DIAGNOSTIC VALUE OF GRAY-SCALE ULTRASONOGRAPHY AND COLOR DOPPLER FLOW FOR THE DETECTION OF AXILLARY LYMPH NODE METASTASES IN BREAST CANCER PATIENTS

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ABSTRACT

Purpose: The aim of our study was to evaluate the diagnostic value of gray-scale ultrasonography and color Doppler flow for the detection of axillary lymph node metastases in breast cancer patients.
Materials and methods: This prospective study included 98 women (39 healthy women and 59 with approved diagnosis of breast cancer). All women underwent examination of gray-scale ultrasonography and color Doppler flow. Morphological lymph node findings, intranodal flow distribution and quantitative blood flow parameters were documented and analyzed. Patients were arranged by ultrasound examination findings in to two groups. First group (experimental (n=29)) – women, who was noticed with abnormal axillary lymph nodes during the ultrasound examination. Second group (control (n=69)) – women, who had normal axillary lymph nodes during the ultrasound examination. Healthy women were repeatedly examined after 3 and 6 months. Women who were diagnosed with breast cancer underwent sentinel lymph node biopsy, ultrasound examination findings were compared with histological sample findings. Metastases in the axillary lymph nodes were diagnosed for 22 patients. The accuracy, sensitivity and specificity of ultrasound analysis were calculated.
Results: Cortical thickening was found in malignant lymph nodes – 4,3mm, in benign lymph nodes – 2,2mm ($p<0,001$). Benign lymph nodes had significantly greater central flow, while malignant lymph nodes had peripheral flow ($p<0,05$). Kinetic findings: benign axillary lymph nodes RI=0,59±0,2, PI=3,06±2,4, DSG=5,34±2,1, MDG=2,53±1,6; malignant lymph nodes RI=0,78±0,2, PI=7,91±4,2, DSG=5,89±1,5, MDG=2,24±1,4, but there was no significant meaning ($p>0,05$). Evaluating just morphological findings, ultrasound analysis' accuracy is 81,4%, sensitivity 90,9%, specificity 75,7%, but combined together with kinetic findings accuracy 88,1-89,8%, sensitivity 95,8-96%, specificity 82,9-85,3%.
Conclusion: Cortex thickness and peripheral flow was statistically significant findings in diagnosing metastasis in axillary lymph nodes. Malignant lymph nodes RI and PI usually have greater value than benign lymph nodes, but there was no significant meaning, therefore we cannot depend only on kinetic findings of a lymph node blood flow. Examining kinetic and morphological lymph node findings together gives us 7% more accurate ultrasound analysis.

Keywords: doppler ultrasonography (DUS), malignant axillary lymph nodes, peak systolic velocity (DSG), pulsatility index (PI), resistive index (RI).

INTRODUCTION

Ultrasound imaging (UI) is one of the most commonly used methods to assess the state of armpit (A) lymph nodes (LM) for women with the breast cancer (BC) (1). Precision of UI upon locating metastasis of the breast cancer in armpit lymph nodes is varies in different studies and depends of the experience of the specialist, size of metastasis and the histological type of the breast cancer (2). State of armpit lymph nodes and the amount of affected lymph nodes in the armpit is the irreplaceable factor, especially important for the planning of systemic chemotherapy as well

