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CASE REPORT

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Contact Thermography as an Effective Tool for Detection of Breast Cancer in Women with Dense Breasts-A Case Report

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Abstract

Breast cancer is the leading cause of death among women worldwide. Breast ultrasound and mammography examinations are routinely used to detect breast pathologies. Breasts have different breast densities (according to Wolfe's classification) and thus carry different risks of developing cancer. The existing routine screening methods have their limitation. Mammography has often been found to be insufficient for the examination of breasts with dense glandular tissue, as some cancerous changes may be undetected. Breast cancer, even at very early stages of development, has been found to have an increased rate of metabolism and therefore an increased temperature. These thermal changes, within the tumor core, can be detected using contact thermography. We present a case of an invasive ductal carcinoma in a patient with dense breast tissue, which was first detected *via* routine ultrasound examination and further confirmed through contact thermography. On mammography, the lesion was undetected. We discuss the potential for contact thermography to become a novel, non-invasive diagnostic tool which can be used as a complementary method to standard of care, especially for women with dense breast tissue, for whom mammography is not effective.

Keywords: Breast cancer; Contact thermography; Breast density

Introduction

Breast cancer is the most common malignant cancer and the leading cause of death in women worldwide [1]. It has become one of the most important health problems in recent decades. The detection rate of breast cancer has increased significantly due to increased awareness of the disease and increased availability of diagnostic tools, as well as implementation of national screening programs.

Due to the high risk of developing breast cancer in women with dense breast tissue, and the problems associated with selecting appropriate diagnostic examinations, breast cancer in these women is often detected at a more advanced stage [2]. There is an urgent need for improved diagnostic methods that can be used as complementary methods to standard of care. One such method is contact thermography, which utilizes a phenomenon of heat transmission to visualize changes in the breast glands. Through development of a pathological vessel system, cancer tissue has an increased metabolic activity compared to healthy tissue resulting in the presence of focal or linear hyperthermia's, which can be registered *via* contact thermography on liquid crystal matrices.

Case

A 39-year old woman came in to the clinic for a routine ultrasound breast examination. The physical examination was unremarkable. A breast ultrasound was performed, which revealed a 17 × 24 mm, irregular, hypoechoic change, partially obscured, located in the left breast at the 5 o'clock axis (Figure 1). The change was classified as BI-RADS 4C and the patient was referred for mammography and core-needle biopsy.

A mammography was performed prior to the planned biopsy. The mammogram revealed dense, glandular breasts, without visible micro-calcifications. In the upper outer quadrant of the left breast, an asymmetric density (Figure 2-circled structure) was visualized, which qualified the patient for a secondary ultrasound evaluation. Based on the type of breast tissue (dense glandular tissue according to Wolfe's classification), mammographic examination has reduced sensitivity [3]. The change was classified as BI-RADS 0.

Both breasts have dense, glandular tissue, BI-RADS 0. An asymmetric density in the upper outer quadrant of the left breast is circled, which qualified for an additional ultrasound evaluation.

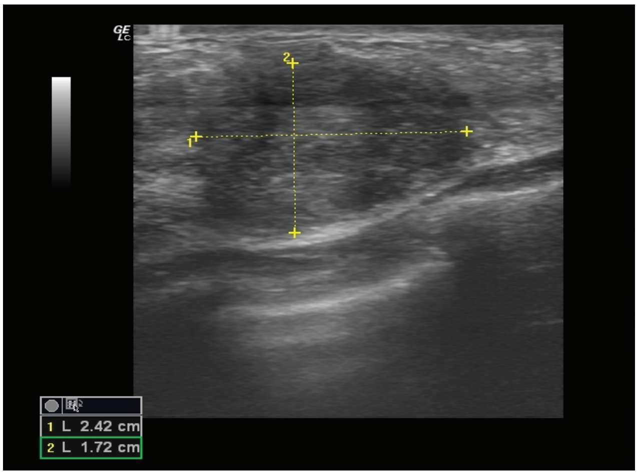

Figure 1: Ultrasound examination of the left breast revealed a 17 × 24 mm solid change in the lower outer quadrant, Classified as BI-RADS 4c.

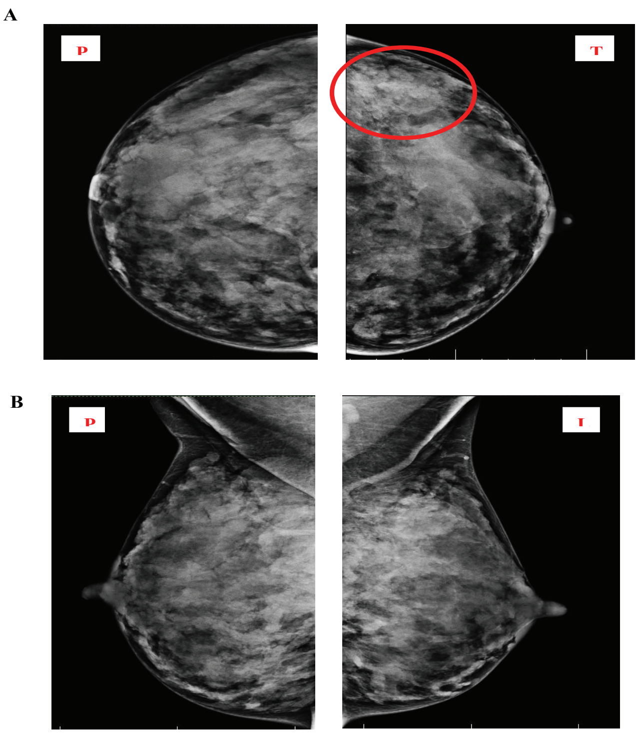

Figure 2: Mammogram of both breasts in CC (cranio-caudal) and MLO (mediolateral oblique) view.

