Association between negative preoperative axillary node staging and surgical sentinel node biopsy in patients with newly diagnosed breast cancer: A retrospective analysis

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Aim. The aim of this retrospective study was to analyse the preoperative ultrasound findings in patients with minimal or almost no morphological changes of axillary lymph nodes (LN) and to correlate these findings with the results of sentinel node (SN) biopsy.

Materials and Methods. Between January 2014 and September 2018, 289 female patients with newly diagnosed breast cancer and negative preoperative axillary staging were examined with preoperative ultrasound evaluation of axillary LNs. Patients with no evidence of LN metastases underwent primary surgical treatment with SN biopsy. Negative predictive value (NPV) of preoperative ultrasound was evaluated and the histopathological findings in positive SN biopsies were correlated with tumour type and preoperative ultrasound LN imaging.

Results. Of 289 patients with negative preoperative axillary staging who had primary surgical treatment, 268 patients had negative SN biopsy while SN metastases were detected in 21 patients. Of patients with positive SN biopsies, 2 patients had negative core biopsy of axillary LN before surgery. The preoperative ultrasound examination was negative in the remaining 19 patients with SN metastases.

Conclusions. Preoperative ultrasonography is very accurate in the detecting of axillary LN metastases. Patients with primary tumour size ≥ 1 cm, with grade ≥ 2 no special type carcinomas (NST - no special type, also known as invasive ductal carcinoma) or multicentric lobular invasive cancer should undergo a more thorough ultrasound evaluation.

Key words: breast cancer, sentinel node biopsy, ultrasound, axillary staging

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INTRODUCTION

Ipsilateral axillary lymph node (LN) metastases are common in breast cancer patients[1] and have important prognostic implications. The risk of axillary LN metastases is associated with the size of primary tumour at diagnosis, tumour grade, the presence of lymphovascular invasion, and multifocality or multicentricity of the tumour. Axillary LN staging is a crucial component in the management strategy of primary therapy. Therefore, the staging of breast cancer routinely includes an ultrasound axillary LN evaluation[1-6]. All patients with newly diagnosed breast cancer undergo an ultrasonographical axillary LN staging. Based on the ultrasound criteria, findings are classified as normal, suspicious, or pathological. All clearly pathological nodes are not necessarily verified by biopsy[6]. This is in cases for instance with distant metastases and pathological axillary LN.

An ultrasonographic image of a pathological LNs is determined by the development of metastases that are embedded subcortically[4] and subsequently leading to the expansion of hypoechoic cortex (Fig. 1). A fatty LN hilum disappears (Fig. 2, 3). Metastases are hyper-vascularized demonstrating a peripheral type of vascularization of the lymph node on Doppler imaging (Fig. 1).

A clearly pathological lymph node is enlarged, hypoechoic, with no fatty hilum, longitudinal to transversal axis (L/T ratio) less than 2 (Fig. 2, 3) and with peripheral vascularization on an ultrasound imaging[2,4,5,7-10].

However, these grossly pathological LNs must be differentiated from those that are not yet morphologically altered, thus presenting a greater diagnostic challenge. In this case of LN with minimal morphological changes, the ultrasonographic appearance may be different. These nodes may have an irregularly distributed cortex (Fig. 4), sometimes with focal thickening or with cortical bulge (Fig. 5), or inhomogeneity in an otherwise hypoechoic cortex, but the fatty hilum and the polar type of vascularization are usually preserved. The node may be small but round and hypoechoic, and the L/T ratio may be abnor-

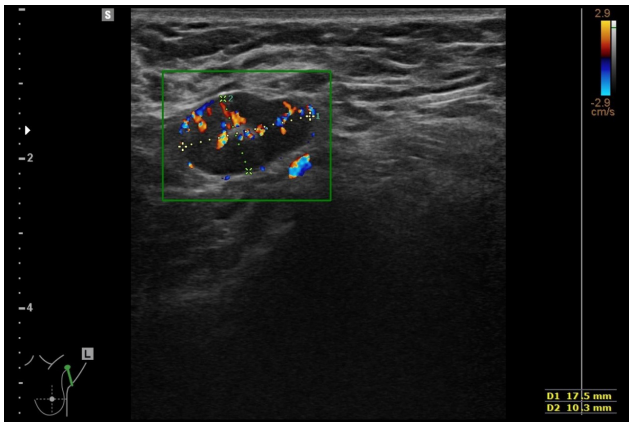

Fig. 1. Lymph node with hypoechoic diffuse cortex thickening and peripheral vascularization.

