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Modern Microwave Thermometry for Breast Cancer

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Abstract

The temperature of a malignant tumour is a universal indicator of the growth rate of the tumor. Tumor temperature can be used as a prediction of the benefit of individual therapies and in monitoring the efficacy of breast cancer treatment. This review provides a systematic analysis of the data available in the current literature on the role of microwave thermometry in risk estimation, the diagnosis of breast pathology and in assessing the effect of neoadjuvant therapy for breast cancer treatment.

Various aspects of the use of microwave thermometry in breast diseases are described: the diagnostic value of the method and the value in differentiating hyperplasia, benign and malignant disease. Research has also suggested a prognostic role of microwave thermometry and its possible application to assess the effect of preoperative chemotherapy in locally advanced breast cancer.

Microwave thermometry is a non-invasive method that can provide valuable information in relation to the diagnosis of various breast pathologies and may have value in screening programs to identify high risk groups for subsequent diagnostics using traditional methods (ultrasound, X-ray mammography, breast MRI, morphology). Microwave thermometry can also be used to assess the effect of ongoing neoadjuvant therapy of the primary non-operative forms of breast cancer in order to allow early detection of response and provide as part of personalized medicine

Keywords: Breast cancer; Microwave thermometry; Diagnostics

Introduction

Delays in diagnosis of breast cancer continue to be a problem in clinical practice that can only be solved currently by using complex and expensive invasive methodologies. Methods like mammography and biopsy, unfortunately, have several disadvantages. The unavoidable radiation dose from mammography prevents repeated screening even in high risk groups more often than once a year. In addition, mammography is not informative for most women younger than 35 years due to high breast density of the breast tissue. Magnetic resonance imaging is one of the most accurate methods of diagnosis of breast pathology, but high costs and the fact that it is a very time-consuming method make it unsuitable for widespread use. Therefore, the search for and introduction of novel diagnostics methods without these limitations is one of the priorities in clinical oncology.

Microwave radiometry is a diagnostic method based on measurement of tissue radiation in the microwave range. The intensity of the intrinsic radiation of tissues in the 4 Gz frequency is determined by their temperature and biophysical parameters. Unlike the well-known infrared thermography, which measures the temperature of the skin, microwave thermometry allows for the non-invasive detection of thermal anomalies at a depth of several centimeters under the skin.

The first use of radiation in the microwave range for the diagnosis of breast cancer (DBC) was proposed by the American radio astronomer A Barrett [1]. Subsequently, scientific schools in other countries also focused on non-invasive measurement of internal temperature [2-6]. Initially, devices measured temperature at a single point and were called “radiothermometers”. At present, modern diagnostic complexes like RTM-01-RES allow for the visualization of the thermal activity of tissues, both on the surface and inside the body. When it comes to the examination of the breast, the term "Microwave Thermography" is commonly used, along with other terms such as microwave radiometry technique or microwave radio thermometry. In this review, we use the term microwave thermometry. This technology has been certified in a number of countries, and approved as a standard of medical diagnostics.

Literature Review

Microwave thermometry has a number of advantages compared to other diagnostic methods. These include its non-invasiveness and the complete absence of ionizing and other radiation. As a consequence, it is harmless and can be used in young women. Traditional mammography and ultrasound provide information on structural changes: the size of the tumor, its location, the presence of microcalcifications, etc. Microwave thermometry provides the doctor with other data on the thermal activity of tissues, and reflects the level of proliferation, and potentially the risk of neoplastic transformation.

In particular, this method could potentially be beneficial to aid the identification of the following [7-10]:

- A cancer recurrence following breast conserving surgery or mastectomy;
- The localization of a small primary breast cancer in cases of an edematous breast; latent forms of breast cancer in patients with multiple metastases from an unidentified primary focus;
- The presence of tumor metastasis in regional lymph nodes;
- Breast cancer during routine screening of the high-risk patients;
- Monitoring the effectiveness of ongoing treatment for malignant and benign breast conditions;

Over the past 10 years, multiple clinical studies have been performed around the world on more than 1500 patients. The results of measuring the thermal activity of tissues have been compared with histological data (Table 1) [11].

