

“Approved”

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**Report on the scientific research work conducted on the assessment of the factors influencing upon the efficiency of radio-thermometric measurements with the use of the diagnostics complex RTM-01-RES (company RES, Russia)**

1. Introduction

During the period from 16 December 2005 and 22 April 2006 in the laboratory of the radio isotopic diagnostics of the radiation medicine unit on the base of “FGU Russian Scientific Center for Roentgen-radiology of the Federal Agency for Healthcare and Social Development” within the framework of the protocol No. 10 of 14/03/05 there has been held a scientific research work with the use of the radio thermometric method (the RTM method) on the diagnostics complex RTM-01-RES with high-frequency sender and noise-protected antenna (company RES, Russia).

2. Objectives and tasks

2.1. The main objective of the tests has been the revelation of the main criteria influencing upon the diagnostics efficiency of the RTM method.

2.2. The main tasks of the clinical tests were:

1	To estimate the correlation of results of radionuclide study of mammary glands based on the study of vascularization, and on the change of the transmembrane potential with the results received with RTM.
2	To estimate the correlation of results of color dopplerography of mammary glands based on the study of distinctive features of the blood flow and RTM.
3	To estimate sensitivity, specificity of RTM depending on the degree of the malignant tumor.

### 3. Materials and methods

The clinical tests of the RTM method have been based on the results of the complex clinical-Roentgen-sono-dopplerography examination of 79 patients with various illnesses of mammary glands. In cases of hampered diagnostics there was conducted the radionuclide study (mammo-scintigraphy) with Reagentum Technetrium and the RTM-diagnostics. For the more precise diagnostics an aspiration biopsy was conducted with up-to-date needle-gun systems under roentgenologic or sonographic control. When necessary, a surgical treatment has been made with post-surgery histological verification. This allowed to accomplish a retrospective analyses of the trustworthiness of the RTM method.

### 4. Assessment of results

The assessment of the efficiency of different results was accomplished by scores estimation.

4.1. At the assessment of blood flow the distribution of points was as follows:

Blood flow is not registered	0
Single colored locus	1
The presence of 2-4 feeding vessels	2
Expressed peripheral blood flow	3-4

4.2. At the assessment of mammo-scintigrams one was guided to the excess of the level of accumulation of the radio-pharmaceutical preparation [RPP] in the hotbed in comparison to the level of accumulation in the native tissue (KDN). Higher values of KDN were witnessing of the more active metabolic processes in the given hotbed. The metabolic activity, as a rule, corresponded to the malignant process, but in a number of cases was noted at some benign neoplasm too. The staging of the metabolic activity in the hotbed was determined in the following way:

Level of excess of accumulation, %	Qualitative evaluation of scintigrams	
	Benign processes	Malignant processes
< 10	0	0
10-25	1	5
25-50	2	6
50-75	3	7
>75	4	8

Apart from qualitative evaluation of scintigrams and determining KDN there was assessed the excess of accumulation of concentration of RPP in the unit volume of the growth over concentration in the analogous volume of adjacent tissues. Here the ratio below 0.7 corresponded to the benign neoplasm.

4.3. The degree of expression of thermal changes (the qualitative evaluation) was determined by the operator on the bases of the program's conclusion (auto diagnosis) with the account of clinical data and anatomic-physiological distinctiveness of the patient. The thermograms were characterized by parameters Th on a six-point scale.

The maximum index is Th5, the minimum – Th0.

No.	Index	Degree of expression of thermal changes
1	Th0	Practically no thermal changes
2	Th1	Decreased thermal activity of tissues
3	Th2	Insignificant thermal changes
4	Th3	Heightened thermal activity without local hotbeds and without high thermal assymetry
5	Th4	High level of thermal activity, with the presence of hotbed assymetry without local increases of temperature
6	Th5	High level of thermal activity, with the presence of hotbed assymetry and with the presence of local increases of temperature

The conclusion of the RTM-expert was considered true if the patient with verified diagnosis "mammary gland cancer" had level of thermal activity higher than Th2 in the corresponding mammary gland.

The conclusion of the RTM-expert was considered true if the patient with verified diagnosis "mammary gland cancer" had the index "result of expert system" of over zero in the corresponding mammary gland.

To simplify work with the RTM-system the qualitative evaluation of thermograms was expressed in absolute values. The values of over 0 testified to the presence of a malignant process.

4.4. With the patients who had a verified mammary gland cancer the level of malignance was assessed after surgical treatment.