The patient was referred to a diagnostic center, in which a secondary ultrasound examination was performed. No changes were detected in the area described in the mammogram, but a solid change in the lower outer quadrant of the left breast at the 5 o'clock axis was confirmed. Next a thermographic examination was performed of both breasts (Figure 3). A focal hyperthermic structure was observed in the lower outer quadrant of the left breast, in the location previously visualized on the ultrasound examination. No significant thermal changes were detected in the right breast.

Due to the appearance of a suspicious change in the left breast, a core-needle biopsy was performed, which confirmed a grade 2 invasive ductal carcinoma, type NOS (Not Otherwise Specified).

Discussion

Thermography-principles in breast diagnostics

The underlying physiological principle of contact thermography in medical imaging diagnostics is the so-called dermo-themal effect, in which cancer cells have a higher rate of metabolism [4]. Furthermore, a process of neo-angiogenesis induces strong hypervascularization around the tumor core, which can occur even at very early stages of cancer development [5]. It has been shown that even within a microenvironment of a 1 mm diameter tumor, there are enough pro-angiogenic factors to generate completely new vasculature [6,7]. This phenomenon leads to permanent, localized, intra-glandular temperature anomalies, which can be observed on the surface of the examined organ [8].

Instruments based on contact thermography, through the application of a liquid crystal foil, can induce a so-called selective light diffraction effect. This effect allows us to obtain a color image on the surface of the liquid crystal foil. By pressing the foil against the surface of the breast, a color thermogram is obtained, the analysis of which enables us to detect hyper-vascular changes in the breast.

A retrospective observational population study performed by Bothmann, et al. [9] on 19,461 females showed that abnormal thermography results were obtained in 86% of women with confirmed malignant lesions. Sensitivity and specificity of contact thermography for all invasive neoplastic lesions was 73% and 71%, respectively, with a false positive rate of 16.6% and false negative of 8.6%.

Breasts with dense tissue-characteristics and methods of evaluation

Numerous classification approaches for the characterization of breast density have been proposed, most commonly used is Wolfe's classification, which relies on mammographic examination of the fibro-glandular densities in relation to fat tissue (Figure 4). Wolfe first proposed this classification system in 1976, following his retrospective study of 7,214 women [10]. Based on roentgen images and several years of observation, Wolfe selected and named specific categories of breast parenchymal patterns [11]. Wolfe then classified women into four groups (N1,P1,P2, and DY), each group with a different risk of developing breast cancer.

Due to the differences in breast densities and the resulting consequences, there is an increased need to evaluate breast density during routine screening examinations. According to a new legislation passed in February 2014 in the US [12], women undergoing mammography screening must be directly informed if they have dense breast tissue. This is because there is lack of female awareness of different breast densities and the associated risks of developing cancer, as well as lack of knowledge among doctors about potential false negative mammograms where a dense breast tissue can mask the tumor [11]. With increasing number of research reports and publications [13,14] relating to the increased risk of breast cancer in women with dense breast tissue, numerous educational organizations have been founded worldwide, which promote routine screening and provide help and support to women.

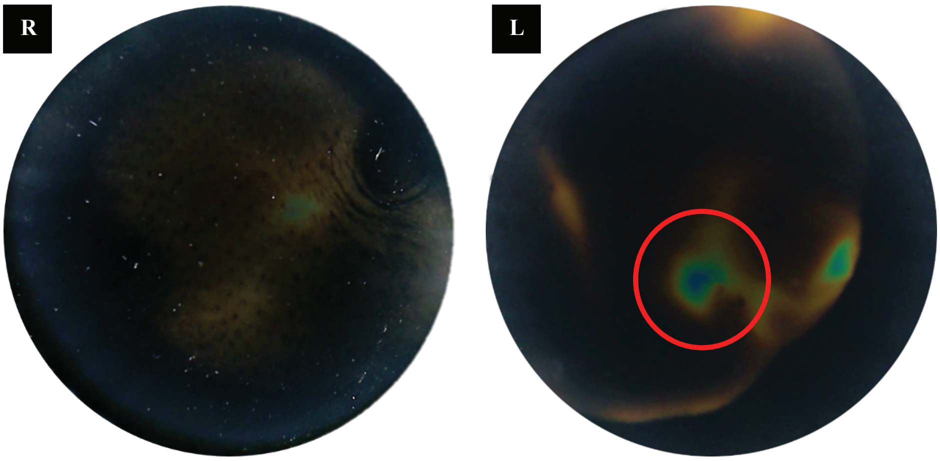

Figure 3: Contact thermography of the lower outer quadrants of both breasts reveals focal hyperthermia in the left breast (circled).

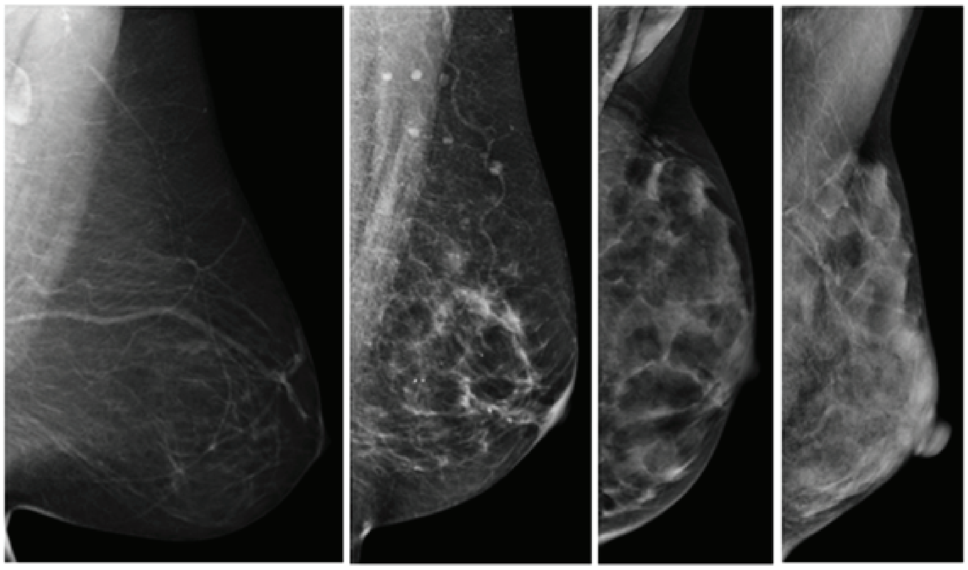

Figure 4: Mammogram classification of breast tissue based on Wolfe's classification (left to right: N1,P1,P2,DY).

