PERIODICUM BIOLOGORUM
VOL. 113, No 4, 393–399, 2011

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Essay

Thermography: is a new diagnostic method necessary for breast cancer detection?

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Received December 2, 2011.

Human history becomes a race between knowledge and catastrophe
Despite everything, the world progresses and will progress
Herbert George Wells

Breast cancer is the most common cancer in women worldwide (in 2010, nearly 1.5 million people were told: »You have breast cancer«). It is also the principal cause of 500,000 deaths from cancer among women globally *(1)*. The progress achieved in diagnosis and treatment of breast diseases offers encouragement to both physicians and diseased women; the physicians have managed to save many lives, and many lives have been prolonged.

The World Health Organization (WHO) has proposed that two components of early detection have been shown to improve cancer mortality rate *(1)*: education – helps people recognize early signs of cancer and seek prompt medical attention for symptoms and screening programs – identify early cancer or pre-cancer condition before signs are recognizable, including breast cancer mammography.

Medical community – and particularly its segment that deals with this problem area – is almost daily exposed to: new guidelines for application of diagnostic and screening protocols *(2, 3, 4, 5)*.

Also, the participation of new genes as predictors of disease prognosis and outcome has been revealed *(6),* the need for new standardization of current immunohistochemistry protocols has been emphasized *(7),* new pharmaceutical preparations have been included for the breast cancer treatment that are at various stages of clinical trials *(8, 9),* some drugs are excluded from standard protocols *(10)* and warnings are issued on the hazards accompanying introduction of new diagnostic methods in clinical practice *(11)*.

Undoubtedly, we are now at a stage when, with a multitude of recommendations, protocols, cautions and new preparations, it is increasingly hard for physicians – and particularly for patients – to decide for optimal solution. Clearly, the present state requires re-examination of existing values, which at the same time poses new challenges, doubts and responsibilities for medical staff.

All the references cited above were published in 2011. except for the article *(11)* that was published in 2010.

The most important points that have been stated in the foregoing references are as follows:

1. The authors observed that American Cancer Society guidelines established in 2007 are not valid any more. Despite the higher sensitivity of MRI, it is uncertain whether MRI screening has provided a survival advantage. »In patients with breast cancer, there is little evidence that MRI improves short-term or long-term outcomes of breast-conserving surgery«, the researchers stated. Ultimately, the true value of MRI might lie in its ability to predict biological behavior, rather than to quantitate low-volume disease. Future research in this field would be most beneficial if directed toward the resolution of clinical problems such as assessment of the extent of residual disease after neoadjuvant chemotherapy or of the need for some form of radiation therapy in all women who undergo breast-conserving surgery *(2)*.
2. The American College of Radiology Imaging Network (ACRIN 6666) protocol – a study to define the rationale for screening breast ultrasound – protocol investigators found that interpretive errors were responsible for 28% (19 of 67) of cancers missed on mammography, 21% (15 of 71) of cancers missed on ultrasound, and 20% (1 of 5) missed on MRI *(3)*. The results point to the need to improve interpretive skills, but whether this is possible is unclear, said the principal investigator Wendie A.Berg. »These investigators had all gone through multiple qualification tasks and were all physicians. You would expect them to be about as good as they can be, yet about 20% of cancers that were visible and documented on both mammography and ultrasound were misinterpreted.« The investigators believe automated scanning and computer-assisted detection and diagnosis would improve breast cancer detection rates.
3 The reduction in mortality associated with screening mammography is relatively small for women aged 40–74 years at average risk of breast cancer *(4)*.
4. A greater reduction in mortality is seen with mammography for women at average risk aged 50–74 years than among similar women aged 40–49 years; however, harms of over-diagnosis and unnecessary biopsy may be greater for younger women than for older women *(4)*.
5. When deciding whether to recommend mammography to a specific patient, providers should first discuss the tradeoff between benefits and harms, as well as the patient's values and preferences *(4)*.
6. For women at average risk who choose to have screening mammography, an interval of every two to three years appears appropriate *(4)*.
7. There is no evidence that screening women at average risk of breast cancer using magnetic resonance imaging, clinical breast examination or breast self-examination reduces the risk of mortality or other clinically relevant adverse outcomes *(4)*.
8. MRI detects cancer not identified with other types of screening. In two randomized trials, this increased sensitivity did not translate into improved selection of surgical treatment or a reduction in the number of operations *(5)*.
9. Gene expression profiling studies have shown that estrogen-receptor (ER)-positive and ER-negative breast cancers are distinct diseases at the transcriptomic level, that additional molecular subtypes might exist within these groups, and that the prognosis of patients with ER-positive disease is largely determined by the expression of proliferation-related genes *(6)*.
10. The 21-gene assay, when applied in a consistent manner at an early stage of breast cancer, changes treatment recommendations in one quarter of patients tested *(6)*.
11. The assessment of HER2 status in breast cancer is critical for the management of disease and therefore a priority for pathological standardization. The selection of the most appropriate adjuvant treatment regimen, including whether a patient is a candidate for HER2-targeted therapy, is heavily dependent on reliable and accurate laboratory results assessing the HER2 status as part of their diagnostic evaluation *(7)*.
12. Everolimus (EVE), an inhibitor of the PI3K/Akt/mTOR pathway, has single-agent activity and provides additional efficacy to long-term estrogen deprivation when combined with letrozole in the neoadjuvant setting. Combination of EVE and exemestane may improve outcomes for patients ER+ breast cancer refractory to nonsteroidal aromatase inhibitors (NSAI) *(8)*.
13. Roche's investigational medicine T-DM1 shows improvement in progression-free survival compared to the standard of care in HER2-positive metastatic breast cancer. First randomized trial of an antibody drug conjugate (ADC) for metastatic breast cancer has highlighted importance of personalized approach to cancer care *(9)*.
14. Avastin used for metastatic breast cancer has not been shown to provide a benefit, in terms of delay in the growth of tumors, that would justify its serious and potentially life-threatening risks. Nor is there evidence that use of Avastin will either help women with breast cancer to live longer or improve their quality of life *(10)*.
15. The new methods are breast-specific gamma imaging (BSGI) and positron emission mammography (PEM), both of which have been recently approved for use in the United States. They are marketed as diagnostic adjuncts to mammography and breast ultrasound, but they can also be considered for breast cancer screening, particularly in women at an increased risk for breast cancer, he adds. However, the radiation involved in a single BSGI examination poses a risk that is 20 to 30 times greater than that from digital mammography in a woman 40 years of age, and the risk from a single PEM screen is 23 times higher *(11)*.