The patho-morphologic assessment of malignance was carried out by the following criteria:

I. Formation of tubular and duct-like stryctures:

>75% - 1 point; >10<75% - 2 points; <10% - 3 points.

II. Number of mitoses (at the magnification of 400)

<10 mitoses in 10 fields of vision – 1 point;

>10<20 mitoses in 10 fields of vision – 2 points;

>20 mitoses in 10 fields of vision – 3 points;

III. Cellular polymorphism: cell of the same size and shape, small, with disperse distribution of chromatin, without nucleuses - 1 point; modest polymorphism of nucleuses, some enlargement of cells – 2 points;

the nucleuses large, of different shapes, with one or more nucleuses, with rough chromatin – 3 points.

The sum of points determines degree of malignance:

I (low degree) – 3-5 points

II (modest) – 6-7 points

III (high) – 8-9 points.

### 5. The material and method of study

For the X-ray examination of mammary glands the roentgenologic mammograph “MammoDiagnost UC (Phillips, the Netherlands) was used.

For ultrasonic research we used apparatus “Sonoline Elegra” (Siemens, FRG) with the software to perform color Doppler-sono-graphy and 3D reconstruction of the image.

To perform invasive intervention we used digital X-ray system SenoVision (GE, USA), the X-ray mammographic system MammoDiagnost 3000 with the stereotactic console Cytoguide (Phillips, the Netherlands).

For mammoscintigraphy the Gamma-chamber Millennium from GE, USA was used. For radio-thermometric measurements we used the diagnostics complex RTM-01-RES with the high-frequency sender and noise-protected antenna (company RES, Russia).

### 6. Subjects of study

Of 79 patients by the data of the retrospective analysis 30 were found to have the histologically verified mammary gland cancer.

With regard to the results of the histological and cytological researches the patients were divided into 4 groups depending on the nosologic form of the illness and the results of cytological study:

	Pathologic changes	Absolute number of patients
1	Simple duct hyperplasia	23
2	Fibroadenoma	11
3	Epithelia proliferation, atypical cells	15
4	Mammary gland cancer	30

Of 30 diseased with the mammary gland cancer 6 (20%) had noninvasive cancer.

## Histological characteristics of cancer

Type of cancer	Absolute number of patients	%
Noninvasive cancer	6	20
Including:		
<i>Duct cancer in situ</i>	2	7
<i>Lobular cancer in situ</i>	1	3.3
<i>Noninvasive duct cancer</i>	3	10
Infiltrative duct cancer	15	50
Infiltrative lobular cancer	2	7
Other types of cancer	7	23
Total	30	100

With 5 patients (50%) was noted modest degree of malignance, with 9 patients (30%) low degree of malignance, with 6 patients (20%) high degree of malignance.

### 7. Conditions of conducting the clinical tests

7.1. All patients went through diagnostics on the standardized regular equipment. In cases of hampered differential diagnostics at the X-ray mammography, US, puncturing biopsy etc the radionuclide research (mammo-scintigraphy) and RTM was prescribed. When necessary, the patients were assigned for surgical treatment with the definitive histological conclusion on the degree of malignance of the tumor.

#### 7.2. The procedure of performing radio-thermometry

The research was done in the horizontal position of the patient bared above waist for the purpose of natural cooling of the skin. While the registration chart was being filled in, the skin of the patient was cooling in a natural way. Further was done the measurement of the temperature at 8 points proportionally dividing the virtual circle of mammary gland. The measurements were done on nipples, in an area of axillary lymph nodes, and in two base points laying on a straight line separating one mammary gland from the other. Measurements were done using two senders. One sender in itself was a radio antenna and made measurements of radiation in the deep bedded areas of a mammary gland. The second sender measured radiation from the surface of the skin.