S. No	Hospital	Year	Sensitivity %	Specificity %
1.	Clinical Hospital N0 40. Moscow. Russia	1997	94.2	71.4
2.	Branch 1 Mammography clinic. Moscow. Russia	1998	85.1	76.5
3.	Blokhin Oncological National Centre. Moscow. Russia	1998	89.6	81.8
4.	Burdenko Hospital. Moscow. Russia	2001	98	76.2
5.	Branch 1 Mammography clinic. Moscow. Russia	2002	95.2	57.2
6.	Medical College. Arkansas. USA	2003	84.8	70.2
7.	Radiology Centre. Moscow. Russia	2006	96.6	56.7
8.	Blokhin Oncological National Centre. Moscow. Russia	2013	92.1	88.3

Table 1: Clinical studies of microwave thermometry.

These studies have provided extensive experimental data to evaluate thermal changes in breast neoplasia. In addition, experience has accumulated on the practical use of this technology in 150 centers. The RTM-01-RES technology was certificated for use in Russia and in several other countries, where it is now included in the standard of care for cancer patients [12-14].

Below, we give a theoretical explanation of the clinical experimental data obtained in recent years.

The temperature and rate of growth of malignant tumors

Gautherie and collaborators [15,16] have studied thermal processes in the breast for 16 years, and have tried to give answers to the following questions:

- What determines the temperature of a malignant tumor?
- When do thermal changes in breast cancer begin?

The temperature inside the breast has been measured invasively using thermocouples located at the end of the needle. In addition to the internal temperature, all patients have undergone a mammogram and measured the temperature of the skin with a thermal imager. In total, data has been collected from 80,000 patients. The internal temperature of 540 patients with invasive cancer has been measured. The temperature both inside the tumor and in the surrounding tissues has been measured. In addition, temperature measurements have been taken at symmetrical points of the opposite breasts. After utilizing temperature measurements using special mathematical models Gautherie estimated the heat of tumour and the amount of energy released by 1 cm 3 of tumor. Figure 1 shows experimental data showing the dependence of heat emission from breast cancers related to the doubling time (DT).

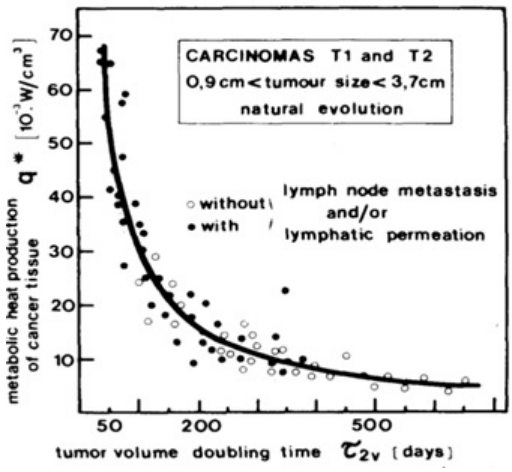

Figure 1: Metabolic heat production and growth rate of breast carcinomas. The data was obtained by observing the progression of small cancers in patients who initially refused treatment and in whom a histological diagnosis was confirmed. Doubling time was evaluated by measurements of tumor sizes on successive mammograms, and heat production was computed by measurements of temperature and blood flow carried out it, if it with fine needle probes.

According to the Schwartz model, the DT is the time interval during which the tumor doubles its volume. From Figure 1 one could see that the heat (temperature) of malignant tumor is closely related to its DT.

The most rapidly growing tumors with short DT have great heat release, whereas indolent, slowly growing tumors with a long DT are characterized by low heat release and, correspondingly, a low temperature.

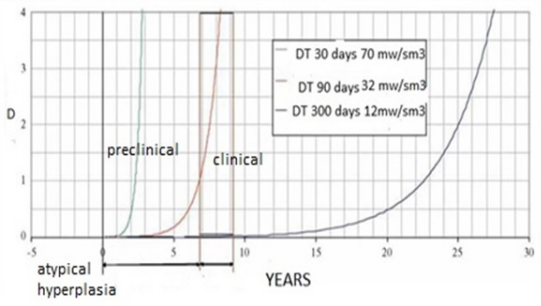

Figure 2: Kinetics of tumor development. D- Diameter of tumor in cm.

Figure 2 shows the kinetics of tumor growth, calculated according to the Schwartz model, depending on its heat (UW). For breast tumors with moderate growth rate, DT is 90-100 days [17], corresponding to a mean value of heat 30-34 mW/cm3. The preclinical phase of tumor development is thus of the order of 7-8 years.

For "hot" tumors with a rapid growth rate (heat dissipation is 70 mW/cm3, DT- 30 days) the pre-clinical development phase is only 2 years.

