNAB was performed. It was positive in 33/49 patients. Definitive histology report revealed LN metastases in 65/165 patients. The sensitivity, specificity, positive and negative predictive value of the US-FNAB, were 84, 91, 97 and 62%. Axillary US in a combination with US-FNAB is a valuable method in preoperative staging of patients with breast cancer. Almost 50% of patients with LN metastases can be spared the second operation. However, it is very much operator-dependent and equipment-dependent.

Keywords Ultrasound · Breast cancer · Lymph node · Fine needle aspiration biopsy

Introduction

The most important prognostic factor for the patients with breast cancer are metastases to the axillary lymph nodes [1]. Over the last decade, sentinel lymph node (SLN) biopsy has been adopted worldwide as an alternative to axillary lymph node dissection (ALND) as a standard method of staging patients with breast cancer [2]. The SLN biopsy has, in comparison with ALND, minimal side effects; however, in all patients with metastatic deposits in SLN, a completion ALND is indicated. Thus, an additional reliable preoperative staging of the axillary lymph nodes would allow selection of those patients who should directly undergo ALND, sparing them the second surgical procedure. Clinical examination of the axilla has a sensitivity of detecting metastatic lymph nodes of only 33% [3]. On the other hand, ultrasonography (US) is a valuable method for detecting enlarged lymph nodes, while morphology and assessment of LN vascularization are useful in the differentiation of benign and malignant disease [4–11]. The addition of US-guided fine needle aspiration biopsy (US-FNAB) in the case of US suspicious/malignant axillary lymph nodes has already been shown to be able to verify lymph node metastases. The patients with cytologically proven axillary lymph node metastases can proceed directly to ALND.

The aim of our study was to evaluate prospectively the utility of gray-scale US and color Doppler flow US with US-FNAB in the axillary LN for the diagnosis of nodal metastases in patients with primary breast cancer. Additionally, the sensitivity, specificity, positive and negative predictive value of different radiological signs of metastatic spread to the lymph nodes were studied and compared.

Materials and methods

Between January 2001 and September 2003, axillary US, as a part of routine preoperative staging, was performed in 165 patients with cytologically proven breast cancer in whom SLN biopsy was planned.

All patients had clinically negative axilla. Mean age of patients was 56 years (range 26–80 years). Ultrasound examination of the axillae was performed by experienced radiologists (three with the same experience), using a linear-array transducer with range 12–15 MHz (Power Vision 8000 model SSA-390A; Toshiba, Otawara, Japan).

The size of each US visible LN was measured by using the longitudinal and transverse axis dimensions to obtain longitudinal-transverse axis ratio (L/T). The presence or absence of central echogenic hilus was documented. If central echogenic hilus was detected, than the maximum cortex thickness of the LN was measured.

Color Doppler examination was performed with color Doppler parameters set at the low-flow setting (wall filter 50–100 Hz and repetition frequency 800–1500 Hz). Color gain was adjusted dynamically to maximize the depiction of blood vessels while avoiding artefactual color noise. For each visible LN, color Doppler interrogation was performed and the distribution of vessels was defined as hilar-central (benign) and non-hilar-peripheral or mixed (malignant) vessel signals.

When LN had L/T <1.5 or the hilus was not seen or the cortex thickness was >3 mm, LN was suggestive of metastatic involvement [11]; therefore, US-FNAB with a 21-G needle was performed and two smears were prepared. One smear was air-dried and the other fixed in Delaunay for Giemsa and Papanicolaou staining. After the smears were prepared, the needle was washed with special solution for cytospin preparations. Cytospins were fixed in Delaunay and, when necessary, immunocytochemical reaction with monoclonal mouse anti-human cytokeratin (MNF 116, 1: 2000) was performed on automatic immunostainer Ventana Nexes IHC.