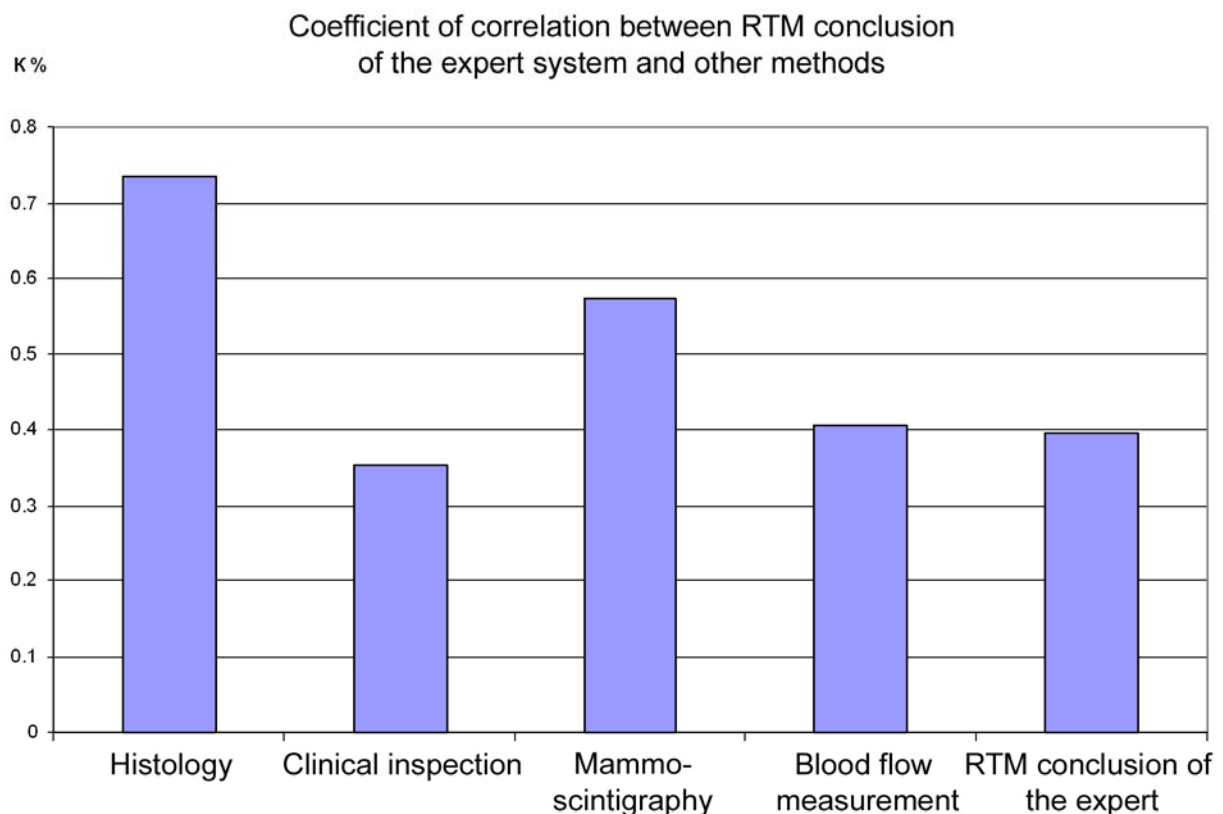
The analysis of the results was done through comparison of the acquired values of the temperature in counter-lateral areas, through evaluation of average values of temperature from all points, as well as through comparison of data, acquired at different senders.

### 8. The analysis of the results of clinical tests

After having compared the data of the complex examination with the results of RTM and of other methods of research we have done comparative analysis of the efficiency taking into consideration the particularities of each of the methods reflecting either the static

morphologic characteristics of tissues (mammography, US), or – the process, including that of uncontrolled fission of cells at the malignant processes (the RTM method). Thus, the qualitative index of the efficiency of RTM in revealing cancer of mammary glands was at 79.2%, of sensitivity – 96.6%, of specificity – 56.5%. in the assessment of absolute values of thermograms sensitivity was at 87%, specificity – 90.5%. Thus, efficiency by absolute values (auto diagnosis) was at 88.6%. the best results in sensitivity (main criterion in screening) there were at the qualitative evaluation of thermograms.

Separately was made the assessment of the RTM's sensitivity for the diagnostics of the cancer in situ. For the RTM conclusion of the program (auto diagnosis) sensitivity was at 80%. For the RTM conclusion of the expert sensitivity made 83%. In the correlation analysis of the data acquired with the RTM method together with the rest of the methods there were revealed following relations.