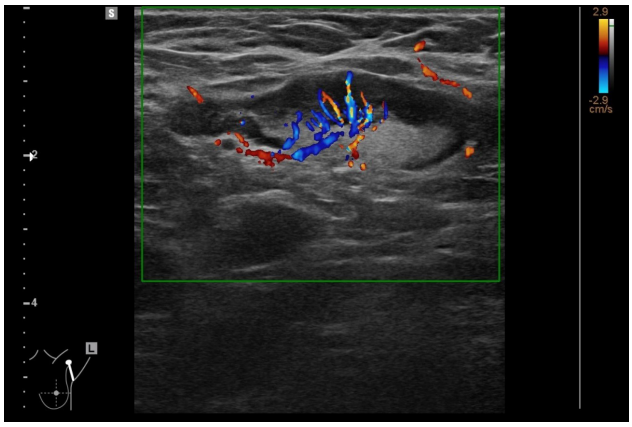

Fig. 4. Metastatic lymph node with diffuse cortex thickening and irregularly distributed cortex (verified by core biopsy).

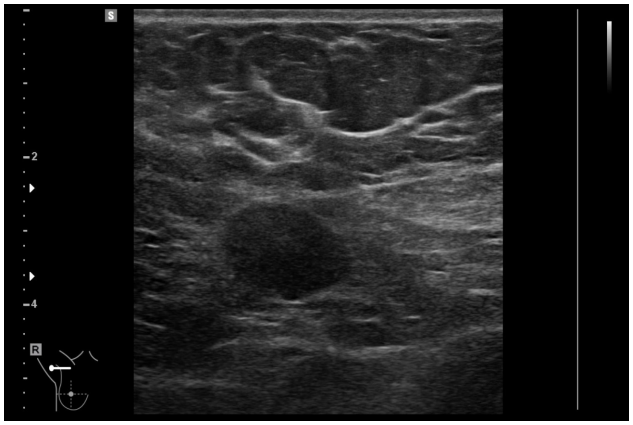

Fig. 2. Lymph node without fat hilum and abnormal L/T ratio.

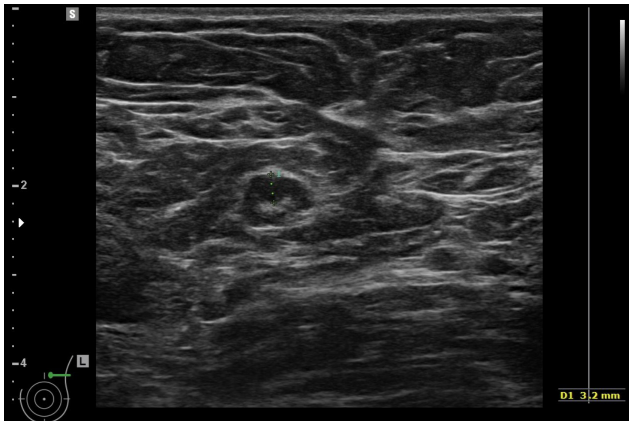

Fig. 5. Metastatic lymph node with focal cortical thickening (verified by core biopsy).

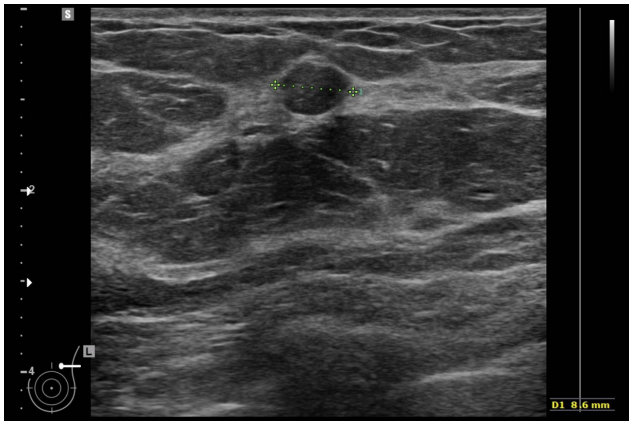

Fig. 3. Small metastatic lymph node with abnormal L/T ratio (verified by core biopsy).

