



Simplified description and interpretation of pathological thermography signs in malignant breast lesions

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Abstract

Background and Purpose: Breast cancer is the leading cause of death among women aged 20–59 years in developed countries, with similar mortality trends, observed among women in Croatia. Breast cancer detection usually relies on mammography, ultrasound (US) and magnetic resonance imaging (MRI), however, thermography is a noninvasive, reliable and applicable diagnostic procedure for early detection of breast disease that has attracted interest in this field. The aim of this study was to establish the frequency and characteristics of pathological thermographic signs in female patients, who were operated on malignant breast lesions. In addition, the authors offered a simplified description and interpretation of pathological thermographic signs, based on published literature.

Material and Methods: The seventy four female patients with histopathologically confirmed breast cancer were included in the study. In all patients breast cancer was diagnosed using standard protocol which have included clinical examination, mammography, ultrasound and for selected patients MRI and/or fine needle aspiration (FNA). Thermographic imaging has been conducted 1 to 14 days before scheduled surgical procedures.

Results: Mean tumor size positively correlated with number of pathological thermographic signs (IR 3 vs. IR 5, $p < 0.05$). Mean number of pathological thermographic signs per patient was 3.5 ± 1 , 72 (range 1 to 8). The most frequently noted singular signs were heat in area of finding and vascular signs, as well.

Conclusion: The simplified description could offer a suitable clinical tool for standardization of pathological thermography signs in malignant breast lesions, taking into account the learning curve of medical teams involved and ethical aspects, as well.

INTRODUCTION

Globally, cardiovascular disease is the leading cause of death in women. Cancers of the breast, lung and colon are among the top ten causes of death of older women globally. Worldwide, breast cancer comprises 22.9% of all cancers (excluding non-melanoma skin cancers) in women. In 2008, breast cancer caused 458,503 deaths worldwide (13.7%) of cancer deaths in women. Breast cancer is the leading cancer killer among women aged 20–59 years in high-income countries (1).

Mortality trends in Republic Croatia are the similar. Leading cause of death among women is cardiovascular disease (14 881) in 2009. Breast cancer is the most prevalent women's cancer with 2473 new cases in 2008, and cause about 1000 deaths in 2010. Both, incidence and mortality trend are increasing (2).

High prevalence of the disease and identification of biological factors important for its development and progression (3) justify the high public interest for new findings and recommendations in this field that would improve its prognosis (4, 5). Advancements in molecular and genetic mechanisms of breast cancer have lead to realization that the breast cancer is heterogeneous disease whose prognosis depends on both biological and clinical parameters. Inclusion of biological tumor markers to the earliest decision-making requires advancements in clinical diagnostic protocols and could mark a new treatment based on individual approach to each patient (6).

Thermography is a non invasive, reliable and applicable diagnostic procedure for early detection of breast disease that has attracted interest in this field (7, 8, 9, 10). Thermography detects the heat emitted by the body of the patient and with the use of sensitive thermal cameras is capable of depicting temperature changes of 0.07 °C. It is comfortable since it is not associated with the use of ionizing radiation or mechanical pressure on the breast tissue that is required for mammography imaging. The method itself is biologically inert and could, therefore, be used without limitations for continuous monitoring of changes without detrimental effects for health of the women. Change of the skin surface temperature that is being measured results from various chemical mediators that create suitable environment for tumor growth and propagation. Therefore, unlike other methods that detect morphological changes, thermography is much more suitable to follow the tumor development (11, 12). It is striking that thermography can detect biological signs of breast cancer up to 10 years before the appearance of clinically significant disease («too early, too right») (8), and has shown its promise in several studies (13, 14, 15, 16). Medical thermography was first applied in 1957, when a surgeon, Dr. R. Lawson discovered that his breast cancer patients had higher skin temperature over the cancer area. Since the 1970's thermography has been used in many areas of medicine. Early problems such as low detector sensitivity, but most significantly, poor training thermography technicians was the source of error in thermography and retarded the acceptance of this technique until 1990. Since that time, thermographic equipment has evolved significantly. Modern thermal imaging systems comprise technically advanced thermal cameras coupled to computers with sophisticated software solutions. The recorded images are now of good quality and may be further processed to obtain reliable information. Contemporary thermal imaging must be performed according to certain protocol aimed at reliability and reproducibility of results (17). The major challenges for acceptance these methods by medical community are (18):

1. Standardization and quantification of clinical data,

2. Better understanding of the pathophysiological nature of thermal signatures,
3. Training in both image acquisition and interpretation.