According to theoretical preconditions on the change of temperature determined by the radio-sender could influence the change of electrostatic properties of tissies, which is determined by the formula  $T = T_0 E^2(r) * G / k_0$ , where  $T_0$  is the base temperature of the body,  $E$  – the criterion of assessing of the direction diagram of the antenna,  $G$  – parameter assessing the dielectric properties of the medium,  $k$  – the integral coefficient characterizing change of parameters  $E$  and  $G$  by volume. Therefore the highest correlation of the RTM method was expected with the data acquired in . This prognosis we have made based on that higher accumulation of RPP is observed in cells with the high negative transmembrane potential. That is in tissues where the electrostatic properties differ from properties of an unchanged tissue. From the histogram of correlation ratios it is seen that in the group with verified

cancer of mammary gland the maximal values of the correlation coefficient were between the data of histological study and the qualitative evaluation on RTM. Thorough analysis has shown that the degree of accumulation of RPP at the mammo-scintigraphy depended predominantly upon the vascularization of the tumor. In this connection the correlation of the RTM with the mammo-scintigraphy should be considered as the correlation of the RTM and an integral parameter that incorporates blood flow and change of the transmembrane potential of the cell, i.e. most likely the main criterion influencing on the efficiency of the RTM diagnostics is the presence of electrostatic changes of the medium. It should be noted that in 66% of cases of the patients with the noninvasive cancer and the cancer in situ the pre-surgery diagnosis had been “fibro-sclerosis” and with one of the patients there was not noted an increase of the blood flow. At the same time, with 83% of patients with noninvasive cancer and cancer in situ there was heightened thermal activity of the tissue. With a half of these patients there were noted significant thermal changes (Th5 and Th4).

This allows to assert that the increase of temperature with the cancer of mammary glands may precede to the initial symptoms of increase of blood flow. Absence of changes of blood flow does not prove the absence of thermal changes. For 23% of patients diseased with the mammary gland cancer RTM was the only method which gave true conclusion on the character of the pathology.

At the time of preliminary clinical tests an assumption had been voiced: “There are grounds to suppose that thermal changes for fast growing tumors precede to the change of blood flow. At the same time there no experimental data that would support this hypothesis. In this connection the continuation of such researches is of interest.”

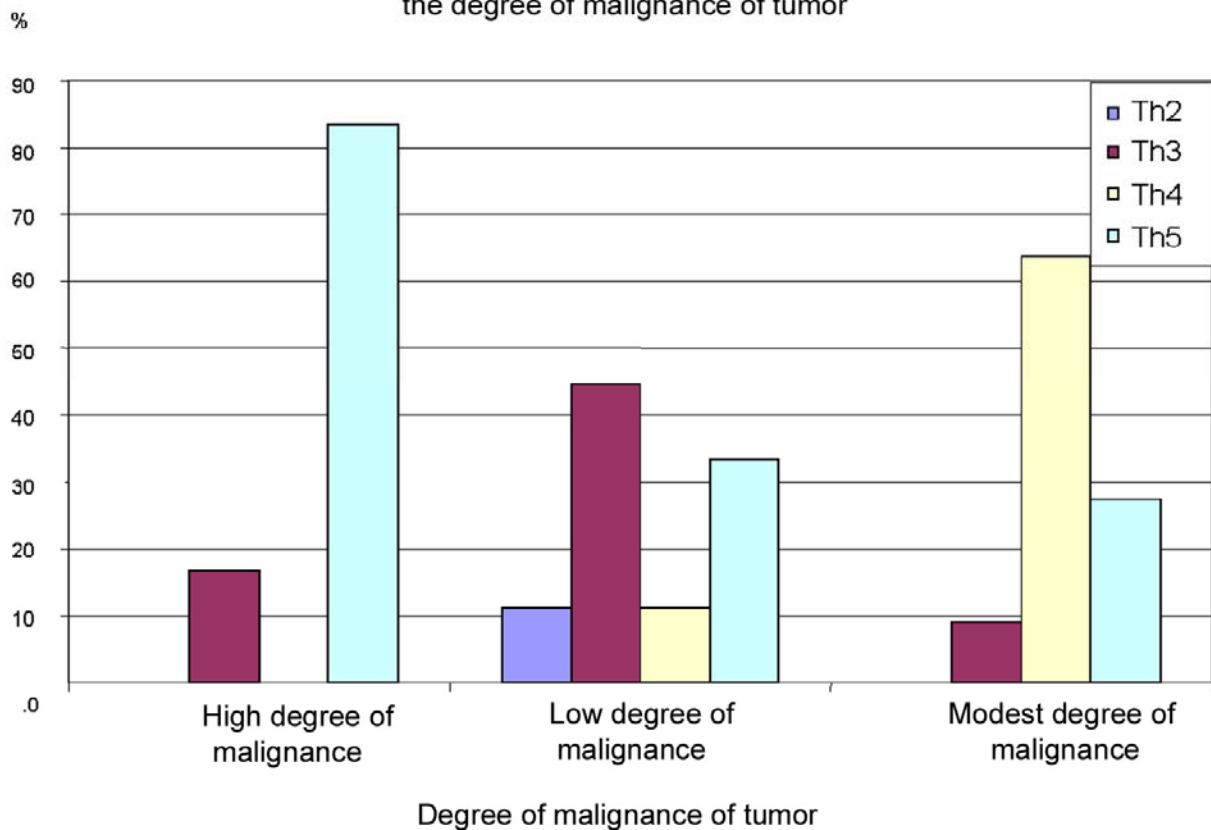
The results of present studies are the experimental confirmations of the earlier proposed hypothesis.

