Ultrasonographic signs as predictors of metastatic involvement in the axillary lymph nodes in breast cancer patients: from minimal changes to the appearance of the pathological lymph node. A retrospective analysis

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Introduction. The aim of this study was to retrospectively analyse the ultrasound findings in the axillary lymph nodes in breast cancer patients with morphological changes that required biopsy. In most cases the morphological changes were minimal.

Materials and Methods. Between January 2014 and September 2019 examination of axillary lymph nodes with subsequent core-biopsy was performed in 185 breast cancer patients at the Department of Radiology. Lymph node metastases were detected in 145 cases, while in the remaining 40 cases benign changes or normal lymph node (LN) histology was observed. Ultrasound morphological characteristics and the sensitivity and specificity were evaluated retrospectively. Seven ultrasound characteristics were evaluated – diffuse cortical thickening, focal cortical thickening, absence of the hilum, cortical non-homogeneities, L/T ratio (longitudinal to transverse axis), type of vascularization and perinodal oedema.

Results and Conclusion. It is a diagnostic challenge to recognize metastases in the lymph nodes with minimal morphological changes. The most specific signs are non-homogeneities in the cortex of the lymph node as well as the absence of fat hilum and perinodal oedema. Metastases are significantly more frequent in LNs with a lower L/T ratio, in LNs with perinodal oedema and with a peripheral type of vascularization. Biopsy of these lymph nodes is necessary to confirm or exclude metastases, especially if it affects the type of treatment.

Key words: lymph node, breast cancer, metastases, ultrasound

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INTRODUCTION

Axillary node staging in breast cancer patients is an important prognostic parameter at the time of breast cancer diagnosis as well as one of the crucial factors determining the strategy of primary therapy. The survival rate is directly dependent on regional nodal staging, where there is a relationship between survival rate and the type of primary breast cancer, its hormone-dependence or Her2Neu (Human epidermal growth factor receptor 2) positivity and aggressiveness[1,2].

Patients with four and more involved nodes at initial diagnosis have a significantly poorer outcome after relapse, regardless of the duration of the disease-free interval[1,2]. This is also one of the reasons why there is a different surgical approach to the axillary region in case of no involved nodes at initial diagnosis, with one to two or three involved nodes in the axilla and in case of more than three or four involved nodes. The new surgical approach for one to two or three involved lymph nodes is a targeted axillary dissection (TAD). This results in greater dependence on the diagnosis of metastatic involvement in the axillary lymph node. The purpose is to recognize metastatic involvement at the beginning during diagnosis, to confirm it, for instance by core biopsy, to mark the nodes to enable the breast cancer patient to have TAD (ref.[3]).

Breast cancer staging in ipsilateral axillary nodes is based on the ultrasound evaluation of the axilla[4-8]. The metastatic involvement is affected by neovascularization of the primary tumour, its chemokines and growth factors. The metastases are implanted by afferent vessels subcapsular to the cortex. This is the reason for expansion of hypoechoic cortex. The fatty hilum disappears. Metastases in the cortex are hypervascularized, and then there is a peripheral type of vascularization on Doppler imaging.

According to the findings, the ultrasound examination is evaluated as normal, suspicious or pathological. The normal or physiological lymph node has a thin cortex without non-homogeneities, with a polar or central type of vascularization, without cortical thickening, with hyperechoic fatty hilum, oval shape and the L/T ratio is greater than 2. The pathological lymph node or lymph node packet is relatively easy to diagnose. There is an enlargement of the lymph node, a hypoechoic wider cortex, round shape or lower L/T ratio, absence of the hyperechoic hilum, peripheral type of vascularization. On the other hand,

there are some lymph nodes in the ipsilateral axilla to the primary tumour with more or less visible changes. It is necessary to evaluate these lymph nodes according to their ultrasound appearance in relationship to the lymph nodes in the contralateral axilla and also in relation to the type of primary breast tumour and its aggressiveness. In some cases, it is a great diagnostic challenge. Usually a core biopsy is necessary.