Diagnosing breast cancer in women with dense breasts-a methods approach

To date, there are various imaging techniques to visualize breast cancer at various stages, including: mammography, ultrasound, MRI, and most recently, thermography [15-17]. In women with dense breasts, the sensitivity of mammography can be as low as 30-45% [18]. Dense breast tissue decreases the sensitivity as well as specificity with which screening mammography is able to diagnose the cancer. Over 50 percent of females participating in breast cancer screening programs have intermediary dense breasts or extremely dense breasts [19]. Henceforth, an increased amount of dense breasts are observed, with the limited sensitivity of screening mammography. Complementary nonmammographic imaging tools have been proposed, including breast MR and ultrasound. Breast MR has a high specificity (97.1%) and positive predictive value (35%), however with increased cost, requirement of intravenous contrast and low sensitivity, breast MR has not become part of routine screening [20]. Complementary breast ultrasound on the other hand has been shown to have a high sensitivity (91.1%), however a lower specificity (87.7%), and low positive predictive value, which may translate to higher costs downstream and increased morbidity [21].

Regulations set forth by the US Food and Drug Administration have cleared thermography as an adjunctive tool to mammography, which is similar to the aforementioned methods [22]. By no means should thermography be used as a standalone method for breast cancer screening or diagnosing early stage breast cancer. Thermography, as an alternative option in the diagnostic pathway, may be used to complement current standards as it is inexpensive, non-invasive, and far more portable than the aforementioned modalities. Further studies are required to see the impact on healthcare costs and its role in breast cancer screening.

Conclusion

In the presented case, analysis of the performed examinations demonstrated the limitations of mammography; while, providing a glimpse for the potential of contact thermography as an appropriate technique for evaluating metabolic changes first detected on breast ultrasound.

Contact thermography is a non-invasive method that does not use radiation and can play a significant adjunctive role in the early detection of breast cancer. Contact thermography is particularly useful in women with dense breast tissue, who have an increased risk of developing breast cancer but for whom mammography is not an effective diagnostic method.

Conflicts of Interest

AN, AB, MT and TP have received compensation from Braster SA for consultancy and services provided with relation to this study.

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ABSTRACT

Investigating the effectiveness of liquid crystal contact thermography in detecting pathological changes in the mammary gland of women compared to standard diagnostic methods of breast cancer - **a multicenter study INNOMED.**

Key Words: breast cancer, liquid crystal contact thermography, BRASTER^{TM}

The Innomed_2016_01 study was a prospective, multicenter, open, observational study that is non-interventional, conducted in specialist breast diagnostic clinics in Poland by persons trained in performing thermographic examinations under the supervision of specialist physicians. Contact thermography examination, with the use of the BRASTER^{TM} device was tested on 3006 patients who agreed to participate in the study and provided access to their medical documentation, of which 2756 patients were included in analysis. Amongst this group, the final analysis included: 648 women aged 18-49 who previously had a breast ultrasound examination assessed as BIRADS-US 4 or 5 (Group A), 1716 patients aged ≥ 50, who previously had an MMG and ultrasound examination with a result of BIRADS-US 4 or 5 (Group B), and 392 women who previously had US or MMG performed and were assessed as BIRADS-US 1 or 2 (Group C). The control group was divided into two subgroups depending on the patient's age; subgroup C1 – women aged 18-49 (n=199) and C2 – women ≥ 50 (n=193).

The primary purpose of the study was to assess the diagnostic effectiveness of breast thermographic examination using the BRASTER^{TM} device operating on the basis of liquid crystal contact thermography.

The secondary objective of the study was to prepare and validate a new algorithm for automatic interpretation of the thermographic images, Braster AI, and to assess the safety of the device, used in clinical practice. The verification of the effectiveness was carried out on the basis of clinical material in the form of data from thermographic examinations performed with the BRASTER device and data from imaging modalities and histopathological tests obtained during standard diagnostics and differentiation of breast cancer in women. The acquired thermographic images were segmented into two sets of 1200 and 1556 tests, each of them into two subsets – training and validation. The transfer of data, whether training or

validation, took place under direct supervision of the CRO and aimed at enabling systematic conducting and evaluating the work on automatic interpretation algorithms. All types of learning and calibration of internal parameters of the learning interpretation system of breast thermograms, based on deep neural networks (DeepBraster) were carried out using tranche I and training set of tranche II (completely separated from tranche II validation set). Only after the algorithmic work was completed, a validation sample was obtained, which was used to calculate final indicators. The validated software version was closed before receiving the test data.

The basic results of the automatic interpretation system are three activation outputs from neural network, whose numerical values are in the range [0,1]. They concern:

- general risk of malignant lesion, i.e. not indicative of a particular breast (general indication),
- risk of malignant lesion in the left breast (detailed indication),
- risk of malignant lesion in the right breast (detailed indication).

