



ЯРОСЛАВСКАЯ ОБЛАСТНАЯ ТОРГОВО-ПРОМЫШЛЕННАЯ ПАЛАТА
YAROSLAVL CHAMBER OF COMMERCE AND INDUSTRY

Translation into English

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December, 2008

Report

On clinical trials "Evaluation of the Informativity of the Electrical Impedance Mammograph in Conjunction with Mammoscintigraphy"

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2008, Moscow

1. Introduction

The report in hand presents materials obtained in the process of clinical test work which was aimed at evaluating the sensitivity of the electric impedance mammography technique in the detection of pathologic changes in the mammary gland by means of the electric impedance computer mammograph ("MEIK"). The testing was done within the terms of the research and development contract signed by the "EPIDBIOMED-IMPEX" Ltd. and the "Russian Scientific Center of Radiology and Nuclear Medicine" (Federal State Institution) subordinate to "ROSMEDTECHNOLOGY".

Electric impedance (as well as electric conductivity) is an essential characteristic of living tissues. It impedes the transfer of the electric charge emerging from the imposition of the external field and reflects the changes of the tissue functional status. The electric conductivity of living tissues depends upon the pass current frequency and increases to a maximum value with the frequency rise. This is accounted for by different mechanisms of the high- and low-frequency current passage through the biological media. Low-frequency currents are mainly transmitted in the intercellular space, while high-frequency currents are transferred both through the intercellular liquid and the cells. Tissue electric properties are significantly affected by the changes of the physiologic status of the organism caused by its exposure to chemical and physical factors as well as by various pathologic processes. Thus, electric impedance tomography can be considered a functional diagnostic technique which provides for the data on the mammary gland physiologic status and is sensitive to the change of the tissue electric conductivity.

The electric impedance mammograph is intended for functional imaging of the mammary gland tissues involved in a pathologic process. The principle is underlain by a supposition that malignant tumors of the mammary gland display far more different electric conductivity (the ability to pass the electric current) than that of the surrounding healthy tissues. The electric impedance mammograph enables to image the distribution of the biological tissue conductivity in several cross-sections of the gland and detect tumors visualizing them as areas with abnormal values of electric conductivity.

2. Tasks and Objectives.

The clinical testing aimed at making an assessment of the device information capacity for electric impedance mammography in combination with mammoscintigraphy.

The tasks included:

- 1) Evaluation of the electric impedance mammography safety rate;
- 2) Assessment of the sensitivity, specificity and accuracy of the technique on the basis of the given guidelines;
- 3) Drawing up of additional guidelines for subsequent improvement of the technique efficiency.

3. Methods and Materials of Clinical Test Work.

Device implementing the technique.

The "MEIK" device is for use in electric impedance mammography. As has been mentioned, it registers the transfer of the electric charge emerging from the imposition of a 50 kHz external field and reflects the changes of the tissue functional status.

As far as the design is concerned, the "MEIK" is a 4-node device. The first diagnostic node is represented by a block of 256 electrodes and an embedded microprocessor controlling system. The electrodes are located in plane with the surface of the mammary gland under examination. They inject a low alternating current in the patient's body and measure the distribution of the correspondent electric potentials on the body surface. The second node is a base electrode which is attached to the patient's wrist and linked to the first diagnostic node. The third node is presented by a cable system which contains a grid power supply unit and an optoisolator providing for the galvanic separation between the circuits of the measurement unit and the personal computer. Software makes up the fourth node of the device. The software enables to integrate the readings taken from the device, acquire the ghost image of the mammary gland at various depths, obtain the data concerning the distribution of the signal registration frequencies by similar parameters and store the information obtained.

Subjects of clinical test work.

The total number of patients participating in the clinical test work amounted to 64. The medical data on the diagnosed pathologic changes are shown in table 1.

Table 1. Types of Pathology Detected in the Mammary Gland. Statistical Data.