as surgeries (3). Upon locating typical pathologic armpit lymph nodes (shape changes, absence of hilus, peripheral blood flow), neoadjuvant chemotherapy is recommended for the patient; in case of non-affected structure (oval shape, thin even cortical thickness, hyperechogenic hilus, hilar blood flow) or suspicious lymph nodes (uneven increased cortical thickness, dislocated hilus, mixed or peripheral blood flow) – surgery with sentinel lymph node biopsy. Removal of a large group of regional lymph nodes has a negative effect on the life quality of patients (lymphedema 15-40 percent, paraesthesia, lower amplitude of the hand movement) (3). More than in 60 percent of primary cases of the breast cancer, lymph nodes are unaffected. Such patients do not need the biopsy of the sentinel lymph node; therefore efforts are put to improve possibilities on non-invasive analysis upon identifying metastasis in armpit lymph nodes for the healthy tissues to remain unaffected (4). A healthy lymph node has oval shape, thin even hypoechogenic cortical thickness and hyperechogenic hilus due to walls of the connective tissue, trabeculae of lymphatic tissue and medullar sinuses. Cancerous cells reach the lymph node via lymphatic vessels and accumulate in periphery of the lymph node – it affects the increases cortical thickness and a rounded shape of the lymph node (5). In the majority of analysis the cortical thickness is considered to be increased when exceeds 3 mm; in some studies cytological or histological analysis is recommended with the cortical thickness >2,5 mm (6). In our survey the cortical thickness is considered as being increased after reaching 3 mm. The rounding shape of the lymph node is indicated by the proportion between diameters of long and short axes: in healthy lymph nodes it should be >2, in those affected by metastasis <2 (7, 8). Architecture and hemodynamics of blood vessels changes in lymph nodes affected by metastasis (9). The majority of studies analyse morphologic features of lymph nodes. Aim of our survey is to assess not only morphological, but also kinetic parameters of lymph nodes (type of the blood flow, resistance index (RI) and pulsatility index (PI), the maximum value of the systolic speed and the minimal value of diastolic speed upon predicting possible metastasis in lymph nodes.

AIM OF THE WORK

To define morphological features of healthy lymph nodes and lymph nodes, affected by metastasis as well as to compare the kinetic parameters of the blood flow. To assess statistical indicators of the ultrasound imaging.

MATERIAL AND METHODS OF THE SURVEY

Since 1 September 2015 to 1 September 2016 the prospective case – control survey was implemented in the diagnostic cabinet for breast diseases at the Radiology Clinics in Kaunas Clinics at the University Hospital of the Lithuanian Health Sciences. 98 women were included into the survey, 39 of them – healthy and 59 – with the confirmed diagnosis of the breast cancer. Criterions: 1) armpit lymph nodes were identified as without changes during the ultrasound imaging (even, ordinary cortical thickness and adipose hilus) with hilum or mixed-type blood flow registered; 2) affected/ suspicious armpit lymph nodes found during the ultrasound imaging (uneven, thickened cortical thickness, dislocated hilus) with hilum or mixed-type blood flow registered. The survey didn't include patients with typical pathological armpit lymph nodes (round shape, absence of hilus) and those women with no lymph node blood-flow registered during the ultrasound imaging.

Ultrasound imaging was done with Acuson S2000, Siemens equipment, with a linear sensor and frequency of 14,5 MHz. Two-dimensional B regime was used for the assessment and analysis of the number of lymph nodes as well as morphological features (size, shape, state of hilus, cortical thickness). Type of the blood flow (hilus of mixed-type) was assessed in the colour Doppler regime with a low-speed parameters (4,4 cm/s) as well as quantitative blood-flow parameters (resistance index (RI) and pulsatility index (PI) the maximum value of the systolic speed and the minimal value of diastolic speed). Under the data of the ultrasound imaging, patients were divided into two groups. The first group (explorato-

ry (n=29)) – women with affected lymph nodes, identified during the ultrasound imaging. The second group – control group (n=69) – women with unaffected lymph nodes, identified during the ultrasound imaging. Healthy women were repeatedly examined after 3 and 6 months. Women with diagnosis of the breast cancer underwent the biopsy of sentinel lymph node and data from the ultrasound imaging was compared to results of the histological analysis. Metastases in lymph nodes were confirmed for 22 patients. The sensitivity and specificity of the ultrasound imaging were calculated.
Permission of bioethics for the survey implementation: No. BEC-MF-408.