In this study, these minimal morphological ultrasound changes were determined and analyzed. A retrospective analysis of the correlation between ultrasound and histopathological findings was performed and the ultrasound predictors for metastatic involvement were determined.

MATERIALS AND METHODS

Between January 2014 and September 2019 185 examinations of axillary lymph nodes in breast cancer patients who had core-biopsy were performed. The sonographic findings in these patients required biopsy because a lymph node with unclear morphological changes in ipsilateral axilla was detected. A linear probe with frequency above 7,5 MHz was used to evaluate axillary LNs. Findings such as diffuse cortex width without absence of hilum, cortical thickening or focal cortical bulge, absence of the hilum without enlargement of LNs, type of vascularization, L/T ratio, and surrounding oedema were evaluated. In the case of diffuse cortex three categories were distinguished, including diffuse cortical width 2–3 mm, 3–4 mm and over 4 mm. In the case of focal cortical thickening, findings were classified into four categories, including focal cortical thickening around 2 mm, 3 mm, 4 mm and above 5 mm. The third parameter, cortical non-homogeneities, were classified as present or absent. LNs with the absence of fatty hilum were also labeled as absent or present. If the absence of hilum was presented, only LNs up to 15 mm in size were included in this study. LNs with a size greater than 15 mm with the absence of fatty hilum were considered clearly pathological. The fifth ultrasound sign was L/T ratio and was classified as being between 1.5–2, 1–1.5 or equal to 1. Perinodal edema was described as being present or absent, and vascularization was evaluated as being central or peripheral. A mixed type of vascularization was considered as the presence of peripheral vascularization. If the axillary LN appearance was considered suspicious, a core biopsy was performed. Standard images of normal or suspicious axillary LN, usually in transversal plane, were performed. Ultrasound images of the axillary region were performed for each patient with subsequent core-biopsy of axillary LN.

Ultrasound morphological characteristics, including sensitivity and specificity, were evaluated retrospectively. All patients signed an informed consent to the ultrasound examination including consent to using documentation anonymously for scientific and statistical purposes. Informed consent is in the Czech language.

For this study approval of the local ethics committee was obtained.

IBM SPSS Statistics, version 22 (Armonk, NY: IBM Corp.) was used to analyze the data. An association between the presence of metastases and the LN sonographic morphological features was evaluated using Fisher's exact test. Tests were performed at a significance level of 0.05.

RESULTS

Between January 2014 and September 2019 185 axillary LN examinations in breast cancer patients with subsequent core-biopsy were performed. Metastases were detected in 145 cases. In the remaining 40 cases, benign changes or normal LNs were observed.

Diffuse cortical thickening (Fig. 1) without the absence of hilum was less than 1 mm in most of the LNs with minimal morphological changes. A relatively larger number of metastases was demonstrated in LNs with diffuse thickening above 4 mm (Table 1), but no significant association between the presence of these features and LN metastases was confirmed (P=0.317).

In patients with metastatic LNs, no significant association between metastasis and focal extension of the cortex (Fig. 2) was observed (P=0.134). A relatively higher prevalence of metastases was evident in LNs with focal cortical thickening above 3 and 4 mm, and even more in LNs with focal cortical thickening above 5 mm (Table 1).

Non-homogeneities in the cortex (Fig. 3) were more common in the LNs with metastases (Table 1). Statistically, cortical inhomogeneity has been observed significantly more frequently in patients with metastases (P=0.005). The specificity of this sign was 90%, but the sensitivity was lower.

The absence of fat hilum without enlargement (Fig. 4) was more often detected in patients with metastases and when this sign was present, only a small amount of patients were without metastases (Table 1). The absence of hilum has been shown to be significantly more frequent in patients with metastases (P<0.0001). The specificity of this sign was 92%, but the sensitivity was lower.

L/T ratio was evaluated and if it was equal to 1 (Fig. 4), a small number of patients were without metastases (Table 1). The sensitivity of this sign was 84%, but specificity was lower. There was a significant correlation between metastasis and lower L/T index values (P=0.002).