Pathology Type	Number of Patients	Percentage (%)
No pathology detected	8	12.5
Breast cancer T0-T1	19	29.7
Breast cancer T2	5	7.8
Breast cancer T3-T4	4	6.3
Fibro-cystic mastopathy with the dominance of the cystic component	4	6.3
Fibro-cystic mastopathy with the dominance of the fibrous component	9	14
Papillomas	4	6.3
Fibrous adenoma	10	15.6
Inflammation	1	1.5
Total	64	100

All patients taking part in the test work were volunteers. The examination was held blindly, i.e. the medical investigator was unaware of the pathologic process type, its localization and rate of expansion preliminarily detected using standard diagnostic techniques. The MEIK-based examination was supplementary and did not affect the drawing up of the treatment protocol. Afterwards the patients whose histograms displayed the electric impedance evidence of breast cancer were selected from the group, the examination results being compared with the clinical diagnosis.

Clinical testing procedures.

The examination was mostly carried out with the patient in prone position. In cases of insufficient gland volume the filming was done with the patient standing. This was necessary for positive contact of the breast surface with the electrodes.

The distribution of the mammary gland geometry is far more homogeneous when the patient is lying, which explains the expedience of the mammary gland's horizontal examination. The patient's breast and wrist to which the base electrode should be attached are to be moistened before the examination starts.

The medical investigator's basic task is to provide for the optimal position of the "contact panel" on the mammary gland, so that the device electrodes should be efficiently pressed to the breast surface. Contact efficiency is controlled through the PC whose screen displays a homogeneous color circle reflecting the number of efficient electrodes. After the examination the computer shows the exact number of inefficient electrodes, which allows to estimate the accuracy of the examination and repeat it if required. When inefficient electrodes are discovered, the investigator is to change the position of the "contact panel" until the optimal amount of efficient electrodes is obtained. Then the image is registered.

4. Result control and estimation.

When analyzing the mammograms as well as the results of the mammary gland ultrasound diagnostics, careful consideration was given to the density characteristic of the mammary gland tissues.

The mammoscintigrams were analyzed into the evaluation of the tissue metabolic activity. When conducting mammoscintigraphy the physician was being suspicious of the radioisotope tracer accumulation level being exceeded in the focus as compared to the accumulation level typical of the native tissue, with subsequent determination of the delayed retention index. A high index accounted for more active metabolic processes in the focus.

The information capacity of the electric impedance technique was assessed through comparisons of the clinical diagnoses made by using standard diagnostic techniques and those formed in the course of electric impedance examination.

To prepare the final report on the mammary gland status the following criteria of the electric impedance mammography were taken into consideration:

- Visual evaluation of the image at various scan depths (searching for focal symptoms, determination of the depth, local electric conductivity, focus coordinates);
- Filtering of the image, highlighting of the required area;
- Presentation of the image in the form of electric conductivity distribution;
- Analysis of the electric conductivity distribution in all seven axial scans. Mean value, standard deviation as well as maximum and minimum values were assessed;
- Analysis of electric conductivity distribution in the tissues of the healthy and the affected gland (modality, symmetry, displacement);

As is clear from paragraph 4.3, the assessment of the electric impedance tomogram involves several stages.

The first stage implies visual evaluation of the image. The software enables to obtain 2 types of images: in the "grey scale" mode and in the "color scale mode".