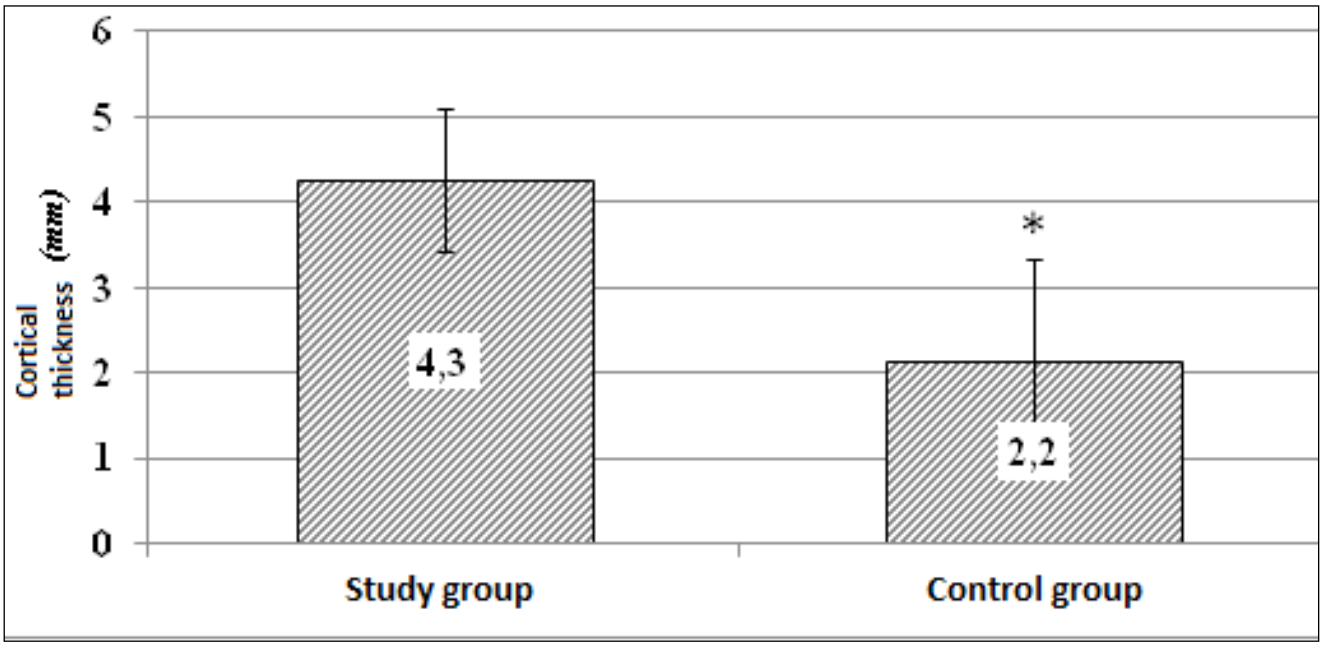
STATISTICAL ANALYSIS

Statistical survey data analysis was done by aids of SPSS 17.0 and Excel 2010. Distribution of analysed features within the scope was assessed by the descriptive data statistics – absolute (n) and percentage frequencies (percent). Quantitative data is presented as arithmetic average (m) with a standard deviation (sn). Comparison of quantitative variables of two independent scopes, the distribution of which supports the principle of normality, average values were compared on Student's T-test; comparison of quantitative variables of two independent scopes, the distribution of which does not support the principle of normality, average values were compared on Mann-Whitney U-test. New tables of interrelating characteristics were composed for the assessment of links between features; dependence was identified on the criterion of chi-square ($\chi 2$). When data is described in the four-field (2x2) frequency table and when at least one expected number of observations is less than 5, the precise Fisher's criterion is calculated. When the significance level $p \leq 0,05$, the difference between features in groups of respondents was considered as statistically significant.