The presence of perinodal edema (Fig. 4) was also associated with metastases (Table 1). Perinodal edema was more common in patients with LN metastases (P<0.0001). The specificity of this sign was 95%.

Peripheral vascularization (Fig. 1) was associated with the presence of LN metastases (Table 1), P<0.0001. Sensitivity was 73%.

DISCUSSION

There are some prognostic factors which more or less affect the prognosis of breast cancer disease described in the literature. These are the age of the patients at the

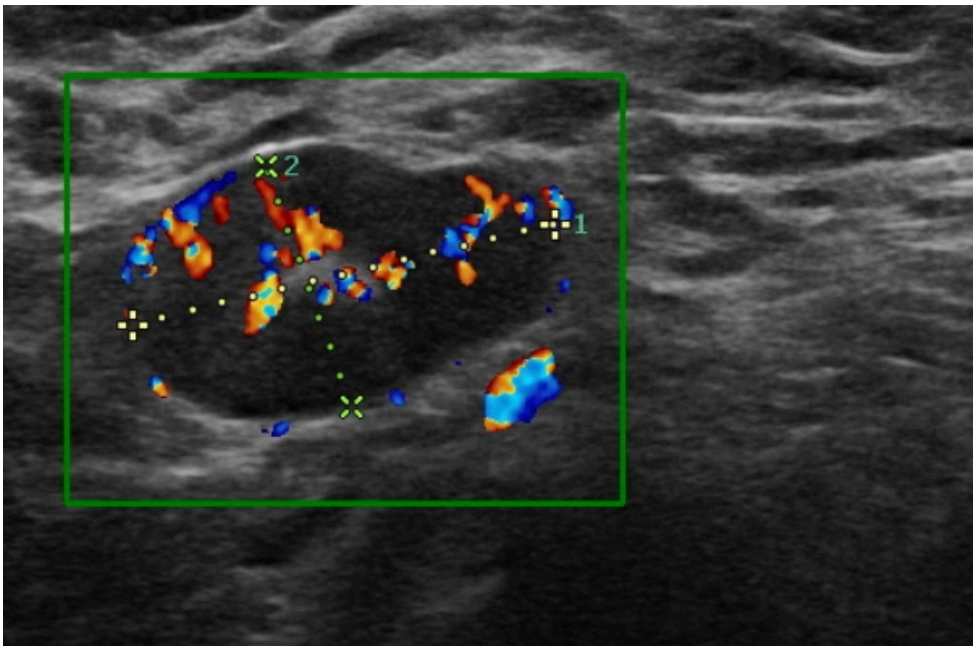

Fig. 1. Ultrasound of an axillary lymph node with diffuse cortex thickening and peripheral type of vascularisation, metastasis was confirmed.