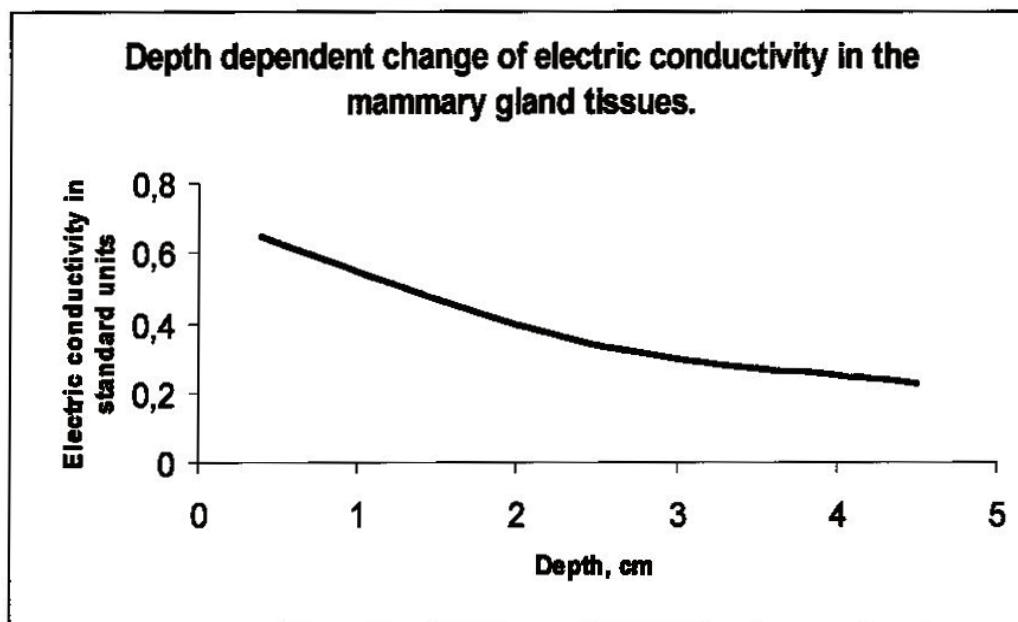
The mammary gland image in the "grey scale" mode has a mosaic structure with transitions from darker (negative) to lighter tones. The presence of darker and lighter tones is conditioned by the electric conductivity distribution in the mammary gland tissue, i.e. the presence of areas with low and high electric conductivity (hyperimpedance and hypoimpedance areas respectively) and various interim options. Healthy tissue images are characterized by even distribution of hyper- and hypoimpedance areas, the former dominating the image. When the tissue is involved in a pathologic process, the image displays a more contrasting distribution of hyper- and hypoimpedance areas. However, the image-based estimation of the degree to which the pathologic process has developed cannot be fully reliable. This is accounted for by the individual nature of hyper- and hypoimpedance area distribution, determined by the influence of many factors – age, the phase of the menstrual cycle, seasonality, medication taking, etc. All this prevents from accurate evaluation of the image and may be considered as an approximate (investigatory) stage of the pathologic status analysis.

Image filtering and highlighting of the required area is the next stage of data processing. The preliminary visual analysis of the image allows to define the so-called "area of interest" which is to be compared with the correspondent area of the other mamma and to serve the reference point of other calculations. To properly

estimate the image and the electric conductivity distribution in the mammary gland tissues one is to compare the tomograms made at every scan plane (altogether measuring 7). This diagnostic data are of the greatest significance, in our view.