Patients with cytologically proven malignant cells in the axillary LN proceeded directly to the ALND (en-bloc removal of all level I and II lymph nodes with standard pathologic examination). In all other patients, the SLN biopsy was performed according to the standard protocol, which has already been described in detail elsewhere [12]. In brief, on the morning of surgery, 30–60 MBq of ^{99m}Tc labeled nanocolloid (Nanocoll) in 0.2 ml saline, was injected peritumorally at two sites. Next, dynamic lymphoscintigraphy was performed immediately after the injection and 20 min and 2 h after the injection anterior and lateral static images were obtained. If needed, static imaging was repeated after 2–4 h. The first hot spot in regional lymph node basins was considered to represent SLN and was marked on the skin. Additionally, 1 ml of blue dye (Blue Patente V; Laboratorie Guerbet, Aulnaysous-Bois, France) was injected peritumorally at the same two sites in the operating room after the induction of the general anesthesia. Surgical dissection of the SLN was guided by the blue stained afferent lymphatic channel and by a hand-held gamma probe (Navigator GPS System; USSC, USA). The identified SLN was excised and measured for ex vivo radioactivity. Additional hot nodes were removed until the ratio of the background radioactivity to the hottest ex vivo SLN was <10%.

Excised SLNs were bisected along the long axis and then sectioned transversely at 2 mm. All slices were formalin-fixed and embedded in paraffin. The slides were examined with H&E staining. For all negative SLNs, serial sections were evaluated with H&E and cytokeratin immunohistochemistry (IHC) stained levels at 250 μm. IHC stainings were performed using the avidin–biotin–peroxidase complex method with commercially obtained monoclonal anti-cytokeratin antibody, clone MNF 116 (Dako, Glostrup, Denmark).

Statistical analysis

The US and US-FNAB diagnoses were compared with the histological diagnosis either of SLNs or of LNs from ALND and the sensitivity, specificity and positive and negative predictive values (PPV, NPV) were calculated.

Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity and specificity of individual LN features in the task of distinguishing between malignant and normal LN. The area under the ROC curve (A_z) quantifies the accuracy of the classification. The ROC technique selects the cut-off point for trade-off between sensitivity and specificity [13].

Results

In 132 patients in whom SLN biopsy was performed, 251 SLNs were excised, average 1.9 SLN per patient (range 1–10). In another 33 patients, who proceeded directly to the ALND, 591 lymph nodes were excised, average 17.9 lymph nodes per patient.

Definitive histology revealed metastatic involvement of axillary LNs in 39% of patients (65/165). There were 48 patients with macrometastases (>2 mm) and 17 patients with micrometastases (0.2–2 mm). Tumor characteristics are listed in Table 1.

Table 1 Clinicopathological characteristics of the 165 patients

Tumor	Number	Percentage of total
Invasive ductal cancer	147	89
Invasive lobular cancer	10	6
Ductal cancer in situ	8	5
T1a/b	32	19
T1c	68	42
T2	55	33
T3	2	1
Ductal cancer in situ	8	5

Final pathology revealed invasive ductal cancer in 147 patients; three of them were multifocal, ten were invasive lobular, and eight DCIS. At pathological examination, the size of the breast tumor was less than 10 mm (T1a and T1b) in 32 patients, 11–20 mm (T1c) in 68 patients, 21–50 (T2) in 55 patients and more than 51 mm in two patients. In 36 patients (22%), breast cancer was non-palpable.

In 90 patients (54%), at least one lymph node was detected by US. In 49 out of these 90 patients, LNs were suspicious according to the US criteria (at least one of the suspicious criteria present: L/T ratio under 1.5, cortex thicker than 3 mm, absence of echogenic hilus or non-hilar vascularization). In these cases, US-FNAB was performed.

Cytology revealed malignant cells in 33/49 samples; in 11, there were only normal lymphoreticular cells and five were non-informative for diagnosis (insufficient quantity of material); in 4/11 with negative cytological diagnosis and in two of the five non-informative samples, histology revealed LN metastases. Three out of these six patients with false negative US-FNAB had micrometastases in their LNs. In another two patients, LN metastases were smaller than 4 mm, and in only one patient, LN metastasis measured 9 mm.