In addition, the system takes into account a fourth indication, regarding the overall risk, including the patient's age. Considering the patient's age is important in the diagnosis of breast cancer, as it is a factor correlated to the risk of developing the disease, as well as breast structure and the choice of diagnostic methods. The studied system may take into account the patient's age by training (using the same training set) an additional learning element, which during classification, modifies the general indication of the basic part of the system that does not use age as information. Basic results (without taking into account age) were marked as DeepBraster_T, and parameters including age were marked as DeepBraster_A.

The main purpose of the study, i.e. the assessment of the diagnostic effectiveness of the BRASTER device operating on the basis of liquid crystal contact thermography was realized. In the group of women <50 years of age with abnormal breast ultrasound (BIRADS US 4 and 5) the sensitivity of thermographic examination according to DeepBraster_T system was 59.3% with a specificity of 69.3%. The area under the ROC curve was 0,697. For the DeepBratser_A system (taking into account age) the sensitivity of thermographic examination was 55.6% with a specificity of 84.7%. The area under the ROC curve was 0,703.

Similarly, in the group of women >50 years of age, with abnormal mammography and breast ultrasound (BIRADS-US 4 and 5), the sensitivity of the thermographic examination according to DeepBraster_T system was 60.9% with a specificity of 62.7%. The area under the ROC curve was 0,653. The same parameters for the DeepBraster_A system included: sensitivity 62.3%, specificity 63.1%. The area under the ROC curve was 0.67. In the group of women without breast pathology, the percentage of false positive thermography results was similar to that observed in women with abnormal MMG and/or USG results of women without breast cancer (in women<50 years of age, 29.2% and 14.6% respectively for DeepBraster_T and DeepBraster_A systems and similarly for women ≥ 50 years of age: 37.4% and 35.4%).

Analysis of the results showed that for the designated BIRADS 4 categories in ultrasound examination in a group of young patients, a positive result of Braster interpretation increased the positive predictive values (probability of cancer in studied group) more than two-fold (2,3 times), while a negative result of this interpretation, significantly reduced the positive predictive value (7.7 times). Similar results were obtained in the BRA 11/2014 (ThermaALG) study, which indicated the repeatability of both studies. In addition, an increase in the sensitivity of the method, depending on the degree of differentiation of neoplastic lesions was demonstrated, 61.3% for G1 lesions, to 67.8% for G3 lesions.

Due to the possibility of analyzing thermographic images from individual breasts, the accuracy of pinpointing the cancerous breast was assessed. The estimation of accuracy of the pathological breast was carried out using the true positive results of the DeepBraster_T system. The indicated accuracy for the total number of cancers in the validation test was 73.4%. For 30% of cancers from this sample, with the highest activation, the accuracy was 87%.

The results of this study confirm the complementary use of contact thermography to standard diagnostic methods, such as ultrasound or mammography. Although the diagnostic effectiveness of the method when used alone is moderate, as opposed to standard imaging modalities, this effectiveness does not seem to be strongly dependent on the age of the patients (the area under the ROC curve is 0.7 and 0.67 in the group below 50 and in the group above 50 for the DeepBraster_A system variant). Research on the impact of DeepBraster system when used as a complementary tool to other imaging methods, shows the system's unequivocal usefulness in such application. In all groups of patients with BIRADS 4 category assigned, a positive result from the validated system increased the probability of cancerous changes (PPV), while a negative result reduced the probability – for both MMG and US. The largest usefulness was found to be a complementary tool for ultrasound examinations, especially in the younger patient population, where the impact of positive or negative DeepBraster results increased or decreased the PPV several times. The results also suggest a higher detection of invasive lesions with high histological grade (G3), which may be associated with their increased metabolism. The study confirmed the ability of the system to indicate pathological breast – the higher the degree of the risk of pathology assessed by the system, the higher the accuracy of these indications.

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Liquid crystal foil for the detection of breast cancer

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1. ABSTRACT

Breast cancer is the most common malignant tumor in females around the world, representing 25.2% of all cancers in women. About 1.7 million women were diagnosed with breast cancer worldwide in 2012 with a death rate of about 522,000[1, 2]. The most frequently used methods in breast cancer screening are imaging methods, i.e. ultrasonography and mammography. A common feature of these methods is that they inherently involve the use of expensive and advanced equipment.

The development of advanced computer systems allowed for the continuation of research started already in the 1980s.[3] and the use of contact thermography in breast cancer screening. The physiological basis for the application of thermography in medical imaging diagnostics is the so-called dermothermal effect related to higher metabolism rate around focal neoplastic lesion. This phenomenon can occur on breast surface as localized temperature anomalies[4].

The device developed by Braster is composed of a detector that works on the basis of thermotropic liquid crystals, image acquisition device and a computer system for image data processing and analysis. Production of the liquid crystal detector was based on a proprietary CLCF technology (Continuous Liquid Crystal Film).

In 2014 Braster started feasibility study to prove that there is a potential for artificial intelligence in early breast cancer detection using Braster's proprietary technology. The aim of this study was to develop a computer system, using a client-server architecture, to an automatic interpretation of thermographic pictures created by the Braster devices.

Keywords: breast cancer detection, liquid crystal, contact thermography, Braster device, image analysis, computer vision

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2. INTRODUCTION

Cholesteric liquid crystals capable of selective reflection of the light in the function of the temperature have been known for many years[5-7]. They are applied for the imaging of thermal signatures of technical objects[8], thermal flows and loads[9], as well as in the medical diagnosis[10]. In medicine the research is focused on the possibilities of differentiating the detected thermal anomalies that are caused by pathophysiological processes. This is so as the proliferative pathologies (of neoplastic nature) are characterized by a significant majority of anabolic processes related to an intensive neoangiogenesis[11], what in turn is associated with the occurrence of hyperthermic changes in the thermogram.