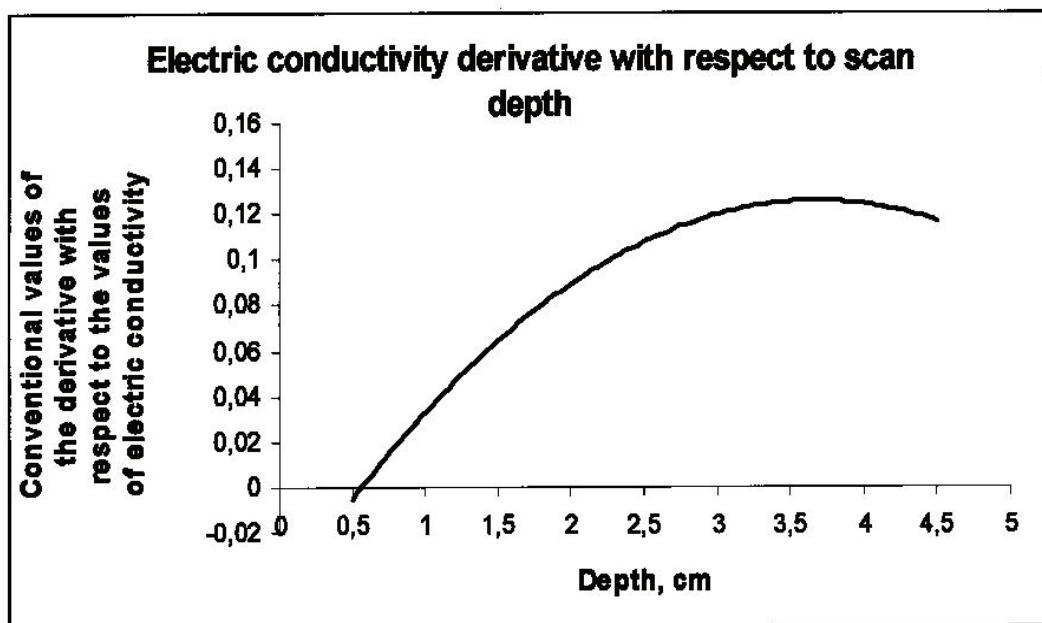
After the images are processed automatically graphs of electric conductivity distribution are plotted for every section. The graphic distribution of frequency ratios for the appearance of areas with similar electric impedance enable to make a reliable estimate of the mammary gland status and draw conclusions upon the availability of a pathologic process. The frequency distribution curve built for healthy tissues is unimodal and follows the law of normal distribution. Thus, distribution curves are to converge for both mammary glands. On principle normal curves are located between 0.1 – 0.6 (in the left part of the standard graph). In graphic display the extremum and mean electric conductivity values went down with the transition from superficial to deep-lying scan planes. To enhance the reliability of assessment we chose to analyze the smoothness of the curves reflecting the loss in the mean and extremum values of electric conductivity while transition was made from superficial to deep-lying scan planes (Figure 1).

Figure 1.



The nature of the curve smoothness was analyzed by the differential of the criteria dynamics derivative to the depth of scanning (Figure 2).

Figure 2. Nature of electric conductivity change smoothness by the dynamics derivative.

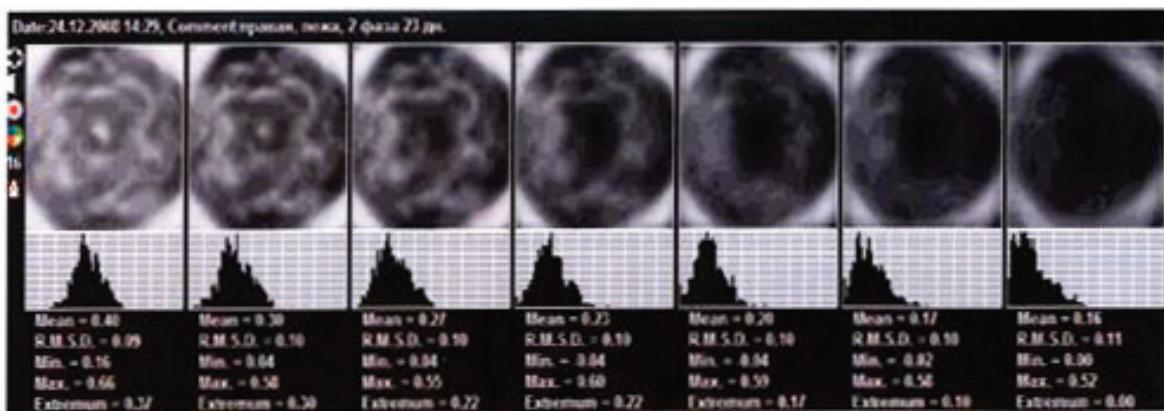


The following parameters were selected as criteria for the assessment of frequency ratio graphic distribution:

- the position of the graph in reference to the normal distribution;
- the number of extrema and their shift as compared with the mathematical expectation (estimated in relation to the X-axis);
- extremum evidence (maximum and minimum) characterizing how frequent the appearance of areas with similar electric impedance is (estimated in relation to the Y-axis);
- the mean value of all registered electric impedances;
- analysis of the curve smoothness for the depth dependent change of the mean and extremum conductivity values.