US characteristics of LNs in those 33/49 patients with a positive FNAB were as follows: mean longitudinal diameter was 16 mm (range 6–29 mm), mean transverse diameter 12 mm (range 4–23 mm), and mean L/T ratio 1.3 (range 1–2.5). In 13 LNs in which echogenic hilus was seen, the mean thickness of the cortex was 6 mm (range 2–7 mm). All LNs showed vascularization on PDU, which was of non-hilar (malignant) type in all except four patients. Figure 1 shows a metastatic LN with a peripheral vascularization.

In 6/16 patients with false negative FNAB, US characteristics of LNs were as follows: mean longitudinal di-

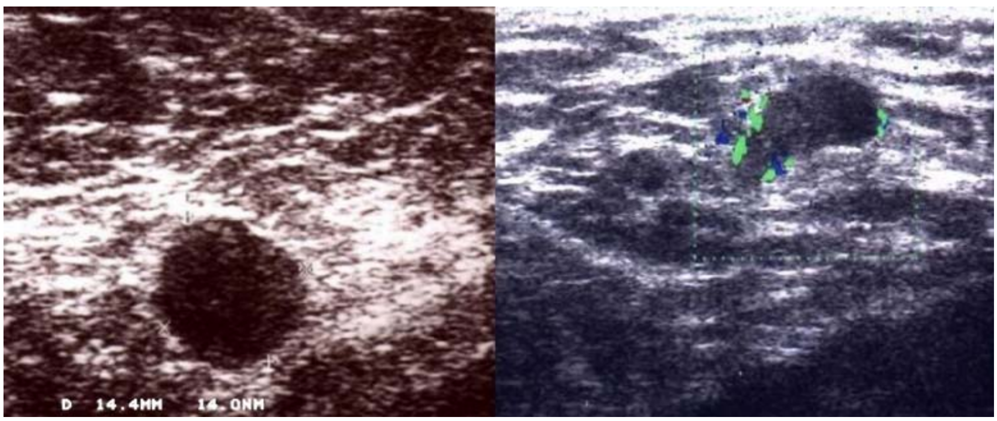

Fig. 1 A transverse scan of round, hypoechogenic metastatic node (measuring 14.4 mm, absent echogenic hilus) and a power Doppler sonogram of a malignant node with peripheral vascularity

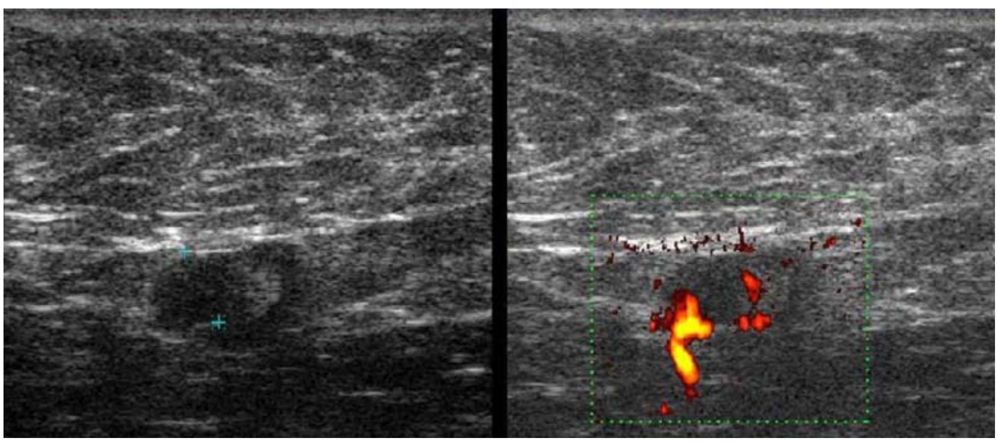

Fig. 2 A gray scale sonogram of a suspect lymph node (asymmetrically thickened cortex to 5 mm) and a power Doppler sonogram of peripheral-malignant vascularity of asymmetrically thickened cortex