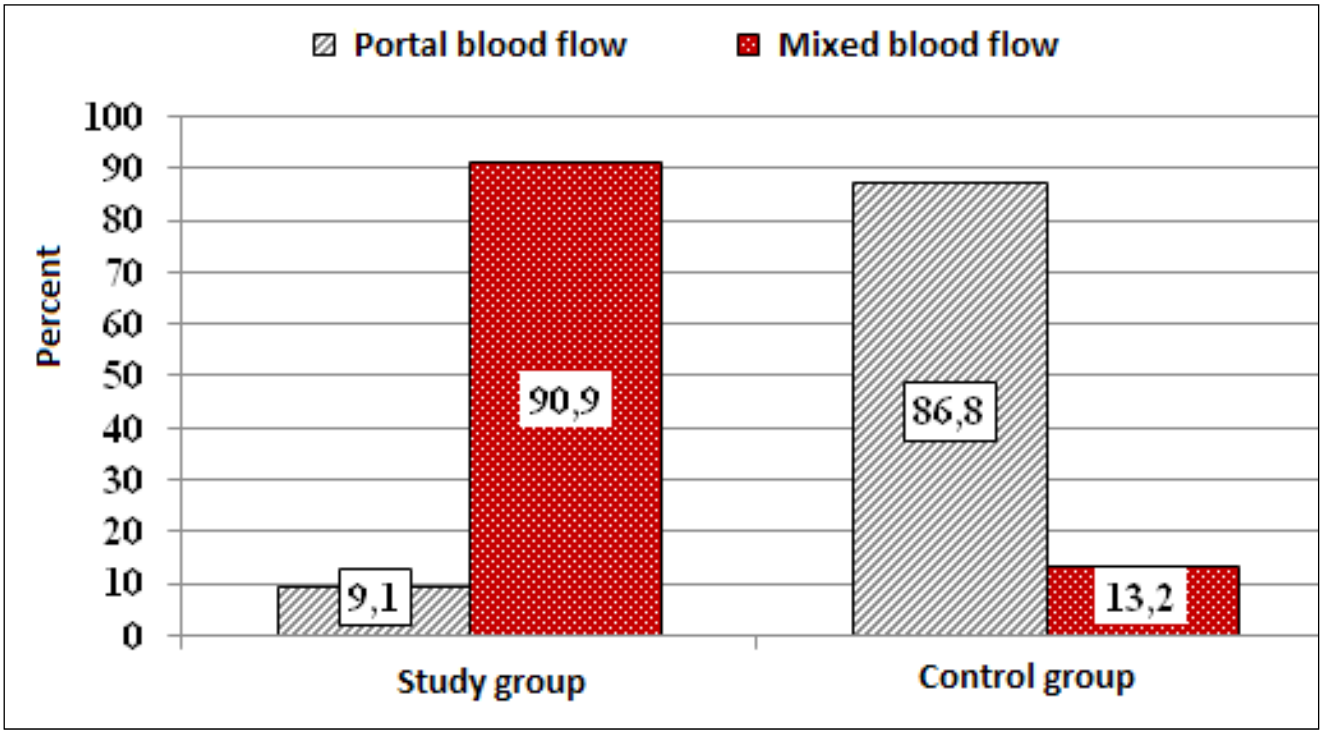
RESULTS

Age average of the women-respondents – 60,7 ($p>0,05$). Age of respondents in the exploratory group was not statistically significantly different from the age of women in the control group. Types of the breast cancer were identified: invasive ductal carcinoma – 25 cases (40,7 percent), invasive lobular carcinoma – 27 cases (44,1 percent), mucinous adenocarcinoma 6 cases (10,2 percent), intracystic carcinoma – 1 case (1,7 percent). The degree of differentiation of the tumour (G1, G2, G3) was analysed as well as the imunomarker expression (estrogen (ER), progesterone (PR) receptors, human epidermal growth factor receptor (HER2)), spread in blood vascular and lymphovascular (LV1) system. Tendency was observed that tumours with a more aggressive form G2, G3 and HER2+ tend to metastases to regional lymph nodes, but his data was not statistically significant. Patients with metastases in lymph nodes were identified with spread by blood vascular and lymphovascular systems.
Cortical thickness of lymph nodes, affected by metastases was higher – 4,3 mm, while in health lymph nodes – 2,2 mm ($p<0,001$) (Picture 1). Proportion between diameters of long and short axes in healthy and affected lymph nodes was similar (>2). Statistically significant difference was defined that the hilar blood flow was more often observed in healthy armpit lymph nodes, while in affected lymph nodes – mixed (Picture 2).
Kinetic features: in healthy armpit lymph nodes RI=0,59±0,2, PI=3,06±2,4, MSS=5,34±2,1, MDS=2,53±1,6; in lymph nodes affected by metastases RI=0,78±0,2, PI=7,91±4,2, MSS=5,89±1,5, MDS=2,24±1,4. It was defined that MSS in the exploratory group is statistically significantly higher ($p<0,05$) than in the control group (Picture 3). PI and RI in lymph nodes affected by metastases are also higher than in healthy lymph nodes, but this data was not statistically significant.
According to our data, the UI accuracy is 81,4 percent, sensitivity – 90,9 percent, specificity – 75,7 percent and if kinetic features are assessed together, accuracy – 88,1-89,8 percent, sensitivity – 95,8-96 percent, specificity – 82,9-85,3 percent. When assessing the state of the armpit lymph nodes for women with breast cancer, it is important to evaluate not only morphological, but also