When the functional status of the mammary glands is relatively normal, the resultant curves are nearly identical as to their shape and position in reference to the axes. The curves reflect the distribution of frequency ratios for the appearance of areas with similar electric impedance, the extremum shifted to the left, the curve itself having a descending plateau (Figure 3).

Figure 3. The image of a healthy mammary gland together with the graphs characterizing the profile of electric conductivity distribution in it.



On principle the mean value of all registered electric impedances depends upon the patient's age. The standard values are shown in table 2.

Table 2. Mean values of electric conductivity in healthy mammary glands.

Age group	Value of electric impedance	Measure of inaccuracy (+/-)
Before 30	0.37	0.08
30 – 40	0.48	0.077
40 – 50	0.51	0.078
After 50	0.54	0.1

The graph built for a healthy mammary gland was to have risen smoothly tracing out a trajectory of the reverse exponent curve (Figure 4). Any deviation from the above-listed parameters may be considered a sign of pathology, which requires extra examinations.

When two or more parameters are deviated from, the patient is assigned to the breast cancer risk group.

5. Clinical results.

The data obtained are based on the research findings made at the Russian Scientific Center of Radiology and Nuclear Medicine (RSCRNM). Electric impedance tomography was held for 64 patients between 40 and 60 years of age. All patients were undergoing a complex clinical radio- and sonographic examination in the Federal mammological center based at RSCRNM. 55 patients were operated on, their diagnoses verified histological afterwards. 8 healthy women made up a control set. 28 patients were suffering from malignant tumors (43.75%), 28 – from benign tumors of the mammary gland (43.75%).

When analyzing its sensitivity, we checked the expedience of complicating the given technique by searching for the focus of superconductivity. For this purpose we examined 28 patients with malignant tumors of the mammary gland using the following three methods:

- 1) Visual analysis of the image and searching for the focus of superconductivity;
- 2) Step 1) followed by the analysis of the electric conductivity distribution graph. The bimodality of the conductivity distribution curve served the criterion for breast cancer suspicion.
- 3) Step 2) followed by the analysis of the curve smoothness reflecting the loss in the mean values of electric conductivity while transition was made from superficial to deep-lying scan planes. The appearance of a negative extremum on the graph reflecting the electric conductivity distribution in the given area was the criterion for breast cancer suspicion (Figure 4).

Figure 4. Analysis of focal conductivity changes at different scan planes.