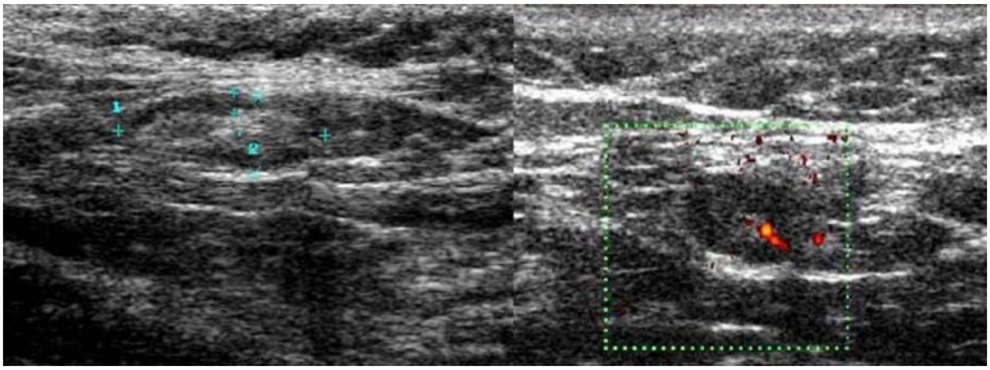

Fig. 3 A gray scale sonogram of a benign lymph node (central echogenic hilus and thin hypoechogenic cortex) and a power Doppler sonogram of benign-hilar vascularity

ameter 10 mm (range 8–18 mm), mean transverse diameter 7 mm (range 5–9 mm), and mean L/S ratio 1.7 (range 1.2–2). In all LNs, echogenic hilus was seen; the mean thickness of the cortex was 3.2 mm (range 2–4 mm). Vascularization on PDU was seen in 5/6 LNs and was of hilar—benign type in 4/5, and of peripheral—malignant type in 1/5 LN. Figure 2 shows a suspect lymph node with a peripheral vascularization.

In another 10/16 patients with a true negative FNAB, US characteristics of LNs were as follows: mean longitudinal diameter was 17 mm (range 4–25 mm), mean transverse diameter was 8 mm (range 4–15 mm), mean L/T ratio was 1.7 (range 1–3.1), and mean thickness of the cortex was 3 mm (range 1–4 mm). All LNs had echogenic hilus and hilar vascularization.

In 41/90 patients, US-FNAB was not performed because LNs were not suspicious according to the US criteria. The US characteristics of these LNs were as follows: mean long diameter was 15 mm (range 4–35 mm), mean transverse diameter was 8 mm (range 4–23 mm), mean L/T ratio was 1.8 (range 1–3.1). In all LNs, the hilus was seen, the mean thickness of the cortex was 2.3 mm (range 1–3 mm), and in 34 LNs, also vascularization of a hilar—benign type was seen. Figure 3 shows a normal LN with hilar vascularization.

In 75 patients with US undetectable axillary lymph nodes, SLN biopsy was performed. Final pathology revealed lymph node metastases in 18 (24%) patients. Only six had macrometastases (12/18 patients had micrometastases). The mean time for performing US with US-FNAB was 15 min (range 11–25 min) per axilla.