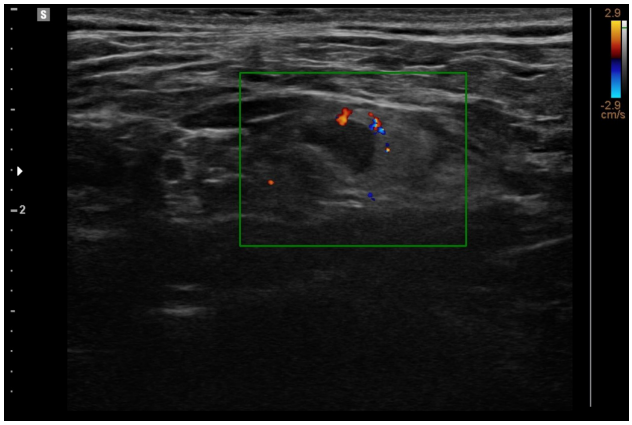

Fig. 6. Metastatic lymph node with cortex thickening and perifocal edema (verified by biopsy).

mal (Fig. 3). In patients without history of breast cancer and symmetrical presence bilaterally, these nodes are usually not considered suspicious. When the finding of a node with an irregularly distributed cortex or with a cortical bulge is unilateral and there is a history of cancer in the ipsilateral breast, these signs should be viewed in relation to the findings in contralateral axilla and considering the biology and size of the breast tumor. The expertise of the investigating radiologist is also crucial in reporting the axillary LN as suspicious and suggesting biopsy for further confirmation. Sometimes, a hyperechoic rim around the node corresponding to edema may be helpful in suggesting a biopsy (Fig. 6). The ultrasound image could be considered as suspicious, but minimal morphological changes may not correlate with metastasis[6,10].

In the present study, the correlation between preoperative ultrasonographic axillary node findings with almost no or minimal changes and the results of sentinel node biopsy were evaluated aiming at the analysis of the preoperative ultrasound findings. The primary aim was to evaluate the negative predictive value (NPV) of the preoperative detection of breast cancer LN metastases. The secondary aim was to correlate positive SN biopsies with histological types of carcinomas and preoperative ultrasound findings.

MATERIALS AND METHODS

A total of 289 consecutive female patients with newly diagnosed breast cancer and negative preoperative axillary staging indicated for primary surgical treatment were evaluated between January 2014 and September 2018. In all patients the primary tumour size was less than 23 mm and in cases of multicentricity the largest tumour was less than 21 mm. A preoperative ultrasound evaluation of axillary lymph nodes was performed. The patients signed an informed consent for the examination as well as for the processing of the data for statistical purposes. The ultrasound findings were evaluated as normal or suspicious with minimal changes. Patients with clearly pathological LN or with suspicious LN with concurrent positive core LN biopsy did not undergo primary surgical treatment and were reffered for neoadjuvant therapy and were not included in the present analysis. Patients with suspicious LNs and with negative preoperative core biopsy underwent primary surgical treatment as well as women with negative preoperative ultrasound of axillary LNs a they were included in this study.

A linear probe with frequency greater than 7,5 MHz was used to evaluate axillary LN. Findings such as LN size, cortex width, cortical thickening, focal cortical bulge, absence of the hilum, type of vascularization, L/T ratio, and surrounding edema were evaluated. If the axillary LN appearance was considered as suspicious, a biopsy was performed. Standard images of normal or suspicious axillary LN, usually in transversal plane, were performed. If no node was visible on the examination, one standard axillary image in transversal plane on each side was performed. The evaluation of the preoperative ultrasound was subsequently correlated with the results of SN biopsies obtained during surgical treatment. Negative predictive value of the preoperative ultrasound was evaluated. Retrospective analysis of the ultrasound findings in patients with positive sentinel node biopsy was also performed. The MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium) was used to perform the statistical analysis.

RESULTS

Among the 289 patients with negative preoperative axillary staging undergoing primary surgical treatment including sentinel node extirpation, 268 patients had no metastases while in 21 patients SN metastases were detected. From these 21 positive SN biopsies 19 patients (90.4%) had negative preoperative ultrasound and 2 cases (9.6%) were considered suspicious based on ultrasound examination but the results of core biopsy were negative. The negative predictive value of preoperative ultrasound was 93.4% (95% confidence interval for NPV 92.3% - 94.3%).