Besides, high correlation of the results of RTM with the degree of malignance allow to suppose that the RTM method allows to register weak signals (or their harmonics) occurring at the fission of cells (weak over-background electromagnetic radiations arising as a result of the displacement of the Plank’s distribution curve). Within the framework of this research it is not possible to differentiate the electrostatic component from electromagnetic one. It was only managed to capture small correlation of the RTM indices with the malignance of tumor.

In the table and on a histogram the results of the RTM diagnostics are presented depending on the degree of malignance of the tumor.

	High degree of malignance	Low degree of malignance	Modest degree of malignance
Th2	0	11.1%	0
Th3	16.7%	44.4%	9.1%
Th4	0	11.1%	63.6%
Th5	83.3%	33.3%	27.3%
Total	100%	100%	100%

The Histogram of the degree of expression of thermal changes depending on the degree of malignance of tumor



From histogram it is seen that to the high degree of malignance correspond very strong thermal changes (Th5), making 83%, to the low degree of malignance – Th3 (44%), to the modest degree – Th4 (64%).

Thus, the obtained results convince that with tumors of high degree of malignance there are always noted the strong thermal changes, while the same changes (Th5) of low degree of malignance – with just 33% of patients. It should be noted that with high degree of malignance all patients have significant changes in blood flow and the high level of accumulation of radio-pharm-preparation. With high degree of malignance all three methods show significant changes of indices.

Obviously, it is tumors with low degree of malignance that cause main difficulties at the RTM diagnostics, assessment of changes of blood flow and mammo-scintigraphy.

In particular, for growths with low degree of malignance the sensitivity of mammo-scintigraphy is 62.5%, and the change of blood flow is 37.5%.

It should be noted that with 80% of patients with heightened proliferation and atypia of cells there is a significant change of thermal activity of tissues. One can draw a conclusion that the thermal changes of mammary glands appear at the stage of heightened proliferation and atypia, when there is a high risk of malignization. Thus, the RTM method allows in 70% of cases to reveal patients of the risk group who need complex further examination.

The high specificity of RTM results of the expert system (70% for the patients of the “risk



group” and 90% for hotbed hyperplasia) give grounds for optimism for the cases of suspicion of high malignization as well.

### 9. Conclusions:

- The RTM method captures changes of temperature inside the mammary gland and on the skin surface that reflect functional processes in mammary glands.
- In 90% of patients diseased with the mammary gland cancer there are noted significant thermal changes.
- With the noninvasive cancer and the cancer in situ in 80% thermal changes are revealed of mammary glands captured with the use of RTM-01-RES.
- In 50% of cases the noninvasive cancer and the cancer in situ are accompanied by very strong thermal changes (Th5).
- The thermal changes of at the cancer of mammary glands are also registered in the absence of change of blood flow.
- At the stage of atypic changes and the heightened cells proliferation in 80% of patients there are manifested thermal changes of mammary glands that are captured with the use of RTM-01-RES.
- In 44.5% of patients with simple duct hyperplasia of cells there are significant thermal changes.
- Application of computer processing of the results allows to increase the specificity of the RTM method (90% with simple duct hyperplasia, 70% with proliferation and atypia) at the sensitivity of 87%.
- At the high degree of malignance predominate the maximal thermal changes (Th5), at the modest degree of malignance predominates the index (Th4), at the low degree of malignance over half of the patients have the index Th3 and Th2.
- The RTM method allows to reveal patients having high risk of malignization and needing further complex examination.

#### Conclusion:

The results of the conducted research allow to recommend the RTM method for the screening and differential diagnostics at the boundary states of a mammary gland.

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