The first attempts to apply the liquid-crystal technology for the detection of breast cancer were made already in the 70s of the 20th century. At the beginning, in order to obtain a colorful representation of thermal distribution, the breast surface was covered with a soot followed by a layer of properly prepared liquid-crystal mixture[12]. However, due to an oily nature of the liquid crystals and the necessity of using organic solvents to remove them from the breast surface after examination, this method was abandoned and the scientists began to search for a new, more flexible method that would be based on the dispersing of the liquid-crystal material in a film-forming material. In this way the first thermographic films were created which served as a detector of thermal changes on the body surface.

In the 80s. the first tests with the use of thermographic film were carried out[13-17]. Initially, in the breast screening the film was applied against the breast surface and an attempt was made to interpret the thermal image obtained during the examination. However, it quickly became clear that the quality of the thermograms obtained with the use of the film available at that time left a lot of room for improvement. Moreover, it was still not possible to analyze visually the thermographic images during the examination. The problem with the interpretation forced the use of techniques for thermographic image processing, which, at that time, were not yet available. The thermograms were photographed for archiving purposes. Unfortunately, the analysis of photographs also did not prove effective. Additionally, a parallel development of mammography and thermovision contributed to the fact, that the use of contact thermography with regard to medicine has been given up for 20 years.

Together with the contact thermography another method of thermal imaging has been developed – thermovision. Thermovision, unlike contact thermography that is based on conducting, consists in radiation heat transfer. The thermovision allowed for obtaining a more accurate representation of thermal distribution in the breasts, and following the digital revolution in the 90s., it also allowed for obtaining a digital image that was easy to process. Moreover, in the second half of the 90s. of the 20th century, a significant technological breakthrough was achieved, namely, relatively cheap matrices for uncooled thermal detectors were constructed what resulted in radical reduction in the price of thermovision camera. Thermovision became much more common and broadly used also in medicine, in particular in the breast cancer screening[18-23]. Despite the easier access, the unit price of a thermovision camera was still very high. Additionally, the unsolved problem of the analysis and processing of thermal images resulted in a very limited application of thermovision in breast cancer screening.

Nowadays, the ultrasonography and mammography are used together with histopathological confirmation as a gold standard for breast cancer diagnosis. There are, however, several disadvantages of the above-mentioned modalities what makes it reasonable to continue research and development in the area of alternative methods for diagnosing and screening breast cancers. Since the liquid-crystal matrix technology enables programming a temperature range of detection with a thermal resolution that corresponds to the difference in physiological temperature between the developing cancerous tumor and surrounding healthy mammary gland, the contact thermography introduces significant potential in breast cancer screening as a complementary and adjunctive modality to the current clinical gold standard.

3. LIQUID CRYSTAL MATRICES

The liquid-crystal thermographic films, also referred to as the thermochromic liquid-crystal matrices (TLC), are composite layered materials containing thermo-optic liquid-crystal layer in their structure (fig.1). In physics, the thermo-optic layer is a suspension of dispersed spheres of 2–10 μm that contain liquid crystals inside.

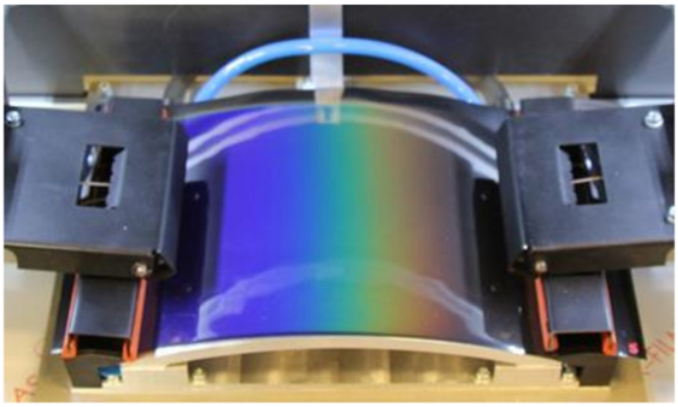

Fig.1 Thermographic film placed on a heating table

The thermo-optic liquid-crystal layers are formed in a process of micro-encapsulation or emulsyfication[24], in which a properly prepared mixture of liquid crystals[25] is sealed through the dispersion in a film-forming material, and in this form the is applied on the base material.

Depending on the designation and the planned scope of the thermal detection of the TLC matrices an appropriate composition of liquid crystals, e.g. chiral nematics, is chosen. For instance, in order to obtain a color response in the temperature range of 31–36°C, the mixtures of cholesteryl nonanoate and cholesteryl oleylcarbonate are used. By modifying the composition of the liquid-crystal mixtures it is possible to adjust the scope and the resolution of the temperature–color dependency.

The production of liquid-crystal matrices (TCL) consists in an application of a properly prepared thermo-optic layer on the base material (support). Among many methods of matrix production, a particular attention should be driven to the one developed by the Braster company – the so called CLCF method, which is a modified version of the Knife Coating method. In the CLCF technology (Continuous Liquid Crystals Film) two micro-layers are simultaneously applied on the base polyester film and subsequently are dried under the conditions of a quasi-laminar air flow. When the drying process is over, the last layer – i.e. the absorption layer – is applied, which ensures contrast for the radiation selectively reflected in the thermo-optic layer.

The liquid-crystal matrices produced with the use of this method consist of several layers. The most important of them are: the polyester base layer, the thermo-optic liquid-crystal layer, the protective layer and the absorption layer, as illustrated in fig. 2.