ROC analysis of L/T index was performed on lymph nodes of all 90 patients with US-detectable lymph nodes. Additionally, ROC analysis of maximum cortex thickness was performed on all lymph nodes with the presence of central echogenic hilus (70 patients). The area under ROC curve (A_z) was 0.715 (±0.053) for L/T index (Fig. 4) and 0.674 (±0.072) for maximum cortex thickness. Different cut-off points can be selected for L/T index and for maximum cortex thickness. With a cut-off point for the maximum cortex thickness of 3 mm, the sensitivity was 40% (26.4–54.8) and specificity was 87.5% (61.1–98.1). Accordingly, with a cut-off point for L/T index of 1.2, the sensitivity was 46.9% (32.5–61.7) and specificity was 91.3%

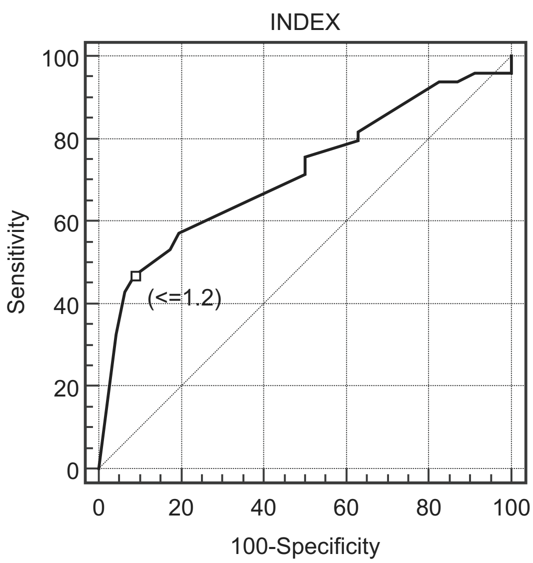

Fig. 4 ROC curve of longitudinal-transverse axis ratio—index L/T

Table 2 Results of axillary US and US-FNAB in 165 patients with breast cancer

US	US-FNAB	Histology negative LN	Histology positive LN	Total
LNs not detectable		57	18	75
LNs detectable	NP*	32	9	41
	Positive	1	32	33
	Negative	7	4	11
	Non-informative	3	2	5
Total		100	65	165

*NP not performed.

(79.2–97.5). Table 2 shows the results of the axillary US and US-FNAB in 165 patients with breast cancer.

One patient was false positive on FNAB. The sensitivity, specificity, PPV and NPV of the US alone were 58, 89, 77 and 77%, respectively, while in the case of US-FNAB, the respective values were 84, 91, 97 and 62%.

Discussion

SLN biopsy was proved to stage accurately the axillary LN status in breast cancer patients and has been adopted worldwide as an alternative to the ALND [2]. However, the method has a disadvantage—the need for a completion ALND in the case of LN metastases. Since approximately 40% of all breast cancer patients harbor LN metastases, this is not a negligible problem [4, 6–8]. There are, at the moment, two approaches to address this problem. One is the intraoperative SLN evaluation by way of frozen section, or imprint cytology [12, 14]. An alternative approach is by preoperative US of the axilla.

It is well established that preoperative US in combination with US-FNAB can reduce the number of SLN procedures [4, 6–8]. In our study, we spared 32/165 (19%) patients with LN metastases in the axilla a second surgical procedure. This is comparable to the results of other studies [4, 6–8]. Table 3 shows the results of preoperative US in combination with US-FNAB in four published studies.

The results of our study are mostly in agreement with the results of other studies. However, there are minor differences that probably reflect slightly different patient populations. The reported incidence of axillary LNs involvement varies between 30% and 50%. The higher amount of positive LNs in the study of Bonnema et al., compared with our study, reflects a difference in the number of T1 and T2 tumors [4]. Bonnema had 51% of T1 and 43% of T2 tumors, while we had 60% of T1 and 33% of T2 tumors [4]. Additionally, we also included DCIS (eight patients) in the study which were excluded in all other studies, except in Sapino's [8].

The main difference between the studies is in the percentage of US visible LNs and, consequently, in the percentage of performed US-FNABs. In our study, we identified LNs in 54% of the patients, which is higher than in all other published series. Additionally, we performed US-FNAB in only 54% of patients with visible LNs. Sapino and DeKanter, in contrast, identified LNs in only 32% and 37% of the patients and performed US-FNAB in all of them [6, 8]. A logical consequence of this is the higher percentage of positive US-FNAB results in our series (cytology positive in 67%) in comparison with Sapino's and DeKanter's (49% and 45%, respectively) [6, 8]. The percentage of negative cytological diagnoses is also much smaller in our series. On the other hand, the percentage of cytologically non-informative samples is the same (10–11%) in all series.