1 Picture. Mean cortical thickness (*- p<0,001).

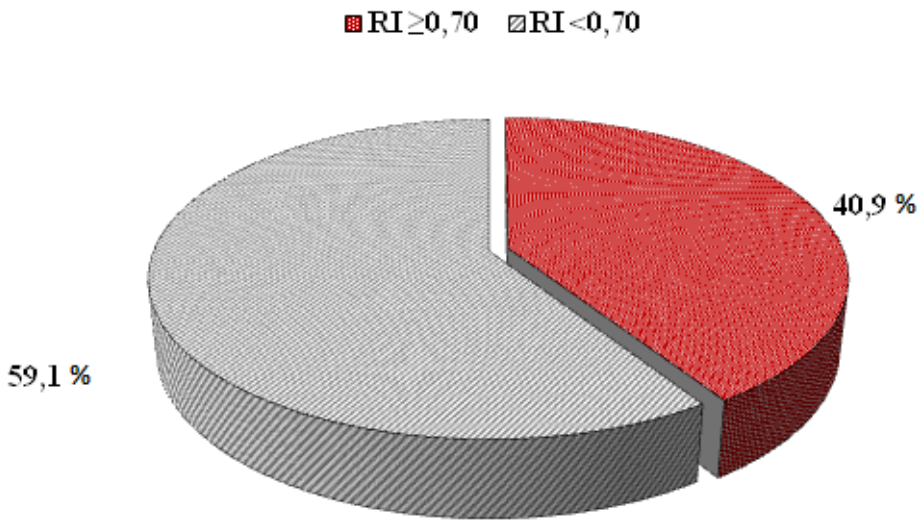


2 Picture. Circulation type (χ^2=48,56; p=0,001).

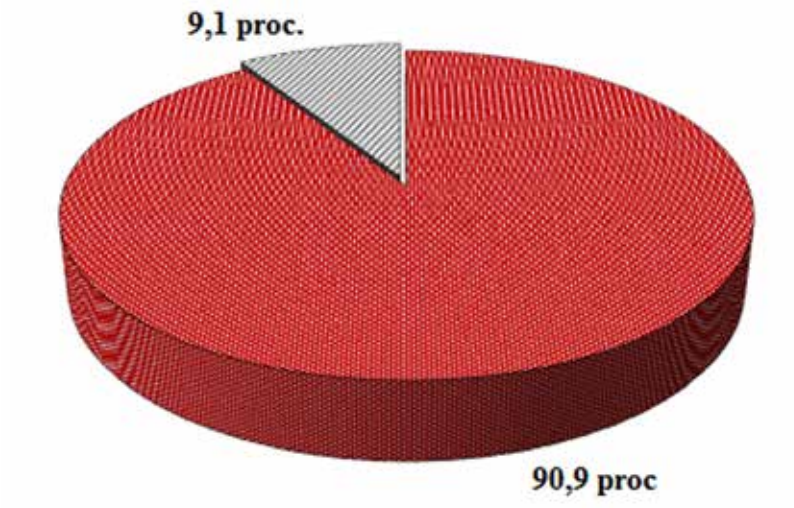


3 Picture. (a,b,c) Flow velocity of metastatic lymph nodes.

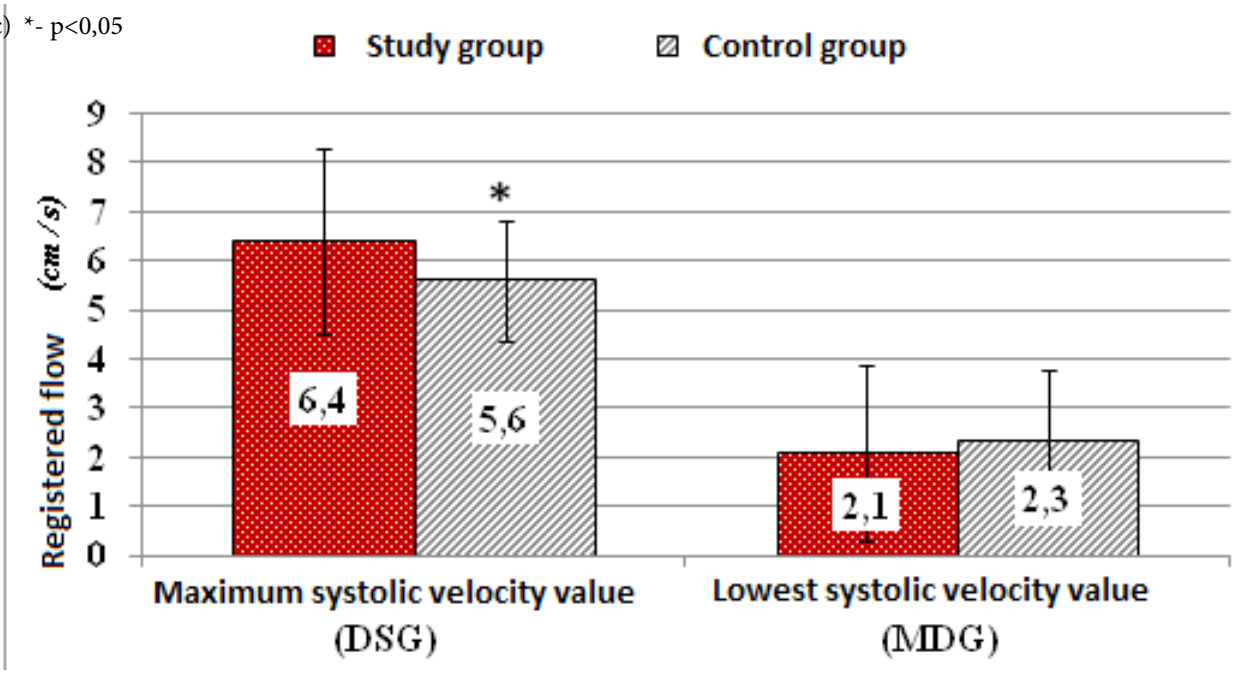
a)



b)



c) *- p<0,05



kinetic features of the lymph node, because in such case the UI accuracy increases.

DISCUSSION OF RESULTS

State of armpit lymph nodes and the amount of affected lymph nodes in the armpit is the unchangeable prognostic factor for women with breast cancer.

In over 60 percent of all primary cases of the breast cancer the armpit lymph nodes are unaffected. It is strived to improve possibilities of non-invasive examination possibilities for identification of metastases in armpit lymph nodes for the healthy tissues to remain unaffected.

Tendency was observed in the exploratory group that tumours of the more aggressive form G2, G3 and HER2+ tend to metastases to regional lymph nodes, but this data was not statistically significant. Jalini study also defined that patients with healthy of affected lymph nodes identified during UI have different clinic-pathologic factors, therefore upon existence of these symptoms (LV1, G3) and healthy lymph nodes in UI , state of such women should be treated carefully and the possible repeated UI could be offered (10). For patients, with metastases in lymph nodes in 95,5 percent of cases the spread by blood vascular and lymphocascular systems was identified. Study of Nwaogu et al. indicate this feature as statistically significant (p=0.0007), therefore it is recommended to assess the state of patients with this symptom with more attention in order to avoid falsely negative results (11).