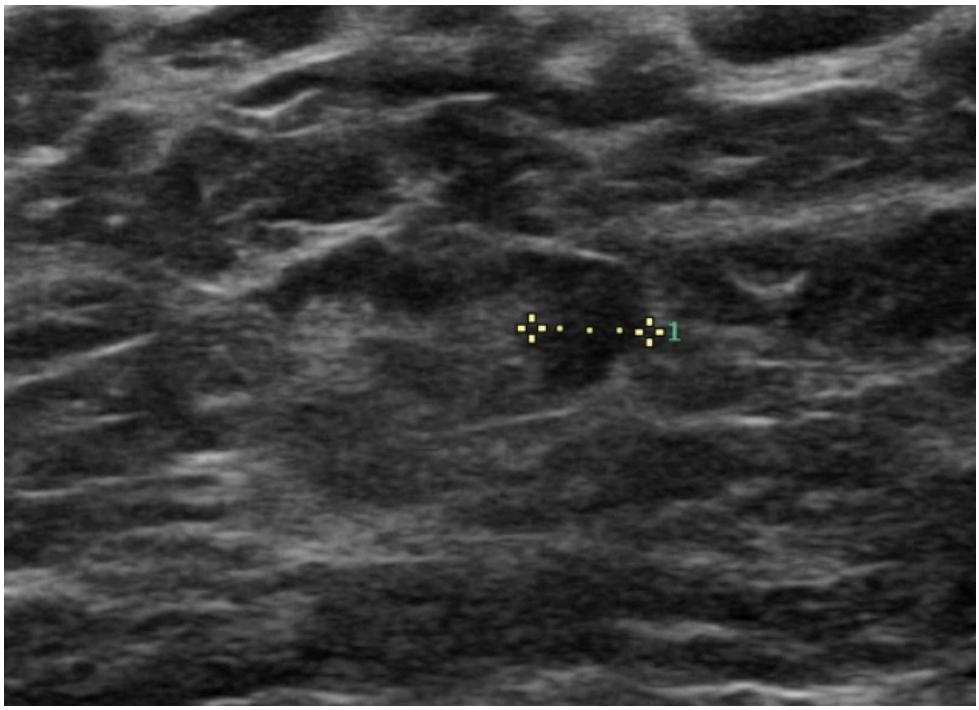

Fig. 2. Ultrasound of an axillary lymph node with focal cortical thickening or cortical nodule, metastasis was confirmed.

time of diagnosis, size of primary tumour, type of primary tumour and its biological behavior, metastatic involvement in the axillary lymph nodes, patient's overall health, response to treatment and many others. Axillary node staging in breast cancer patients is one the most important parameters, which affects the prognosis and the survival rate and is one of the main factors determining the type of primary therapy. Patients with four and more involved nodes at initial diagnosis have a significantly worse outcome after relapse, regardless of the duration of the disease-free interval[1,2]. The ACOSOG Z1071 trial demonstrated that targeted axillary dissection (TAD) could be performed instead of axillary dissection in some patients who meet the criteria of this trial[3]. In this study, lymph nodes with metastatic involvement before therapy, had to be marked. Targeted axillary dissection is the resection of the sentinel node as well as nodes with metastatic involvement at the time of diagnosis following their biopsy and marking for instance with radioactive seeds. TAD provides the opportunity to avoid axillary dissection

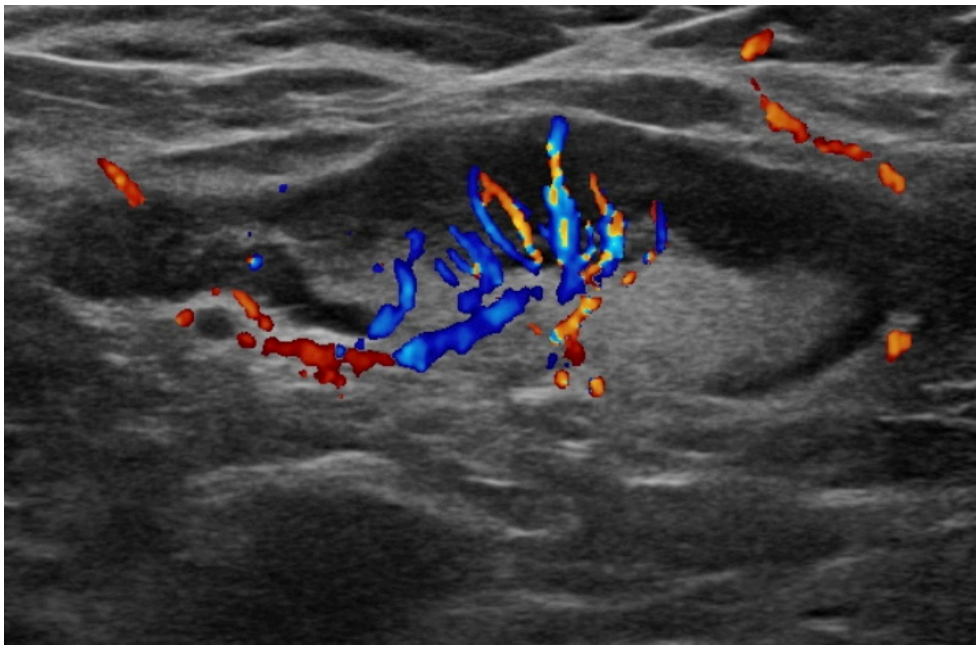

Fig. 3. Ultrasound of an axillary lymph node with inhomogeneities in the cortex with diffuse thickening, metastasis was confirmed.