»Modern science has entered a stage when »facts are uncertain«, values are controversial, stakes are high, and decisions urgent.«

Jerom Ravetz

OVERVIEW

We live in a world characterized by critical rationalism where scientific insight has become a paradigm for interpreting life and the world, and a signpost for quality living. Nevertheless, changes have never been occurring so quickly as in our time nor did the criticality have such a freedom of influence. This is particularly evident in the area of knowledge related to new inventions.

According to Herman *et al. (12),* the biological initiation of breast cancer occurs as early as 9 years before it could be observed mammographically while, according to the Collins' law *(13),* the time from the biological onset of breast cancer until the moment of its diagnosis has been estimated to be 5–6 years. According to Herman, as many as 15 years may pass from the biological onset of the disease until the appearance of clinical manifestations of the breast cancer. A woman has, on average, three years of life since the appearance of clinical symptoms of the breast cancer. Preclinical and clinical stages could be distinguished in the progression of disease. Three crucial elements are prominent in the preclinical stage of disease: biological onset of disease, the disease that can be verified by a screening test, the critical point, and the beginning of treatment. The clinical stage of disease begins with the appearance of symptoms. It is indisputable that the optimal beginning of treatment should occur at the moment of diagnosing disease at the preclinical stage, since otherwise no effect is achieved. On the other hand, the effect of screening may be questionable if a detected change is too slight, is at the lower limit of detection, and perhaps represents a pseudodisease. Pseudodisease is a condition that does not require treatment since it does not affect the duration or quality of a subject's life.

In this regard, a question may be posed if mammography is satisfactory as a recent method of choice, or a more effective procedure could be applied *(12)*.

So far, four sets of problems related to diagnosis and treatment of breast cancer have been formulated, considered and developed, and are open for discussion. Those are as follows:

1. **Revision of current diagnostic and screening protocols**

The survival of individuals with the diagnosed breast cancer depends on the size of tumor, its biological characteristics, expansion of disease, and patient's age.