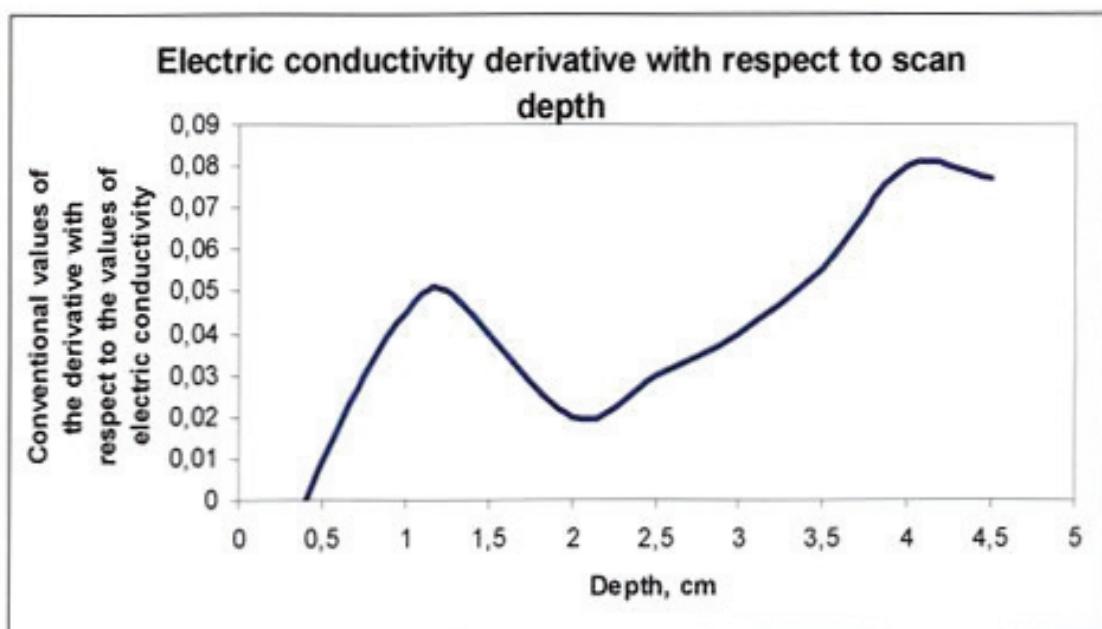
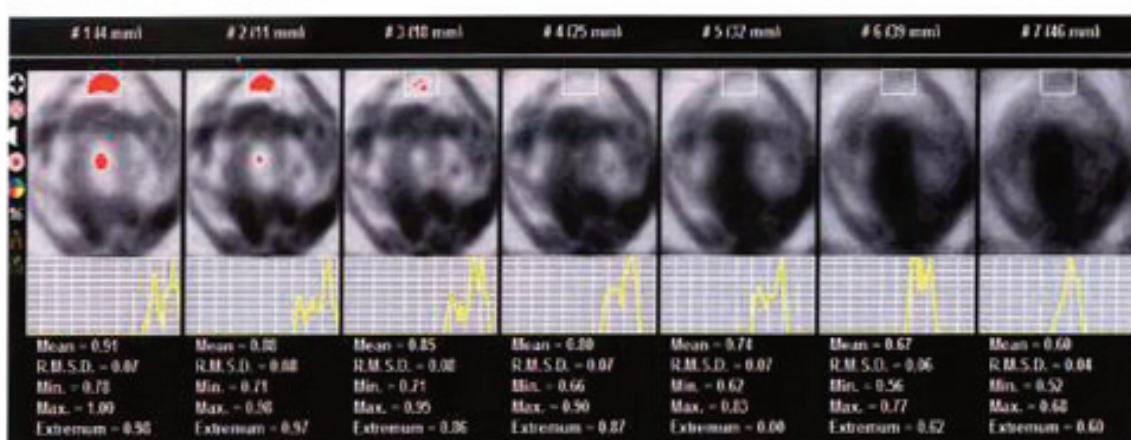


Table 3 contains data on the sensitivity of the above-listed methods in the detection of breast cancer.

Table 3. Sensitivity of the methods for electric impedance data evaluation in the primary detection of breast cancer.

Stage	Total number of patients	Conclusion on hyperconductivity		Conclusion on bimodality		Conclusion on the extremum in the graph reflecting the smoothness of the conductivity fall	
		Sensitivity, %	False negative	Sensitivity, %	False negative	Sensitivity, %	False negative
T0 – T1	19	63	7	79	4	84	3
T2	5	60	2	60	2	80	1
T3 – T4	4	50	2	50	2	75	1
Mean sensitivity, %		57,7 %		63%		80%	

As is clear from the table, the complication of the diagnostic technique enabled to raise the sensitivity by 21.2% at early stages of breast cancer, by 20% at the T2 stage, by 25% at the advanced stages of breast cancer. The mean rise of the technique sensitivity thus amounts to 22+/-2.1%.

Besides, we managed to analyze the possibility of electric impedance mammography and mammoscintigraphy application for the diagnosis of more complicated cases: when no well-defined focus is observed and only indirect indicators of malignance are available (increase of blood flow detected by ultrasonography, presence of micro-calcification and focal changes of the string structure imaged by radiography). Comparative data on the above-mentioned cases obtained by various diagnostic techniques are displayed in table 4.

Table 4. Sensitivity of diagnostic techniques for x-ray negative cancer detection.