It should be noted that the data obtained by Gautherie does not contradict the general concept of increased malignant tumor metabolism. In his famous work, Warburg [18] in 1924 found that the basic biochemical feature of tumor cells is their ability to receive energy from glycolysis and grow due to energy production from this process. Respiration with the use of oxygen in cancer cells is replaced by fermentation of glucose. For this work, he was awarded the Nobel Prize. Cells use the anaerobic glycolysis path to dissipate significantly more energy, which leads to an increase in temperature of tumors and surrounding tissues.

The second important conclusion, which can be drawn from the analysis of the data presented in Figure 1, is the correlation between heat emissions from tumors and metastases in lymph nodes. In 18 out of 19 patients with high heat emission, metastases were present in the lymph nodes. However, for tumors with low thermal activity, metastases were detected only in 5 out of 30 patients. The prognostic potential of thermal measurement was also demonstrated by Napalkov [19], who studied the survival of patients with breast cancer, depending on the thermal changes on a cancer in different stages of development. To evaluate the thermal properties, the following classification was used:

- "Thermo-positive" are tumors with a significant increase in temperature.
- "Thermo-negative" are tumors with no increase in temperature.
- "Burning" are tumors with a very large temperature rise (>2°C).

Figure 3 shows the survival data for patients with stage III b breast cancer.

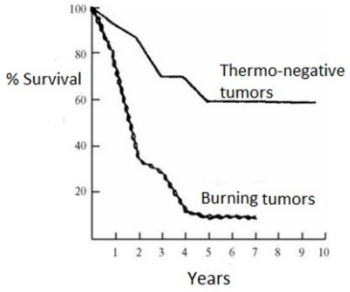

Figure 3: Patients survival of patient with breast cancer Stage IIIb with burning and thermo-negative tumours.

For burning tumors, the 5-year survival was 9%, while survival for patients with thermo-negative tumors at the same stage of development was 6.5 times higher (60%).

The predictive potential of thermal methods was demonstrated by studies conducted in the Center of Radiography and Radiology in 2006 [7]. These studies assessed the level of thermal changes of the tumor as a method for classifying the degree of malignancy. The temperature was measured non-invasively using a microwave radiometer thermometer RTM-01-RES and was evaluated on a 6-point scale: Th1- no thermal changes, Th5- maximum thermal changes. In 80% of patients with a high-grade cancer, there were maximal thermal changes (Th5). For patients with a low grade of malignancy, values of Th3 (50%) prevailed. Consequently, thermal changes correlate well with the grade of malignancy. Grade of malignancy has been established as an important independent predictor. According to Blamey et al. [20], 90% of patients with a low-grade cancer live after the operation for 30 years or more, and 90% of patients with a high-grade cancer live no more than 8 years. Thus, information on the internal temperature of the malignant tumor could have considerable prognostic potential.

Kinetics of thermal processes in breast cancer

The next important question is associated with the kinetics of the thermal processes in breast cancer. When do the thermal changes associated with malignancy occur? To answer this question Gautherie [15,16] identified a group of 1245 patients. Mammographic screening did not detect breast cancer (461 women were diagnosed with benign changes, while 784 patients showed no structural changes), but there were thermal changes. All of these patients had annual mammography for 12 years. After 8 years, 38% of patients without structural changes but with elevated temperature were diagnosed with breast cancer. Among the patients found to have benign changes, this number increased to 44% [16]. For patients with thermal changes but an elevated temperature, this percentage was much higher for 8 years. Thus, Gautherie showed that thermal changes precede structural ones, which provides opportunities to identify patients of high risk. It should be noted that the percentage of breast cancers identified as having high temperature is much higher than that seen with mammographic screening in asymptomatic patients. In particular, in the UK for 10 years of mammographic screening of 1000 women, breast cancer is identified in only 36 (3.6%) women [21].

In the studies conducted by Rozhkov et al. [7], thermal changes do not develop when the tumor reaches a certain size, but at the stage preceding malignant growth. Histological assessment showed that 80% of patients presented no cancer cells, but only atypical cells. These women already had significant thermal changes. This rise in temperature cannot be explained by an increased metabolism of malignant cells only, as they were not detected during histological examination. Increasing thermal activity of tissues with proliferative changes is known to every specialist who is engaged in microwave thermography.