Table 1. The number of positive sentinel node biopsies depending of morphological characteristics of lymph nodes on preoperative ultrasound examination.

Normal LNs with cortex width < 2 mm	15
Diffuse cortex thickening ≥ 2 mm	3
Diffuse cortex thickening ≥ 3 mm	1
Focal cortex thickening > 2 mm	1
Absence of hilum, peripheral type of vascularization, abnormal L/T ratio, edema	0

Table 2. The number of positive sentinel node biopsies depending on type of primary breast cancer.

Histological type of breast cancer	lobular invasive cancer	6
	NST carcinomas	15
Grade	1	4
	2	11
	3	2
Size	< 1 cm	0
	≥ 1 cm	16
	≥ 2 cm	5
Number of lesions	solitary	16
	multicentric	5
Immunoprofile characteristics	oestrogen positive	20
	progesterone positive	15
	HER2/Neu positive	1

In the retrospective analysis of the standard images of ultrasound findings in 21 women with positive sentinel node biopsy, cortex thickening of more than 2 mm was evident in 5 cases, 3 cases with cortex thickening without core biopsy and 2 cases with cortex thickening with negative preoperative core biopsy. Of 3 cases without preoperative core biopsy one exhibited diffuse cortex thickening of 3.5 mm with the metastasis growing through the node capsule and that was underestimated on preoperative ultrasound. The second case among these 3 cases showed a focal cortical thickening above 2.5 mm and it was patient with invasive lobular cancer. Diffuse cortex thickening above 2.5 mm was observed in the third case with multicentric invasive lobular carcinoma. In two other cases the focal thickening above 2 mm was evident, but the results from biopsy were negative and the patients underwent primary surgical treatment.

In a single case, in all 21 patients with positive SN no node was detected during standard preoperative ultrasound evaluation. In all the other cases, normal LN with

cortical thickening of less than 2 mm, normal hyperechoic hilum, physiological L/T ratio and polar type of vascularization without perifocal edema were visualized (Table 1).

In 20 cases micrometastases limited to the cortex of SN biopsy were found, and only in a single case a metastasis growing through the LN capsule was observed.

The primary breast tumour size of more than 10 mm was associated with positive SN biopsy (Table 2). In patients with NST carcinomas there was a relatively higher frequency of positive sentinel node biopsies in NST tumours with higher grade, in this study especially with grade 2 (11 out of 17). Six cases of invasive lobular carcinoma and multicentric tumours exhibited positive sentinel node biopsy (Table 2). In the present cohort 20 SN positive carcinomas were oestrogen-receptor positive.

DISCUSSION

The present data demonstrate a high NPV of axillary ultrasound examination with regard to the results of SN biopsy. NPV was over 90% and preoperative screening failed in detecting LN metastases only in 21 out of 289 patients. In addition, among these 21 patients, two cases were with suspicious preoperative ultrasound findings, but with negative axillary core biopsy, so the failure to detect metastases was attributed to LN biopsy. In this setting, SN positivity was associated with tumour size, grade and multicentricity.

Axillary LN staging is an important prognostic procedure during the diagnostic work-up of breast cancer as well as one of the crucial factors determining the strategy of primary therapy[3,5,6,9-10]. Ultrasonography, including imaging of potential pathological LN findings, is a basic examination method in the diagnostic algorithm[1,4,6,7,13]. For ultrasonographic investigation of the axilla high frequency ultrasonic probes are used[2,14]. A range of pathologies in the axillary region could be detected during ultrasound examination including nodal syndromes such as leukaemia, lymphomas, inflammatory diseases or metastases of other primary tumours. However, the present study is focused on the image of the LN in patients with breast cancer. Axillary LNs are characterized by a typical ultrasound image with an oval shape[10,15-16], L/T ratio greater than 2 (ref.[14]), LN size is variable[17] with benign LN usually being less than 2 cm (ref.[2,18]). A normal LN usually has a well-preserved hyperechogenic hilum[10,15,16]. Cortex of the LN is usually thin, without irregular extensions[15]. Nodular vascularization is normally of a polar type[2,10,15]. Benign LN do not show structural changes in the cortex or focal cortical nodules, necrotic districts or calcifications[2,10,15,16]. Clearly pathological LNs in the axilla are not necessarily followed by core biopsy. Pathological LNs of breast cancer patient are typically enlarged, with extended cortex (Fig. 1), sometimes greater than 20 mm, with L/T ratio less than 2 (Fig. 2 and 3), is significantly hypoechogenic and has peripheral vascularization type without presence of fat hilum (Fig. 2 and 3).