Ignoring any of the principles worked out leaves thermography open to error and thus reduces acceptance of this technique in medical diagnostic.

PATIENTS AND METHODS

Patients

The study was conducted from September 2010 to May 2011 at University Hospital for Tumors and at University Hospital Centre »Sestre milosrdnice« in Zagreb, Croatia. The seventy four female patients with histopathologically confirmed breast cancer were included in the study. In all the patients breast cancer was diagnosed using standard protocol which have included clinical examination, mammography, ultrasound and for selected patients MRI and/or fine needle aspiration (FNA). Thermographic imaging was conducted 1 to 14 days before scheduled surgical procedures. Patients with previous breast surgeries, bilateral carcinomas and patients whose histopathologically findings included cancer and some of the benign lesions (fibroadenoma, phyllodes tumor, and atypical hyperplasia) were excluded from the study.

The study was approved by the Ethics committee of the University Hospital for Tumors at University Hospital Centre »Sestre milosrdnice« in Zagreb, and all participants have signed informed consent.

Thermographic system

Thermographic imaging was performed using a new generation of digital infrared camera – Thermo Tracer TH7102WL (NEC Sanei Instruments, Ltd., Japan). This thermovision camera contains an uncooled focal plane array detector (micro bolometer) with geometric resolution of 76.800 pixels per picture (320×240). Spectral range is from 8 μm to 14 μm and the temperature range lies between – 40°C and 120°C (optional 500°C). The minimum detectable temperature resolution (difference) is 0.07° C at 30°C (Normal mode) and spatial resolution is 0.48 mm at measuring distance of 30 cm (IFOV 1.58 mrad). For remote control and transfer of data from infrared camera TH7102WL to a computer, we used the previously developed an open source thermoscan analyses software Thermo WEB (Thermo MED version) (19). This software supports thermal analysis and image presentation in numerical and graphical forms of temperature values of any part of surface inside the thermographic scan.

Patient preparation and imaging

The room temperature was stable at approximately 22°C. Patients were asked to remove their clothes from their waist upwards and were left to equilibrate with ambient conditions for 10–15 min. The thermographic im-

aging was carried out by having the patient sit at a 0.9 m distance from the camera.

According to standardized image acquisition protocol (15), the patients raised their arms above the head and 5 images were taken: front, right and left semi-oblique, right and left oblique, in order to obtain images of complete breast skin area.

Data analysis

In order to assure consistency in the reporting of the thermal images all pictures were analyzed by the trained radiologists. Thermal features are divided into signs and analyzed based on our modification of four established protocols for characterization of breast disease (Marseille, Villa Marie, Hobins, Hoekstra).

In all instances the contra lateral breast was used for comparison.

Established protocols for thermographic characterization of breast disease include:

Ville Marie Infrared (IR) Grading Scale is most used and recommended protocol in today's everyday clinical practice. Thermographic image findings have been divided into five categories (15):

- IR1 – absence of any vascular pattern to mild vascular symmetry
- IR2 – significant but symmetrical vascular pattern to moderate vascular asymmetry
- IR3 – one abnormal sign
- IR4 – two abnormal signs
- IR5 – three or more abnormal signs

Marseille protocol, which was developed at the Pasteur Institute in Paris, recognizes also five categories:

- TH1: No abnormal features

- TH2: Some unusual metabolic activity is present, but probably due to causes such as hormonal imbalance
- TH3: Abnormalities are present in metabolic function, but the results are inconclusive
- TH4: Abnormalities are found which are possibly cancerous, but it's too soon to diagnose with certainty (approximately 38% of TH4 patients develop cancer within five years)
- TH5: Metabolic abnormalities suggest a very high probability (about 96%) of cancer

Hoekstra thermography signs: asymmetric and hyperthermic vascular patterns, focal patterns with $+2,5^{\circ}\text{C}$ differential, asymmetric and atypical complexity of a vascular pattern, asymmetric and diffuse hyperthermia ($+2^{\circ}\text{C}$ differential) patterns involving the periareolar area or entire breast, localized heat along an abnormal physical contour (edge sign), lack of an adaptive response to an autonomic challenge procedure (8).

Thermography criteria (Hoekstra): anarchic or complex vascular features, hyperthermic focal patterns greater than 3°C differential, asymmetric and abnormal complexity of a vascular pattern, asymmetric and abnormal physical contour of more than one quadrant of a breast, and any combination of these thermography signs.