Diagnostic techniques	Sensitivity (%)
X-ray mammography (indirect indicators)	56
Ultrasonography	55
Blood flow evaluation	40.5
Mammoscintigraphy	79.5
Electric impedance mammography	86.5

8 patients followed up in RSCRNM (see above) concerning non-neoplastic pathologies of the mammary gland were selected for the evaluation of the technique specificity. A complex preliminary examination of the mammary glands confirming their normal age-related functional status served the criterion for the patient's inclusion in the control set. Only 1 patient from the group was suspected to be suffering mammary gland pathology. The conclusion on the possibility of pathologic process development was based on the bimodality of the conductivity distribution curves and the appearance of an extremum in the graph of the mean conductivity change derivatives. No focus of hyperconductivity was detected. Thus, the specificity of the technique amounted to 100% when following the instructions of paragraph 1) and it made up 88% when following the instructions of paragraphs 2) and 3).

The general diagnostic accuracy of the technique for different principles of data processing and various stages of the disease are given in table 5.

Table 5. Statistical conclusions upon the application of various principles of data processing at various stages of the disease.

Stage	Conclusion on hyperconductivity			Conclusion on bimodality			Conclusion on the extremum in the graph reflecting the smoothness of the conductivity fall		
	Sensi- tivity	Speci- ficity	Accu- racy	Sensi- tivity	Speci- ficity	Accu- racy	Sensi- tivity	Speci- ficity	Accu- racy
To - T1	63	100	82	79	88	84	84	88	86
T2	60	100	80	60	88	74	80	88	84
T3 – T4	50	100	75	50	88	69	75	88	82
Accuracy, %	79			76			84		
Measure of inaccuracy	3,605551			7,637626			2		

Besides we examined 28 patients followed up in the RSCRNM mammological center on the occasion of benign tumors of the mammary gland, fibro-cystic mastopathies and fibrous adenomas mostly.

The analysis of their tomograms revealed the predominance of high electric conductivity (hypoimpedance) areas as compared to normal tomograms characterized by the predominance of hyperimpedance zones. No specific features were reveled in the course of visual analysis of hypo- and hyperimpedance area distribution.

More significant diagnostic data can be obtained when assessing electric conductivity distribution as well as analyzing the graph of electric conductivity change in the focus projection at various depths. In cases of unpronounced mastopathy the

frequency distribution curves for both mammary glands are nearly identical as it is in normal tomograms. The curves are located in the left part of the graph as is the case in the norm.

The tomographic images of the 40 and over year-old patients suffering from benign tumors of the mammary gland displayed a big number of light (hypoimpedance) areas with various degrees of density. The extension of hypoimpedance areas to all scan planes is also typical of such cases.

The analysis of conductivity distribution curves enables to outline several characteristic features:

- 1) the divergence of the curves;
- 2) the right-hand shift of both curves;
- 3) the presence of two or more extreums;
- 4) difference in the amplitude of curve.

The sensitivity of electric impedance mammography in the detection of benign tumors of the mammary gland made up 78.6%, while its specificity amounted to 88%.

6. Conclusions.

Electric impedance tomography of the mammary gland conducted with the help of the "MEIK" computer mammograph is a non-invasive and no-dosage technique. Acquisition of data concerning the functional changes in the mammary gland, 3-D images, reasonable material inputs as well as low time and energy consumption are among its numerous advantages. Electric impedance tomography displays high sensitivity in the primary diagnosis of benign tumors of the mammary gland and, which is no less important, enables to distinguish patients with a high risk of the neoplastic process development.

All this makes it rational to use electric impedance tomography for the dynamic follow-up of patients with the diffuse and nodular types of mastopathy. Electric impedance tomography may also be effectively practiced as a screening technique in the consulting rooms of the out-patient departments and women's health clinics. Besides, it seems reasonable to employ the technique for specifying the indications to invasive diagnostic manipulations as well as exercising indirect control over the patient's endocrine profile in the course of conservative treatment of mastopathy and selection of appropriate hormonal contraceptives.

04.03.2009

Hereby the Yaroslavl Chamber of Commerce and Industry certifies the authenticity of the translation with the document in Russian.

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External Relations