In the majority of studies (12-14) the cortical thickness in lymph nodes affected by metastases was >3 mm. On the base of our data, the cortical thickness is also a statistically significant feature upon defining metastases in armpit lymph nodes. It was increased – 4,3 mm in the affected lymph nodes and it was 2,2 in healthy lymph nodes (p<0,001).

Several studies analysed the proportion between diameters of long and short axes as it may indicate the round form of the lymph node (in healthy lymph nodes it should be >2, in those affected by metastasis <2 (7, 8). In our survey this proportion was not different (>2), maybe because patients whose lymph nodes seemed healthy or suspicious (with increased cortical thickness) during UI were included into the survey.

Statistically significant difference was defined when the hilar blood flow was observed in healthy armpit lymph nodes while in those affected by metastases – mixed blood flow. Jabbar and Das studies also indicate this feature as statistically significant (12, 15).

One of the essential tasks of our survey was to assess kinetic data of blood flow in the lymph node: resistance index (RI) and pulsatility index (PI), the maximum value of the systolic speed (MSS) and the minimal value of diastolic speed (MDS). Data in literature upon assessment of these features is rather controversial. In several studies where the neck lymph nodes were assessed, kinetic features were identified as being important upon differentiating lymph nodes affected my metastases from the reactive ones (16-19). However, Das survey, when assessing morphological features of lymph nodes together with kinetic blood flow data, indicated the reduced statistical indicators (15). On the base of the literature data, theoretical hypothesis was prepared that RI in lymph nodes affected by metastases should be >= 0,70, PI> 1,8, while in healthy armpit lymph nodes RI <= 0,65, PI <1,0. Results were obtained that in healthy lymph nodes I=0,59±0,2, PI=3,06±2,4, MSS=5,34±2,1, MDS=2,53±1,6, in those affected by metastases - RI=0,78±0,2, PI=7,91±4,2, MSS=5,89±1,5, MDS=2,24±1,4. It was defined that MSS in the exploratory group is statistically significantly higher (p<0,05) than in the control group. Even though there is no statistically significant difference, RI and PI in lymph nodes affected by metastases tend to be higher than in healthy lymph nodes.

Statistical data from UI analysis in different studies was different (accuracy 63-90 percent, sensitivity – 53-100 percent, specificity – 65-100 percent) (8,12,14,15,20). According to our data, upon assessment of morphological features only, UI analysis' accuracy was 81,4 percent, sensitivity

1 Table. Statistical summary.

	Sensitivity (%)	Specificity (%)	TNV (%)	NNV (%)	Accuracy (%)
H.Abe, 2013 B(2)	56,28	80,83	61,88	76,98	72,09
S.E.Song, 2012 B(2)	82,3	89,1	80,0	86,6	-
B.Lee, 2013 B(2)	53,7	85,1	81,o	60,0	67,9
J.A.Jabbar, 2012 B(2)	95,0	95,0	95,0	5,0	-
Komb. su dopl.	100,0	100,0	100,0	0,0	-
A.Das, 2012 B(2)	87,0	89,0	82,0	92,0	88,0
Komb. su dopl	59,0	65,0	50,0	73,0	63,0
Our data, 2016 B(2)	90,9	75,7	69,0	93,3	81,4
Combination with doppler. (RI)	95,8	82,9	79,3	96,7	88,1
Combination with doppler. (PI)	96,0	85,3	82,8	96,7	89,8

– 90,9 percent, specificity – 75,7 percent. While if kinetic features are analyses together, the accuracy increases by 7 percent (Table 1).

CONCLUSIONS

Cortical thickness and the mixed-type blood flow are statistically significant features for identifying metastases in armpit lymph nodes.

RI and PI in lymph nodes affected by metastases tend to be higher than in healthy lymph nodes, however statistically significant difference was not found therefore only kinetic lymph node blood flow data cannot be trusted.

Upon assessment of morphological and kinetic lymph features of lymph nodes together, the UI accuracy increases ~7 percent.

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