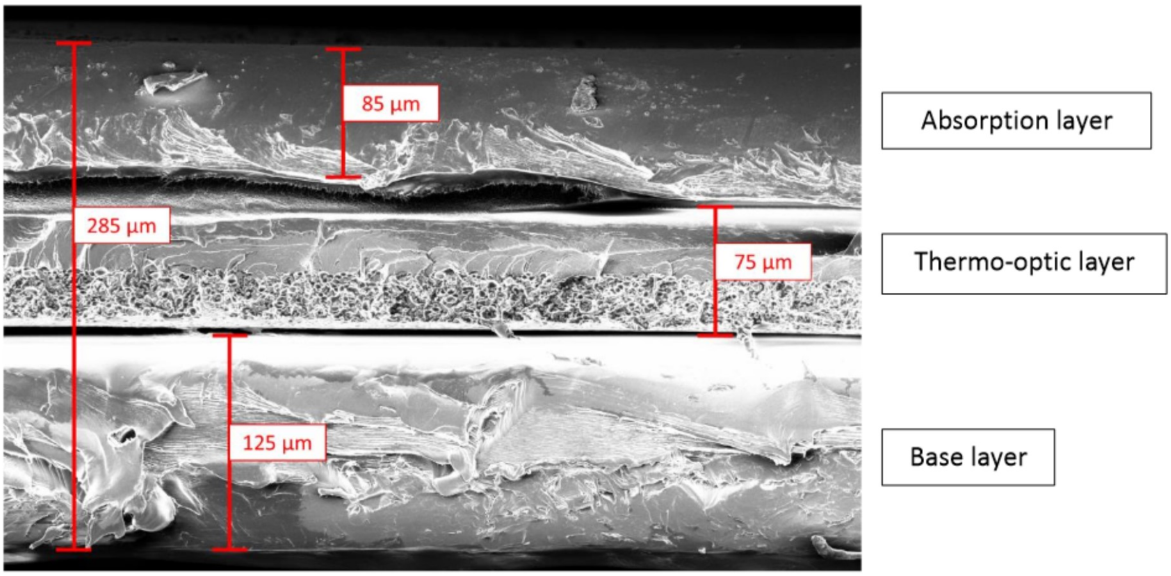

Fig. 2 Sectional view of the TLC matrix obtained with the electron microscope.

By applying the TLC matrix to a surface under examination with a temperature corresponding to the scope of responsiveness of the thermal matrix, a color image of thermal signature occurs already after a few seconds. This phenomenon results from the optical rotation, i.e. a selective reflection of light in the liquid crystals. The thermochromic phases of the liquid crystals have created layered structures, in which the molecules contained in a single layer take the same direction vector (along director). For each layer this vector changes the direction by the same value, depending on the temperature. Therefore, as the temperature rises, the pitch of the helix is changed, what determines the capability of selective light reflection. When the TLC matrix is illuminated with the polychromatic light (white), a certain length of wave is selectively reflected, and the remaining part is absorbed by the absorption layer. In this way, as the temperature on the matrix rises, there appear consecutively the red color, the green one and, in the end, the blue one. Figure 3 presents the dependency between the color, represented in the HSV or RGB space, and the temperature[26].

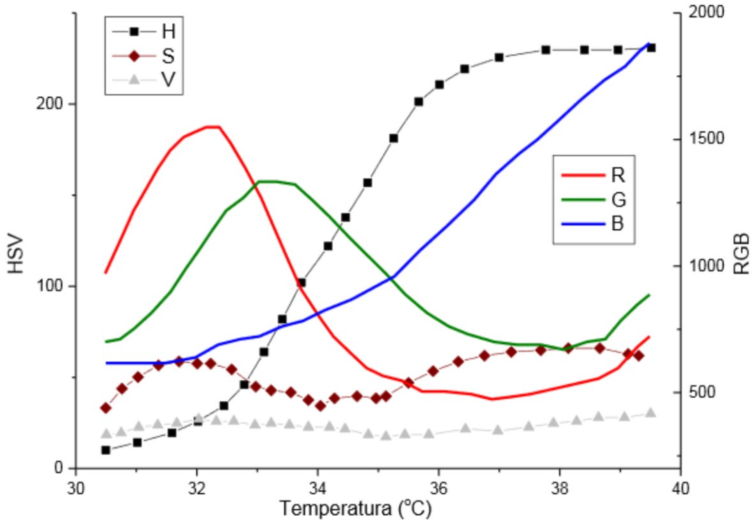

Fig. 3 Dependency between the color, represented in the HSV and RGB space and the temperature in TLC matrix, a) RGB space, b) HSV space

4. DIAGNOSTIC THERMOGRAPHIC IMAGES - THERMOGRAMS

A result of a single application of the liquid crystal matrix to a breast surface is a colorful map in RGB scale which represents a thermal distribution of contact area, which is called a thermogram. Since the matrix is totally passive detector of the temperature changes, an image acquisition system is needed for registering and storing the thermograms. As soon as the matrix is applied to a breast surface, so-called heating process starts. A process of liquid crystal film heating from "0" status, through the stabilization stage of the colour map, until the moment of gaining a stabilized image is about ca.15 seconds. Return to the initial state, when there is no colour answer on the matrix, takes ca.10 seconds (Figure 4).

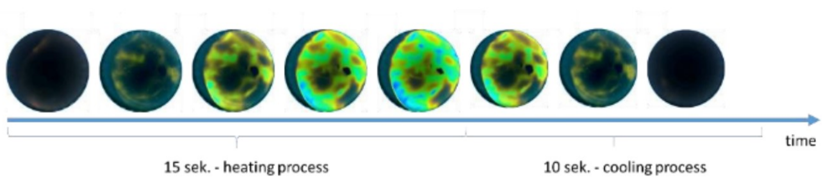

Figure 4. The process of heating after application and cooling down after putting away of the liquid crystal foil

To make the thermographic examination complete, it is necessary to perform the sequence of 6 or 10 applications (depending on breast size) to a breast in a specific order. For small breast it is suggested to perform 3 applications for left and right breast – summary 6 applications and for bigger breast 5 applications for left and right breast – summary 10 applications. It is crucial to cover whole surface of breast skin with matrix application in purpose of acquire complete thermographic map of breast.

Each thermogram consist of several contours depended of local temperature distribution, especially a difference between hotter and colder areas. Basing of these contours and other characteristic features of overall examination, the medical interpretation can be performed.