Mammography is currently the elementary diagnostic test for breast cancer detection, and is the basis of all screening programs worldwide. Satisfaction and enthusiasm that lasted for over 30 years has today, mildly speaking, been replaced by scepticism *(14, 15)*. The sensitivity of mammography depends significantly on the density of breast parenchyma and declines in proportion to this density, amounting to 48% for very dense breasts, which makes it a very unreliable method for cancer detection in young women (under 50 years of age) *(16)*. Based on the data reported in the Journal of the Americal Medical Association in 2008 from the American College of Radiology Imaging Network (ACRIN 6666), more than half of the women under 50 years of age have dense breasts, as well as 30% of women older than 50 years in whom the sensitivity of mammography ranges from 38% to 48% and is accompanied with higher cancer frequency, more frequent incidence of interval cancers, and poorer prognosis. The authors point out that the inclusion of ultrasound examination in a standard clinical protocol raises the sensitivity to 77.5%, and therefore support this inclusion. However, despite the fact that the number of affected women is high and has a rising tendency among younger age groups, each new solution should without exception undergo reexamination *(15, 17)* concluded in their study that none of the diagnostic or screening methods does by itself fulfill the expectations of the present time.

2. **Detection of the biological properties of the breast tumor that indicate the need for individual therapy**

Breast cancer is a complex genetic disease characterized by accumulation of altered molecules that cause the clinical heterogeneity of the disease, and that affect not only the treatment but also its prognosis. These molecules are presently used as prognostic factors (the status of lymph nodes, tumor size, histological grade, hormone receptor status, protein HER2/human epidermal growth factor/patient's expression and age), yet they have shown to be insufficiently accurate predictors of the clinical course and outcome of the disease for about 30% of patients *(18)*.

According to molecular classification of the breast tumor, there are several molecular subtypes that are dependent on the presence or absence of steroid receptors (estrogen and progesterone), i.e. on the presence or absence of reaction to the presence of HER2 protein (human epidermal growth factor) *(19)*.

In addition to the above mentioned predictors, the determination of tumor cell proliferation has been introduced into the clinical practice as one of the most significant prognostic factors for tumors in general.

Depending on the foregoing predictors, the treatment of the breast cancer is based on the following: neoadjuvant chemotherapy, surgical treatment, adjuvant chemotherapy and hormone therapy and radiation.

3. **Detection of those biological properties of the carcinoma in situ that point to its potential for transition to invasive cancer**

The term carcinoma in situ is used to define tumors in which the proliferation of malignant epithelial cells takes place within the boundaries of the basal membrane. The concept of the carcinoma in situ as a predictor of invasive

cancer has remained active to serve like a bridge that covers the gap between benign epithelial proliferation and invasive cancer. In approximately 50% of patients, invasive cancer progresses from carcinoma in situ, which means that approximately 50% of patients are treated more invasively than required by the nature of the disease itself.

The diagnosis of DCIS »is a 30-year history of confusion, differences of opinion and under- and overtreatment«, said Shahla Masood, MD, the head of pathology at the University of Florida College of Medicine in Jacksonville, in the *New York Times* article *(20)*.

What are the most critical research questions for the diagnosis and management of DCIS?

The diagnosis and management of DCIS is highly complex with many unanswered questions, including the fundamental natural history of untreated disease. Because of the noninvasive nature of DCIS, coupled with its favorable prognosis, strong consideration should be given to remove the anxiety-producing term »carcinoma« from the description of DCIS. The outcomes in women treated with available therapies are excellent. Thus, the primary question for future research must focus on the accurate identification of patient subsets diagnosed with DCIS, including those persons who may be managed with less therapeutic intervention without sacrificing the excellent outcomes presently achieved. Essential in this quest will be the development and validation of accurate risk stratification methods based on a comprehensive understanding of the clinical, radiological, pathological, and biological factors associated with DCIS *(21)*.

According to the latest studies by Kerlikowska *et al. (22),* two basic characteristics of the ductal cancer in situ were found that make it a cancer precursor:

1. size
2. pronounced presence of biological markers (p16, cyclooxygenase (COX)-2 and Ki67).

4. Biological properties of benign diseases that are breast cancer precursors

A broad range of changes in the breast, »typical« benign on one hand and »typical« malignant changes in the breast on the other, fills up a still unclearly defined space that comprises changes with some (undefined) role in the transition from one of these states into another. Benign atypical hyperplasia (BAH) does not represent a direct precursor of the breast cancer but is rather an indicator of increased risk for its occurrence. Some studies have demonstrated the existence of strong correlation between the amount of estrogen found in biopsied lesions and subsequent occurrence of cancer *(23)*. Also, the absence of expression on CK5 (cytokeratin 5) in atypical ductal hyperplasia is considered a malignant disease, i.e. ductal carcinoma in situ *(24)*.

WHAT IS THERMOGRAPHY?

Thermography is a biologically inert, contactless diagnostic method based on the recording of the heat emitted from the human body using a sensitive infrared camera.