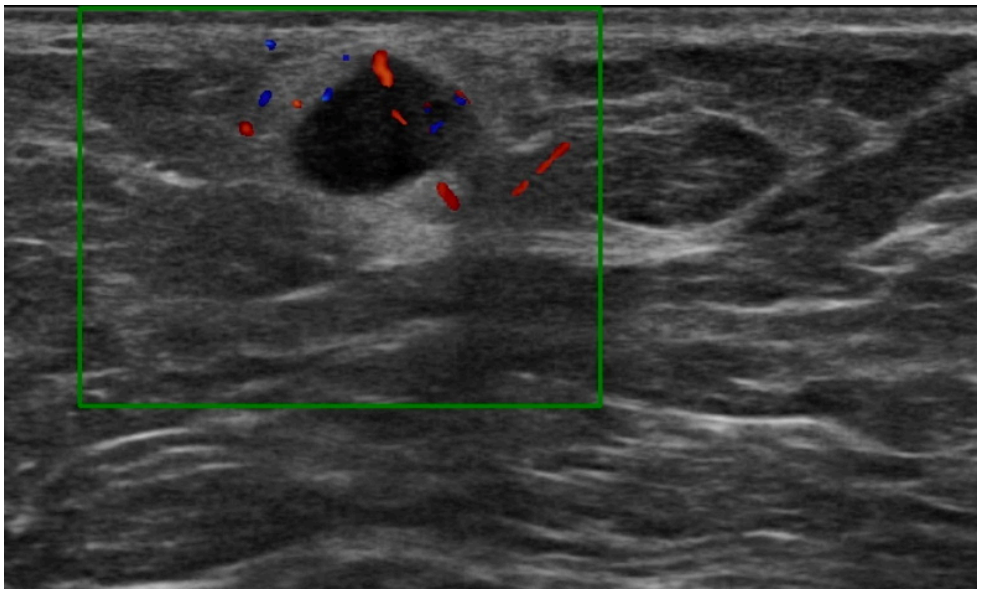

Fig. 4. Ultrasound of an axillary lymph node with absence of fat hilum, round shape, abnormal L/T ratio and mild perinodal oedema, metastasis was confirmed.

and to reduce the risk of postoperative lymphoedema of the upper limb in patients with node-positive breast cancer disease. There are other methods for marking lymph nodes, such as radioactive seeds, 4% suspension of carbo adsorbens, magnetic seeds or tiny titanium or stainless steel markers. TAD may be performed in the early-stage of metastatic involvement in the axillary lymph nodes[9,10]. This places a great demand and emphasis on accurate diagnosis of early or minimal changes in the lymph nodes of the ipsilateral axilla.

Lymph nodes of the ipsilateral axilla are the most common site of metastasis in breast cancer patients and the presence of these metastases is an important prognostic factor. The risk of metastasis to the axillary nodes is related to the size of the primary tumor at the time of diagnosis, the degree of tumor cell differentiation (grading), the presence of lymphangioinvasion and the number of tumors present in the breast, i.e. multicentricity or multifocality[6]. All patients with newly diagnosed breast cancer undergo ultrasonographic examination of the axilla. Based on certain ultrasonographic criteria, nodes are classified as physiological (normal), suspicious or pathological.

The normal or physiological lymph node has a thin cortex without non-homogeneities, with polar or central type of vascularization, without cortical thickening, with

Table 1. Frequency of the ultrasound morhological characteristics in LNs with and without metastases.