The temperature and density of the microvascular network

Japanese scientists [22] gave the first original explanation for this phenomenon of increasing temperature. They combined invasive temperature measurement of a malignant tumor and surrounding tissue with measurement of microvascular network density (MVD), an important parameter to characterize tumor angiogenesis. In Figure 4, the vertical axis represents the increase in temperature in tissue surrounding the tumor (dTs) and in the tissue in the non-affected breast without tumor (dTt), compared with the temperature at symmetric points in the opposite breast. In the horizontal axis, microvascular network density (MVD) is the number of microvessels in 1 cm3 of tissue surrounding the tumor. MVDc is the contralateral breast, MVDs is the surrounding tissue. The MVD measurements were carried out using electron microscopy.

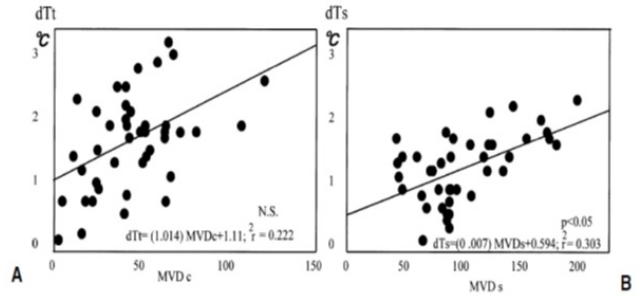

Figure 4: Correlation between MVD and dTt, dTs. (A) MVD-dTt; (B) MVDA.

It is clear from their experiments that dTt and dTs correlate well with MVDc and MVDs. Thus, the internal temperature serves as an indicator of angiogenesis. Recent years have seen a large number of studies of MVDs in breast cancer being conducted, with numerous studies showing that tumor growth depends on its ability to form a new vasculature [23].

As the growth of tumor cells increases, the cancer becomes cut off from nutrient sources necessary for survival and division. As a result, the tumor stops growing, reaching steady-state volume (typically of the order of 2-3 mm), at which the increase in cell mass is compensated by cell death due to a lack of essential nutrients. Cancer may remain *in situ* in this state for many years [24]. Further growth is possible only after the induction of angiogenesis, and the growth rate of the tumor is determined by the density of the microvascular network.

Weidner et al. [25] showed that the MVDs are directly correlated with the incidence of metastases in a number of solid tumors. In addition, Weidner et al. [26] found that in the area of most active vascularization MVDs could be used as a highly significant and independent predictor of survival in early breast cancer.

On the other hand, the MVDs study for the non-invasive disease has been demonstrated that MVDs may serve as a clinically important indicator for predicting the transition from in situ cancer to invasive carcinoma [27]. A similar conclusion was reached by Cao et al. [28] who examined the relationship between MVDs and histological characterization of non-invasive cancer. This work established that comedocarcinoma DCIS with a high degree of malignancy, which has a high probability of transforming to invasive breast cancer, is significantly associated (p <0,001) with high density of micro vessels. Given that the temperature of the tissue surrounding a lesion correlates with the MVDs, it is believed that non-invasive cancers with a high potential for invasive transformation will have a high temperature. In this regard, Rozhkova et al. [7] showed by non-invasive measurement of internal temperature that 50% of in situ cancers have a high temperature signal (Th 4, Th 5), despite the small size of initial tumours.

Guinebretiere [29] has demonstrated the potential value of microwave mammography for the detection of patients at risk. The probability of malignancy and tumor growth depends on its ability to form vasculature around itself. The risk of cancer was evaluated in patients with benign breast pathology based on the density of microvascular networks. It is known that diffuse fibrocystic disease has a relatively low probability of malignancy. The relative risk of malignancy (RR) in these patients is 1.9 [30]. Patients with fibrocystic disease and high density microvascular network, the RR ranges from 7 to 11. Thus, the density of the microvascular network, and consequently the temperature, appears to be increased at the stage preceding malignant growth. Other researchers have shown similar results. This opens up the opportunities for screening using microwave thermometry, with potential to identify risk groups. Microwave thermometry primarily identifies patients at high risk of potential malignancies, including fast growing tumors. This method allows for multiple readings to be performed at any time interval to continuously monitor potential pathological changes without additional radiation exposure for patients of all ages. Abnormalities can be detected at depths of 3 to 7 cm, with an accuracy of 0.2 degrees in the determination of the internal tissue temperature. In addition, computer processing of the results enables objective evaluation of the data [26-30].