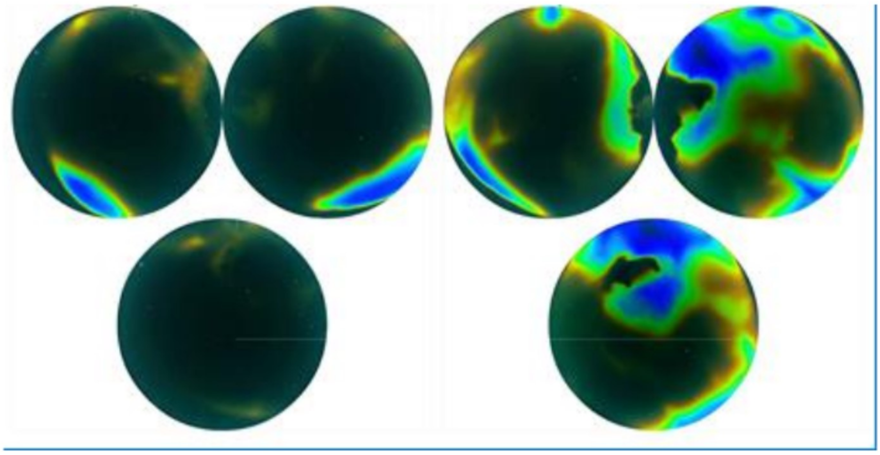

Figure 5. Full thermographic examination of a medium size breast consisted of 6 thermograms

During a medical examination, some additional information is collected by means of survey or questionnaire in which such data as age, breast size and structure, potential BRCA1/BRCA2 mutation, hormonal treatment are included. The set of thermograms together with the collected information can be analyzed and interpreted by thermographic expert or advanced image processing and classification system.

5. DIAGNOSTIC INTERPRETATION OF THERMOGRAMS

There are two major kind of approach to interpretation of the thermograms. First one is called a manual interpretation and is performed by experienced specialists – contact thermography experts, who use a manual interpretation algorithm. The manual interpretation algorithm is a kind of guidance which includes basic rules of interpretation, characteristic features definitions and features-based check-list equipped with graphic examples and exclusions definitions. The expert performs the interpretation by following the algorithm step by step, answering questions, analyzing the images and looking for characteristic features of the thermograms. During the manual interpretation process, several aspects are assessed:

- Is the examination informative? Was the examination performed according to procedure properly?
- Are there any undesired contours which can come from a belly or armpit?

- Is there any asymmetry in temperature distribution between left and right breast? If yes, is the asymmetry significant?
- What kind of contours can be recognized on the thermogram: hot spots, linear shapes, uniform areas?
- What are characteristic features of contours in terms of shape, localization, color gradient, sharpness of edges?

Second one is called an automatic interpretation as is performed by advanced computer system based on artificial intelligence algorithms and advanced image processing, which provides a result of interpretation without involvement of human. This system processes the thermal images of breasts to produce information for end user whether more detailed examinations (like mammography) are required. The image processing and machine learning algorithms are used. The system includes modules to remove noise from images, to find contours, to calculate features of contours [28,29] and to find asymmetry of corresponding images[27]. There are modules to classify contours [30] and finally classify examinations [31, 32]. The isolated incidents, examinations potentially hard to classify, are detected [33].

6. CLINICAL STUDIES

Braster has conducted 3 official observational studies under the supervision of the Ethic Committee and professional CRO, covering approx. 1350 women, which included almost 500 cancerous cases (table 1)

Observational study	Population (cancers)	Dates
ThermaCRAC	736 (72)	06.2013 – 03.2014
TharmaRAK	318 (318)	10.2014 – 05.2015
ThermaALG	278 (87)	04.2015 – 05.2016

Table 1. BRASTER clinical trials details

The observational studies were conducted in women with symptoms of breast anomalies, referred for enhanced diagnostics in specialist diagnostic units. The primary study objective was to determine the efficacy of the Braster device versus standard diagnostic procedures and therefore its clinical utility for breast cancer detection in women.

On the basis of the most important results obtained during the ThermaCRAC study, the study parameters for the Braster device were as follows: sensitivity and specificity of the thermographic examination versus standard diagnostic procedures was respectively 72% and 58% for the whole population. However, if we take into account the lack of experience with this method at that time, which was a pioneer attempt at establishing manual interpretation path for thermographic images and the resulting limited experience of the team of investigators and interpreters, the above results should be seen as a feasibility study. Recommendation formed on the basis of the ThermaCRAC study was to collect data of thermographic breast images and to improve manual interpretation algorithms. which were done after next observational study – ThermaRAK.

In April 2015 Braster has conducted an observational study – ThermaALG, which like ThermaCRAC had one primary objective: to determine the efficacy of new, improved manual interpretation algorithms. Sensitivity and specificity of the thermographic examination versus standard diagnostic procedures were improved, and amounted to approximately 80% and 70% for the whole population. Additionally, thermographic images were evaluated by a system of intelligent analysis and classification, which makes parametric evaluation through the use of artificial intelligence algorithms, including neural networks, support vector machines and regression analysis. Validation of the system of automatic interpretation in the range of sensitivity and specificity was respectively 71.8% and 75.2%.

7. CONCLUSIONS

Based on abovementioned description and considerations, a following conclusion can be drawn:

1. Contact thermography based on liquid crystal matrices is an innovative diagnostic modality used for early breast cancer detection as a method complementary to ultrasonography and mammography. The goal for contact thermography is not to be a competitive modality to gold standard in breast cancer diagnosis (ultrasonography, mammography) but to be adjunctive one, which gives to a user an early warning regarding her breast health and give opportunity to undergo a proper diagnosis process.
2. The interpretation of thermograms performed by experts is based on characteristic features of contours and quadrants asymmetry. During thermograms assessment, the expert follows a special guidance called the manual interpretation algorithm which includes basic rules of interpretation, characteristic features definitions and features-based check-list.
3. The thermograms can be processed using an algorithm of advanced image processing in order to enhance the human perception as well as define attributes.
4. There is a significant potential for machine learning and artificial intelligence in area of automatic recognition and classification of thermographic images.
5. Combining expert's experience with automatic recognition and classification may result in remarkable efficiency with early breast cancer detection.