Axillary node core-biopsy				
Pathological morphological sign		Metastases present	Without metastases	*P*
Diffuse cortex thickening	2–3 mm	16 (29.1%)	9 (28.1%)	0.317
	3–4 mm	16 (29.1%)	14 (43.8%)	
	above 4 mm	23 (41.8%)	9 (28.1%)	
Focal cortical thickening	2 mm	9 (17.6%)	4 (51.7%)	0.134
	3 mm	11 (21.6%)	1 (14.3%)	
	4 mm	11 (21.6%)	0 (0.0%)	
	above 5 mm	20 (39.2%)	2 (28.6%)	
Cortex inhomogeneities	yes	47 (32.4%)	4 (10.0%)	**0.005**
Absence of fatty hilum	yes	58 (40.0%)	3 (7.5%)	**< 0.0001**
L/T ratio	1.5–2	36 (35.0%)	13 (72.2%)	**0.002**
	1–1.5	43 (41.7%)	1 (5.6%)	
	1	24 (23.3%)	4 (22.2%)	
Perinodal edema	yes	47 (32.4%)	2 (5.0%)	**< 0.0001**
Type of vascularisation	peripheral	38 (26.2%)	0 (0.0%)	**< 0.0001**

hyperechoic fatty hilum, oval shape and an L/T ratio greater than 2.

The clearly pathological node is enlarged (usually the size is more than 2 cm, but the size is not a main determinant, it depends more on morphological changes), hypoechogenic, without a visible fat hilum, L/T ratio is less than two (it is round in shape) and has a peripheral type of vascularization on color mapping[6].

However, nodes that are not yet as morphologically altered should be distinguished from clearly pathological nodes. Lymph nodes with little-expressed morphological changes may have a diffusely wider cortex, or a diffusely normal-width cortex with focal cortical enlargement or cortical nodulation, or may have noticeable non-homogeneities in an otherwise less wide cortex, with a mostly preserved hyperechogenic hilum and polar type of vascularization. On the other hand, there may be a small nodule up to 10 mm that does not have a fat hilum and its L/T ratio is equal to one. Such a node also does not have to be clearly pathological because it is not enlarged and must be considered suspicious with subsequent histological verification, if it changes the type of primary therapy. In some cases, the presence of oedema around the nodule manifested on ultrasound by the hyperechogenic rim may contribute to the biopsy decision. The experience of the examining radiologist is also an important factor in the indication for node biopsy. Insignificant morphological changes may not always correlate with the finding of metastasis[6,11].

Metastatic involvement is based on afferent vessels in the cortex of lymph nodes. The first sign of metastatic involvement could be focal bulging or focal cortical thickening. The cortex of the nodule should be slender with no irregular thickening[11]. The vascularization of the physiological lymph node is of the polar type[11]. The lymph node should not contain structural changes such as focal cortical nodules, necrotic areas, or calcifications[11]. In the case of diagnosed breast cancer, the ipsilateral axilla nodule is clearly pathological in appearance if it exceeds 20 mm in size, has an L/T ratio of less than 2, is markedly hypoechogenic, has peripheral vascularity, and is characterized by the absence of a hilum[12]. An axillary finding may also be considered clearly pathological if these pathological nodes form a packet or are clinically palpable. If these characteristics described above do not occur concurrently, but only some or only one of them is expressed, then in the case of diagnosed breast cancer, these nodes must be considered suspicious and their histological verification is appropriate. Thus, a nodule is highly suspected of malignancy if it is markedly hypoechogenic without hilar differentiation. The characteristic absence of a fatty hyperechogenic hilum is most specific for the detection of metastasis and has the highest positive predictive value, namely 93% (ref.[11,12]). The high specificity of this symptom was demonstrated in our group of patients. The node is also highly suspicious if its cortex is dilated[4] and concurrently has peripheral-type vascularization. This symptom also has a high positive predictive value, 81%, compared to an isolated cortex extension, where the positive predictive value is 73% (ref.[13]). The cortex of the nodule should not exceed 3–4 mm in width[13]. If it exceeds 4 mm, the sensitivity of this symptom for metastatic detection is 88% (ref.[13]). Most publications consider width of cortex more than 3 mm as a pathological value according to Bedi classification and this value is a cut-off point for cortical thickness[8,14-19]. Minimum lymph node involvement, with deposits between 0.2 and 2 mm (micrometastasis), and < 0.2 mm (isolated tumor cells) is not related to significant morphological changes, but it could be the reason, why some authors also report cortex widths over 2.5 mm as suspicious and cite this value as an indication for histological verification[8,20]. In the evaluated group of patients, no significant correlation was demonstrated between the diffuse enlargement of the cortex without the absence of hilum and the occurrence of metastasis. A relatively larger number of metastases was demonstrated in LNs with diffuse thickening above 4 mm. In the presented study, a significant correlation was demonstrated between the