Hobins pathological thermographic signs (two categories):

Major factors (hot spot, global heat, heat in area of finding, nipple heat, periareolar heat, star vascular anarchy, edge and bulge sign) and secondary factors (inverted V vascular pattern, fragmented vascular anarchy, closed vascular anarchy, vascular completeness, inferior vascular pattern, hot spot, bifurcated vascular peduncles, pointed vascular peduncles, Moa-moa sign and transverse vascular) (12).

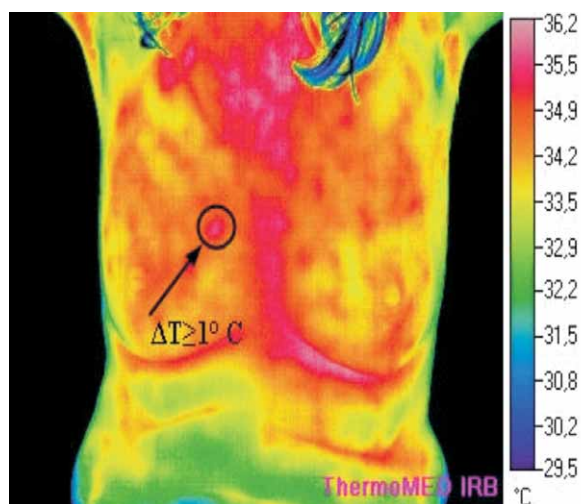


Figure 1(a and b). Quantitative thermographic signs heat in area of finding: A: Black arrow points to encircled area of raised thermal activity $\geq 1^{\circ}\text{C}$ in upper medial quadrant of right breast; B: Red arrow points to the same lesion of the right breast detected by MRI.

Our modified protocol that includes quantitative (A) and descriptive (B) pathological thermographic findings has two groups with overall eight pathological thermographic signs:

A. QUANTITATIVE THERMOGRAPHIC SIGNS:

One breast only:

1. heat in the area of finding – thermal activity $\geq 1^{\circ}\text{C}$ on any area of the breast that has been previously de-

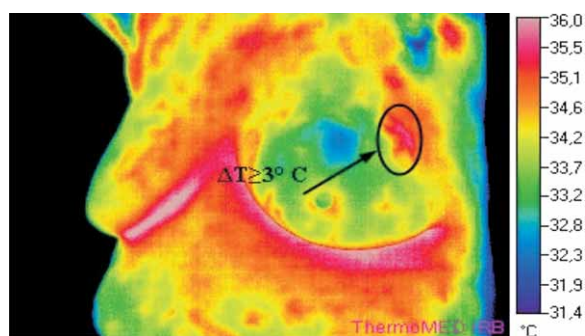


Figure 2. Quantitative thermographic signs delta 3 sign: black arrow points to encircled area of raised thermal activity more than 3°C compared to the surrounding breast tissue in the outer upper quadrant of the left breast.

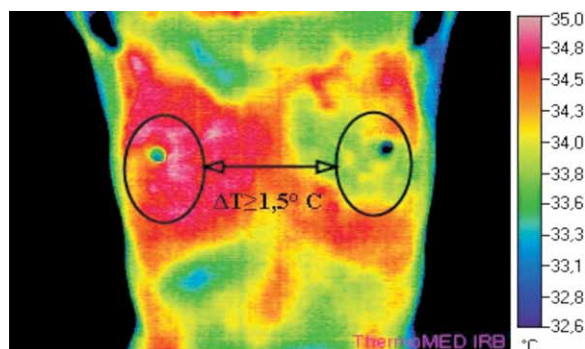


Figure 3. Quantitative thermographic signs global heat: encircled thermal activity of right breast which is more than 1.5°C higher than another (healthy left) breast.

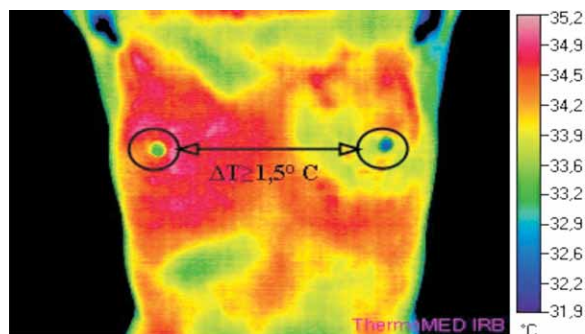


Figure 4. Quantitative thermographic signs periareolar heat: encircled areas show thermal activity of the surface around the right nipple which is more than 1.5°C higher than around left periareolar area.

icted as suspicious (clinical examination, US, mammography, MRI) (Figure 1.)