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ABSTRACT

Observational study evaluating the diagnostic efficacy and clinical utility of the new version of interpretation algorithm for Tester BRASTER thermography in the diagnosis of breast pathology in women.

keywords: breast cancer, liquid crystal contact thermography, Tester BRASTERTM

BRA/11/2014 was a prospective, multicentre, open-label, observational, non-interventional study, conducted in specialist breast diagnostic outpatient clinics in Poland by persons trained in the thermography procedure, under the supervision of specialist physicians. Contact thermography using the Tester BRASTER device was performed in 274 women who consented to participate in the study and disclose the medical records. Out of this group, the final analysis included: 95 women aged 25–49 years with prior breast ultrasound scan assessed as BIRADS-US 4 or 5 (group A), 73 women aged ≥ 25 years with prior breast ultrasound scan assessed as BIRADS-US 1 or 2 (group B), and 87 women aged ≥ 50 years with prior breast ultrasound scan assessed as BIRADS-US 4 or 5 (group C). In total, the analysis included the testing results obtained in 255 women.

The primary objective of the study was to evaluate the diagnostic efficacy of the new versions of the interpretation algorithm for thermographic images obtained by liquid crystal contact thermography (TA-02 and TA-03), and to compare them with the previous version (TA-01).

The secondary objectives of the study were: 1) to verify the usefulness of liquid crystal matrix with a wide range of thermal detection (31°C–37°C), so-called yellow matrix (“IV”); 2) to compare each version of algorithm interpretation and classification of the result of breast thermography (TA-01, TA-02, TA-03) obtained using the Tester BRASTER device with the results obtained in the BRA/03/2013 study (THERMACRAC); 3) to validate the Automatic Interpretation System; and 4) to assess the safety of device use in clinical practice. The usefulness verification was done on the basis of clinical material in the form of thermographic data recorded with the Tester BRASTER device, and data from imaging and histopathology examinations obtained in the process of standard diagnosis and differentiation of breast cancer in women.

For statistical purposes, the interpretation of thermographic testing was conducted according to the algorithms developed by BRASTER S.A. on the basis of past experience, based on a holistic method of determining thermal asymmetry and classification of the recorded hyperthermic changes. The interpretation was done by an independent radiological team of three persons, who had limited access to the patients’ clinical data.

Additionally, the Automatic Interpretation System has been validated – it is a computer expert system developed on the basis of a set of rules relating to thermal and structural asymmetry of the breast.

The primary objective of the study, which was to compare the diagnostic efficacy of each developed algorithm for the interpretation of thermographic images, has been achieved. In the group of women < 50 years of age with an abnormal result of breast ultrasound scan (BIRADS-US 4 and 5), the sensitivity of thermography using the TA-01 algorithm was 66.7% (95% CI: 47.9; 82.0) at a specificity of 69.1% (95% CI: 57.4; 79.1). Statistics C was 0.679 (95% CI: 0.573; 0.785). The same parameters evaluated by the modified TA-03 algorithm were: sensitivity 81.5% (95% CI: 64.1;

92.6), specificity 87% (95% CI: 79.7; 92.4). Statistics C was 0.842 (95% CI: 0.761; 0.924). When comparing the predictive values in this group for each assessment algorithm, it was shown that the positive predictive value increased from 46.1% (95% CI: 31.2; 61.6) for the TA-01 algorithm to 71.0% (95% CI: 53.7; 85.8) for the TA-03, and the respective negative predictive value increased from 85.4% (95% CI: 74.4; 92.9) to 92.2% (95% CI: 83.7; 97.0). A comparison of the TA-01 and TA-03 (modified) algorithms in this group for statistics C reached significance in favour of the latter algorithm, modified TA-03 (p=0.0002). Similarly, in the group of women > 50 years of age with an abnormal result of breast ultrasound scan (BIRADS-US 4 and 5), the sensitivity of thermography using the TA-01 algorithm was 75% (95% CI: 64.1; 83.9) at a specificity of 60% (95% CI: 35.3; 81.3). Statistics C was 0.675 (95% CI: 0.537; 0.813). The same parameters evaluated by the modified TA-03 algorithm were: sensitivity 77.8% (95% CI: 67.2; 86.2), specificity 62.5% (95% CI: 48.5; 75.1). Statistics C was 0.701 (95% CI: 0.617; 0.786). In the group of women without breast pathology, the rate of false-positive thermography was very similar to that observed in women with abnormal breast ultrasound without breast cancer (22.5% and 37.5% in women < 50 and ≥ 50 years of age, respectively). The obtained results cannot be directly compared to the results of the BRA/03/2013 (THERMACRAC) study due to the differences in obtaining and interpreting the thermographic images; however, the sensitivity and specificity obtained with the modified TA-03 algorithm in women < 50 years of age are significantly better.

The results of this study demonstrate good diagnostic efficacy of contact thermography in breast cancer detection and differentiation between malignant and benign pathologies of the breast in women < 50 years of age. It should be emphasised that the observed lower efficacy in women ≥ 50 years of age may be at least partially explained by the inclusion of women with breast ultrasound results in the category BIRADS US 5, where the likelihood of cancer is > 95%, in this age group.

This could lead to an increase in the proportion of false negative results. The results indicate a very interesting direction in the application of the thermography technology for younger women, for whom the breast cancer prevention offer is fairly limited.

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