There are several reasons for these discrepancies between different series. First, US examination is very much operator-dependent. Therefore, an experienced radiologist, dedicated to breast pathology, is needed to assess adequately LNs in the axilla. With the experience, the differentiation between benign and suspicious/malignant lymph nodes becomes easier and may also reduce the need for US-FNAB. Second, the procedure is also very much equipment-dependent. In our study high-frequency US probes (12–15 MHz) were used. Additionally, we found that the duration of US examination was very important, with prolonged examinations revealing more LNs. The usual US with US-FNAB took us about 15 min (per axilla).

To the best of our knowledge, only Deurloo has used ROC analysis to predict metastatic involvement of the LNs [7]. Contrary to his results, we found L/T index as the most reliable nodal feature to predict LN metastases. With the cut-off point of 1.2, the sensitivity and specificity of the exam were 46.9% and 91.3%, respectively. Therefore, we recommend that in all LNs with L/T index under 1.2, US-FNAB should be performed. With ROC analysis, it is

Table 3 Results of preoperative US in combination with US-FNAB in published studies. *mets* metastases, *pts* patients

Author	Number of pts	Percentage of LN mets	Percentage of US detected LN mets in all pts	Percentage of US detected LN mets in pts with LN mets	Percentage of pts with US detectable LNs	Percentage of pts with US-FNAB	FNAB positive	FNAB negative	FNAB noninformative
de Kanter	185	47	17	36	37	100	45	55	
Deurloo	265	45	14	30	35	71	56	33	11
Sapino	298	33 10% DCIS	18	55	32	100	49	36	10
Our study	165	39 4% DCIS	19	49	54	54	67	22	10
Bonnema	148	41	26	63					

possible to select different cut-off points at a desired trade-off between the sensitivity and specificity.

The absence of central echogenic hilus, which prevent measurement of the maximum cortex thickness, is another sign of metastatic involvement of the lymph node. It was absent in 20/90 of our patients with US-detectable lymph nodes. There were lymph node metastases in 47/90 of these patients (in 18 patients with lymph node metastases US did not detect lymph nodes in the axilla). This means that almost half of the patients (20/47) with US-detectable lymph nodes and absent central echogenic hilus had lymph node metastases. In all other patients with US-detectable lymph nodes and presence of central echogenic hilus, cortex thickness is used as another sign of malignancy. With a cut-off point for the maximum cortex thickness of 3 mm, the sensitivity in our patients was 40% and specificity was 87.5%.

A very useful technique to depict intratumoral vascularization is a color Doppler. Neovascularity penetrates the tumor from its periphery with thin-walled blood vessels and large arteriovenous shunts, as proved histologically by Lee [15]. A peripheral vascular structure pattern has been described as a predictor for malignancy, and it can be used in the evaluation of primary breast lesions [16]. Additionally, several authors have used color Doppler ultrasound to distinguish between benign and malignant palpable LNs [11, 17, 18]. We found color Doppler flow also suitable to identify metastatic involvement of non-palpable axillary LNs because, in our study, color Doppler flow signal was present in more than 80% of US visible axillary LNs. The diagnostic accuracy of color Doppler can be further improved by the use of different contrast agents. We do not have personal experience yet, but we are currently starting a study with a SonoVue (Bracco) contrast agent.

Conclusions

Axillary US in a combination with US-FNAB is a valuable method in preoperative staging of patients with breast cancer. However, it is very much operator and equipment-dependent. In the hand of an experienced radiologist, dedicated to the breast pathology, it has a sensitivity, specificity, PPV and NPV of 84, 91, 97 and 62%, respectively, and can spare about half of the patients with LN metastases a second surgical procedure.

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