FDA (Food and Drug Administration, 1982) approved the thermography procedure as a method for early breast cancer detection. Mammographic and ultrasound examinations are based on the physical change in diseased tissue, similarly to all other diagnostic methods except thermography. Apart from recording physical changes in the structure of diseased tissue, the sensitivity of the magnetic resonance method is also based on the ability to detect newly formed blood vessels in tumor formations, i.e. angiogenesis.

Angiogenesis has important role also in the local breast tumor growth and in formation of distant metastases. Metabolic activity and vascular network in precancerous formations and in the surroundings of a growing breast tumor are always more pronounced than in the normal breast tissue. The concept of angiogenesis as an initial event in the breast cancer formation was demonstrated in 1996 *(25)*. The observation of these authors confirmed that angiogenesis and increased metabolic activity begin before the carcinoma in situ has been microscopically registered. Cancerous breast hyperthermia is seemingly associated with non – neurological vasodilatation modulated by nitric oxide *(26)*. The roles of nitric oxide (NO) in numerous disease states have generated considerable discussion over the past several years. NO can also have a multitude of effects on other aspects of tumor biology, including angiogenesis and metastasis and may impact the initiation and progression stages of cancer *(27)*. The thermographic visualization of »blood vessels« in thermograms is a consequence of need for abundant supply of nutritiens to maintain of the tumor growth. In order to do this, they increase circulation to their cells by sending out NO (nitric oxide) to keep existing blood vessels open, recruit dormant vessels and create new ones (neoangiogenesis).

The basic principle of thermography is detection of increased temperature that is produced by enhanced metabolic activity of a proliferating tumor. The process of carcinogenesis is associated with the process of angiogenesis, which leads to increased temperature of the skin above the growing tumor.

Usual skin temperature increase on the surface of the breast with a growing tumor is 1–3 °C. In studies *(26, 28, 29, 30, 31)* in which the nature of temperature disorders was investigated on the skin of a subject under observation, these disorders are explained with several biological principles, or by the effect of different factors on pathological events characterized by the dynamics of temperature fluctuations:

1. Nitric oxide (NO) is a vasodilatory substance that is normally found in the body. It is produced by white blood cells during activation of the immune system, but is also produced by tumor cells. As a vasodilatory

substance, NO provides the tumor with nutritive substances and gives rise to temperature increase in the environment. Vasodilation that occurs in tumor environment is not under the control of central neurological, sympathetic and parasympathetic impulses. The quantity of NO synthetase found in breast tumors shows some correlations with biological activity of the tumor and its expression of estrogen.

2. Increased amount of ferritin in tumor cells is also associated with the production of nitric oxide (NO) as a source of $Fe^{2}+$ that serves as a catalyst in the process of its formation.
3. Angiogenesis is a process that follows tumor growth. The tumor growth is accompanied with an increased need for nutrients and oxygen which is ensured by formation of additional blood vessels. In this pathological and chaotic process of angiogenesis, the newly formed blood vessels lack a layer of smooth muscle cells in the vessel wall, which makes normal vasoconstriction in these pathological vessels impossible and thus contributes to increased thermal activity.
4. Inflammation is another factor that causes temperature rise in tumor environment. As in the case of wound infection, tumor itself produces inflammation moderators and furnishes additional necessary nutrients.
5. Estrogen is a hormone found in circulation and is one of the mediators of vasodilation that leads to increased local production of nitric oxide (NO) so that abnormal amounts of estrogen may lead to vasodilation in estrogen-sensitive tissues and thus increase environmental temperature.

WHAT IS THE SIGNIFICANCE OF THERMOGRAPHY INTRODUCTION INTO ROUTINE CLINICAL PRACTICE?

The application of thermography in breast cancer diagnostics marks the shift from morphological to biological onset of disease, Figure 1.

How does the possibility of introducing biological properties of disease affect the routine clinical practice?

It questions everything: privileges, habits, inertness.

The method of thermography, as a very sensitive biological method, provides a physician with guidelines for

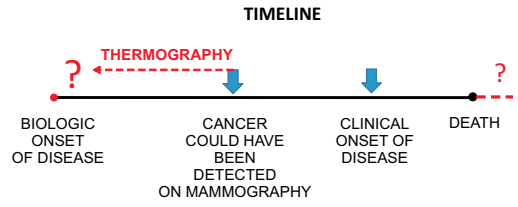

Figure 1. *The diagram shows several time points related to disease appearance and progression: the time of the biological onset of disease and morphological changes which could be seen on mammography, and the time from the clinical manifestation of disease (modified according to Herman)* (12).

the necessary further diagnostic and therapeutic procedures, yet it requires from the physician to become acquainted with the biological bases of breast disease as a prerequisite for the method application.