The most specific sign on ultrasound for metastases is the absence of the fat hilum (Fig. 2 and 3) with the highest positive predictive value of 93% (ref.[16]). LN is considered as very suspicious if the cortex is enlarged with peripheral type of vascularization (Fig. 1). This sign also has a high positive predictive value of 81% in comparison to the isolated cortical extension that has a positive predictive value of 73% (ref.[16]). Cortical thickening of more than 4 mm has a sensitivity of 88% for the detection of metastases[16]. Some reports consider the width of cortex above 2.5 mm as a reliable sign for suspicion and consider it as an indication for further histological verification[15]. The node is also suspected of being metastatic if the cortical parenchyma is irregularly extended (Fig. 4) and inhomogeneous with parenchymal nodules or cortical bulges[2,10,15,16,19,20]. If there is a focal cortical thickening or cortical bulge (Fig. 5), this may be considered an early sign of metastases, but the positive predictive value and specificity are low[2]. A LN is suspicious of being-metastatic if a peripheral halo or perinodal edema is detected (Fig. 6) (ref.[10]). The most important signs for suspicion for metastatic involvement are cortical thickening, absence of fat hilum and peripheral type of vascularization. Morphological changes are more important than the LN size itself.

Patients with suspicious LNs in axilla underwent core biopsy. When core lymph node biopsy and fine needle aspiration are compared, it should be noted that the literature reports a higher sensitivity of core biopsy, hence it should be preferred to verify the origin of morphological changes in axillary nodes[21,22]. But other studies describe that differencies between sensitivity of these two methods in detection of metastases of breast cancer are not statistically significant. According to habits at our Department we use fine needle aspiration when core biopsy is very risky in terms of bleeding complications[23].

Breast cancer spreading to ipsilateral axillary LN is determined by tumour biology. Biological behaviour of breast cancer can be assessed by the determination of biomarkers[24], including expression of hormone receptors and human epidermal growth factor receptor HER-2. Metastatic potential is higher in luminal B, HER-2-positive and triple negative tumours. Axillary metastases of luminal A tumours decrease with age and are directly proportional to tumour size[25], as also reflected by the results of this study. The risk of metastatic LN involvement is also associated with the tumour size which has also been confirmed in the present study. In all of patients with positive SN biopsy the tumour size was above 10 mm. Only patients with negative preoperative axillary staging were included in the present analysis and patients with positive preoperative axillary staging were not included. This selection bias explains a lack of association between the tumour phenotype and the presence of axillary LN metastases. The number of patients with positive sentinel node biopsy was relatively low explaining the discrepancy of the results in comparison to others reported in literature.

Significant differences between detection of axillary metastases in ductal and lobular carcinoma were reported in the literature. Invasive lobular cancer is more likely to be underestimated during ultrasound axillary staging[26] and fine needle aspiration[27] because of an infiltrative growth pattern[26,27], this is in agreement with the results

of the present analysis that found an underestimation during LN evaluation in invasive lobular cancer, specifically in multicentric tumours. In the present study 20 SN positive carcinomas were estrogen-dependent, reflecting a greater frequency of hormone-dependent carcinomas in the population.

CONCLUSIONS

In conclusion, preoperative ultrasound is a very accurate and sensitive diagnostic method to detect axillary LN metastases. The NPV of preoperative ultrasound examination of the axilla is very high. However the examination is prone to subjective errors and depends on experience of examining radiologists. There are specific ultrasonographic signs suggesting malignancy of the axillary LN. All ipsilateral LN of uncertain nature or suspicious from metastatic involvement have to be histologically verified by core biopsy. The ultrasound evaluation should be more thorough in the assessment of axillary LN in patients with primary breast tumour size of more than 10 mm, in the cases of NST carcinomas with grade 2 and higher and in the cases of invasive lobular cancer or multicentricity. High-quality LN diagnosis of the axilla in patients with newly diagnosed breast cancer is crucial for indication of the multidisciplinary treatment, including possible targeted axillary dissection.

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Conflict of interest statement. None declared.

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