peripheral type of vascular supply and the presence of metastasis. A node is also suspected of having metastasis if its parenchyma is inhomogeneous or necrosis or cortical nodules are visible in the nodal parenchyma[4-8,11-12]. In the presented group of patients, a significant correlation between the occurrence of metastases and the presence of inhomogeneities in the cortex was demonstrated. If focal cortical thickening or a cortical nodule is evident in the node, it is considered to be an early sign of metastasis detection, but has a low positive predictive value because it is not very specific[4]. The present study also did not show a significant correlation between the incidence of metastases and the presence of focal cortical nodules, but there was a relatively higher incidence of metastases in the presence of focal enlargement to 3 and 4 mm. The nodule is suspected of malignancy even if the so-called peripheral halo or perinodal edema is visible in its vicinity[21]. In our patient sample, a significant correlation between the incidence of metastases and perinodal edema was demonstrated. When the presence of metastasis in a node is suspected, more emphasis is placed on morphological criteria, such as cortex thickening, absence of fat hilum, and vascularization of a non-polar type, than on the size of the node itself[18]. All nodes of uncertain nature or with suspicion of metastatic involvement are ipsilaterally indicated for unambiguous histological verification in the case of primary diagnosed breast cancer, especially if it affects the treatment strategy[22-24]. Clearly pathological or palpable lymph nodes in diagnosed breast cancer on the same side are not absolutely necessary to be verified histologically especially in the case of metastatic disease, but it can rarely be a coincidence of another malignancy – for example, lymphoma, melanoma metastases and even a sign of benign unilateral lymphadenopathy. Therefore, even from a forensic point of view, it is appropriate to confirm as well clearly pathological or palpable ipsilateral nodes in diagnosed breast cancer using a very reliable and simple method, core biopsy. Axillary lymph nodes of pathological appearance without a clear finding in the mammary gland are also indicated for biopsy to exclude or confirm metastasis of the so-called "hidden carcinoma" of the mammary gland or to exclude other pathological findings in the axillary nodes. Histological verification is also necessary for newly diagnosed pathological nodes or packets of nodes in the axillar or supraclavicular areas in conditions after breast ablation.

The limitation of this study is the small number of patients and the fact that it is only a retrospective single-center evaluation.

CONCLUSION

Differentiation between overtly pathological LNs and lymph nodes with a lower degree of morphological alteration, presents a diagnostic challenge. Each suspicious LN with minimal morphological changes should be evaluated by core-biopsy, in view of change in strategy of treatment. A LN may be suspicious of metastasis even if it is small and without a fat hilum, if it is small and has an L/T ratio of less than 2 or equal to 1, if it is small and exhibits peripheral edema or if cortical non-homogeneities are present. A LN is suspicious of being metastatic in the case of focal cortical thickening above 3 mm and diffuse cortical thickening above 3–4 mm. These signs should be assessed in relation to the contralateral axilla, and are more suspicious if present in the ipsilateral axilla and in the context of the size and biology of the primary breast tumor. The minimal morphological signs detected during ultrasound examination of LNs, tumour size and tumour biology should be considered as the predictors for the presence of LN metastases and could trigger the decision to perform a core-biopsy to confirm metastasis in the ipsilateral axillary LNs. The confirmation of metastatic involvement in the axillary lymph nodes and their marking are necessary for subsequent surgical treatment of the axillary region, such as TAD.

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