Initial experiences in thermography application in Croatia (on experimental model) were registered by Poljak – Blaži M. *et al. (32)* in 2009. First clinical trials that included thermography as a diagnostic method in breast disease diagnostics were registered in the master's thesis by Herceg *(33)* entitled: »Evaluation of benign and malignant signs of breast pathology on mammography and thermography«.

In 2011, the Croatian Ministry of Science, Education and Sports accepted to co-finance: a project »Thermography – a Method of Early Breast Cancer Detection« (BICRO Poc3_03_35). The study was carried out with the aim to compare mammographic and thermographic methods as clinical and screening methods. Preliminary results of the project are as follows: none of the female subjects with clinically confirmed breast disease had negative thermographic finding, i.e. a finding where pathological thermographic signs could not be observed and upon including thermography in the screening program, five more cases of cancer were detected in a sample of 100 women as compared to mammography alone.As result of the study, a new method of simplified description and interpretation of pathological thermography signs in malignant breast lesions was developed on the basis of existing protocols (Marseille, Villa – Maria, Hobins, Hoekstra) *(17, 34)*.

The effect of this new and simplified standardization of interpretation in thermographic method will be easier acceptance of the method by a broad circle of users (diagnosing physicians, surgeons, oncologists, medical radiology engineers and, which is most important, by women).

Past experience worldwide with the application of this method may be divided into two periods: a period of thermography application in the framework of currently surpassed technical solutions and a period when all technical and technological advancements have enabled simple application of thermography.

Our results could be compared only to the results from the second period above when cameras of the same generation and resolution have been used.

Results and experiences of various authors with the use of thermographic technology in the diagnosis of breast cancer are very hard to compare, both among them others and with our results *(17, 35, 36, 37, 38, 39, 40)* for a number of reasons: initial objectives of those studies were completely different, attempts were made in some studies at computerized automated sample recognition, thermography was partly compared with other diagnostic methods, the same standards were not used in reports, there were great differences in the number of examined female subjects, etc.

However, we could point out possible comparison with only two studies where sensitivity and specificity of

the thermography method was estimated in female subjects examined immediately prior to biopsy or breast surgery, i.e. the studies by Parisky *(35)* and by Kontos *(39)*.

On a sample of 875 changes determined by biopsy, Parisky pointed out the high sensitivity of the method (97%) and the specificity of 14%. Unlike him, Kontos reported low method sensitivity (25%) and significantly high specificity (85%) in a study that included samples from 63 subjects (male subjects with breast cancer were also included in the study). Regarding such markedly contrary results, it is difficult to put forward any value judgement at all both on the method itself and the manner of result interpretation. According to our experience based on *(33)*, the sensitivity of the method was 100% while specificity was somewhat lower (74%) since we regarded as a positive result of thermographic examination every recorded change in the breast (atypia, fibroadenomas, phyllodes tumors, invasive cancers, and carcinoma in situ).

Thermography – as a method with high potential for detection of breast tissue changes – is a valuable diagnostic method that should be standardized by implementation of multicentered studies and establishment of identical objectives.

CONCLUSION

Thermography – as a method with high potential for detection of breast tissue changes – is a valuable diagnostic method that should be standardized by implementation of multicentered studies and establishment of identical objectives.

Early detection of breast cancer poses a demanding situation for all physicians, from those engaged in diagnostics to those who deal with therapeutic procedures. Taking into account that new biological and clinical indicators of disease are detected almost daily, we may live in a time that is reminiscent of the time of great geographical discoveries five centuries ago. Unlike then, at the present moment I have a feeling that we lack persons who would delineate each particular finding into a large geographical map.

Employment of a new diagnostic method that shows promise of pointing to the biological onset of disease primarily requires the renouncement of acquired habits and of the pleasure of applying already learnt methods; it also entails additional efforts by already burdened and »confused« physicians. Still, the attempt to attain the ideal of »curability« of the breast cancer as the deadliest cancer that affects women should be an additional motive to all who are engaged in this problem area. The search for new technologies and techniques for early discovery breast changes, while still in curable stage, represents »conditio sine qua non« of future advancement in this area.

A possibility that thermography findings are standardized, that computerized neural network systems are improved, that the findings are assessed by interdisciplinary expert teams, that biologists may also become included in decision-making about the beginning of treatment should be sufficient to ensure an enthusiastic start of the wide application of this method, with the hope that it will in a reasonably short period contribute to reduction in breast cancer mortality.

Acknowledgement: *I whish to thank prof. dr. sc. Stella Fatović-Ferenčić and dr. sc. Sonja Iskrić who helped me with advices and to encouraging me during working on this essay.*

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