Discussion

Comparison of microwave thermometry and traditional mammography

The proportion of breast cancers identified between screening rounds (called interval cancers) is an important measure of screening effectiveness. In UK, mammographic screening is performed in patients aged 50-70 years and more than 75% of invited women attend. Data has shown that, of the 36 cancers diagnosed during 10 years of screening of 1000 women, only 20 were detected during screening and 16 developed between rounds. Thus, the proportion of interval cancers in UK is 33% of all diagnosed cancers [21]. Comparable data have been obtained in other countries. In randomized trials in the HIP project in New York, the proportion of interval cancers fluctuated from 19% to 36% [31]. In a Stockholm trial interval cancer varied from 25% to 46% depending on the age group [32,33]. The 40-49 age group had a particularly high level of interval cancers, at 65.7% [34].

It has been shown that the combined use of X-ray and microwave mammography can reduce the number of false negatives 3-4 times and leads to an increased diagnostic sensitivity of 98% [9]. This is not an unexpected result, as microwave thermography can identify fast growing tumors and results in fewer false negatives in the 40-49 age group. Traditional mammography, in turn, identifies cancers, "missed" by microwave thermography (tumors with a low degree of malignancy and low growth rate). The most recent reports in the UK and other developed countries show a decreasing number of patients who would like to attend regular mammography screenings [35]. Combined diagnostics might increase patients' confidence.

Monitoring the effectiveness of treatment of mastitis is another interesting area of microwave thermography. Slightest changes in the breasts are mirrored by changes in the thermal activity of breast tissue. Thermal changes, as opposed to structural, can be seen within 10-15 days after the start of treatment. Microwave thermometry allows for an estimation of whether the thermal activity increases due to inflammation, proliferation and malignant growth or decreases due to processes like fibrotic changes. In patients with fibrocystic breast disease, thermal changes are not pronounced and do not differ from the norm related to the age of the patient. In inflammatory or proliferative processes, the thermal activity of tissues increases. Strong thermal tissue changes can be seen (Th3-Th5) in 80% of patients with atypical symptoms [7]. Microwave thermography could be used to assess the effect of hormone therapy. It is worth acknowledging that this is a risk-free and painless methodology that provides clear results. Thus, it might be used in any age group, in pregnancy and in lactation.

Orinovskiy et al. [36] showed that mammography does not always give a clear picture when evaluating the efficacy of neoadjuvant therapy. It has been shown that microwave thermometry in patients treated with neoadjuvant therapy can objectively evaluate its effectiveness in 85.2% cases.

Sinelnikov et al. studied the dynamics of temperature during the course of neoadjuvant therapy in a group of patients [37,38]. Prior to the treatment, 100% of patients were classified in the Th5 level. After 4-6 courses of chemotherapy, 41.7% of patients had decreased to the Th4 level, 33.3% to the Th3 level, and 25% to the Th1 level.

The dynamics of changes in temperature during the course of chemotherapy could be detected before structural changes detected by mammography and ultrasound, and can be used to assess the effect of the neoadjuvant therapy as an early predictor of efficacy.

Temperature changes during neoadjuvant chemotherapy correlate with the extent of response pathologically. Response and fibrosis is highly correlated with temperature changes (difference between temperature of the skin and internal temperature in healthy and tumor breasts). Thus, these changes can be used as biomarkers of the disease response. The overall temperature can be used to evaluate efficiency of neoadjuvant chemotherapy.

Conclusion

At the end of the last century, infrared thermography was recognized as insufficiently effective for practical use in breast cancer diagnostics. At the present time, thermography cannot be a replacement for mammography for the early diagnosis of breast cancer.

Microwave thermography is however a huge step in comparison with the thermal imaging of the past because it allows a glimpse deep into the breast, allowing for the evaluation of thermal changes within the breast and on its surface.

A review of the literature has shown that microwave thermometry can identify fast-growing tumors. It may be beneficial to include as part of a comprehensive examination of patients with breast pathologies and in screening programs [39]. False-negative results do occur with slow-growing tumors, the diagnosis of which is more accurately by traditional mammography.

Microwave thermometry allows for the evaluation of thermal changes both at the skin surface and inside the breast tissue. Although microwave thermometry cannot replace mammography or ultrasound because it does not provide information on the structural changes in the breast, it can provide additional information about the severity of proliferative processes, manifested by thermal activity [40-44]. This information may in many cases contribute to the development of an optimal treatment strategy. Historical data on treated patients show the important role of microwave thermography in developing personalized therapeutic strategy.

Thanks to its simplicity, safety and non-invasiveness, microwave radiometry may serve as a promising method for diagnosis, prediction and assessment of the effectiveness of treatment of breast cancer. It may also have potential as a method for risk stratification in breast cancer. Among other advantages of microwave thermometry are its availability, relatively low cost, the absence of radiation and the quick interpretation of results.

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