2. delta 3 sign- thermal activity $\geq 3^{\circ}\text{C}$ compared to the surrounding breast tissue (Figure 2.)

Comparison of breasts:

1. global heat – thermal activity of one breast $\geq 1.5^{\circ}\text{C}$ compared to the healthy breast (Figure 3.)
2. periareolar heat- thermal activity of the area around the nipple $\geq 1.5^{\circ}\text{C}$ compared to the same area of healthy breast (Figure 4.)
3. nipplar heat- thermal activity of the nipple $\geq 1^{\circ}\text{C}$ compared to the nipple of the healthy breast (Figure 5.)
4. hot spot sign – thermal activity of the any spot on the breast $\geq 2^{\circ}\text{C}$ compared to the same spot on the healthy breast (Figure 6.)

B. DESCRIPTIVE THERMOGRAPHIC SIGNS:

1. vascular signs – thermographic imaging of pathological vascular signs (Figure 7.)
2. contour sign- thermographically visible changes at the external shape of the breast (Figure 8.)



Figure 5. Quantitative thermographic signs nipplar heat: encircled areas show higher thermal activity of the right nipple for more than 1°C compared to the nipple of left breast.

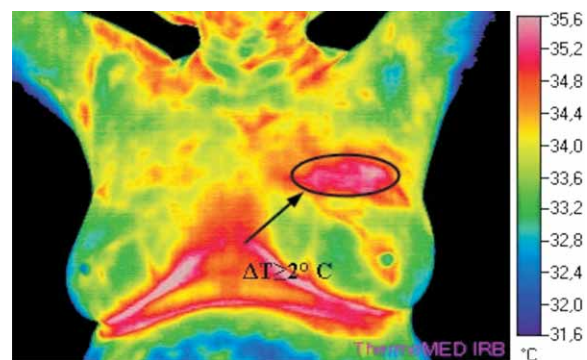


Figure 6. Quantitative thermographic signs hot spot sign: encircled area shows higher thermal activity of the left breast (border of the upper quadrants) for more than 2°C compared to the same spot on the healthy right breast.

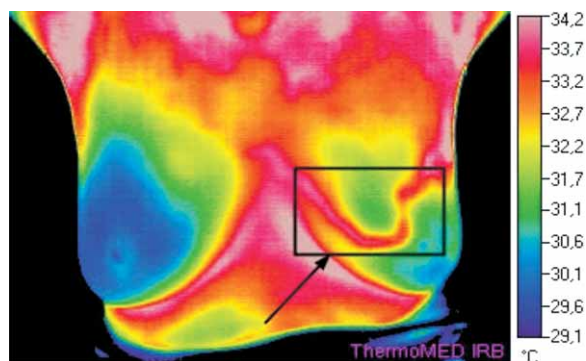


Figure 7. Descriptive thermographic signs vascular signs: pathologic vessel sign on the left breast (rectangle).

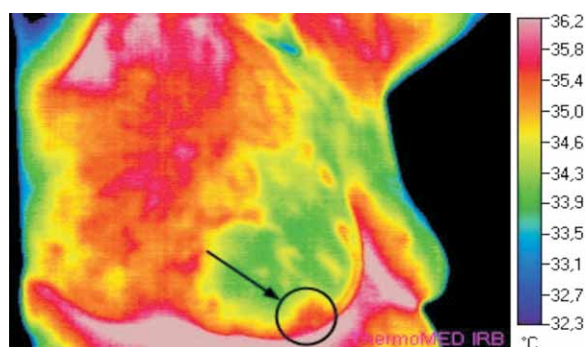


Figure 8. Descriptive thermographic signs contour sign: encircled area shows thermographically visible changes at the shape (border of lower quadrants) of the right breast.

RESULTS

The study included 74 female patients with a mean age of 63.8±12.2 (range=33 to 86) years, who were operated on breast cancer. The majority of malignancies were invasive carcinoma, as shown in Table 1. (72).

Number of pathological thermographic signs and tumor size

According to Ville Marie infrared grading scale (IR) patients have been categorized into three groups: 7 patients with one pathological thermographic sign (IR3), 21 patients with two pathological thermographic sign (IR4) and 46 patients with three or more pathological thermographic signs (IR5).

TABLE 1

Pathologic findings of operated lesions (n = 74).

Pathohistologic diagnosis	n=74
Invasive ductal carcinoma	68
Invasive lobular carcinoma	2
Invasive papillary carcinoma	1
Invasive medullary carcinoma	1
Ductal carcinoma <i>in situ</i>	2

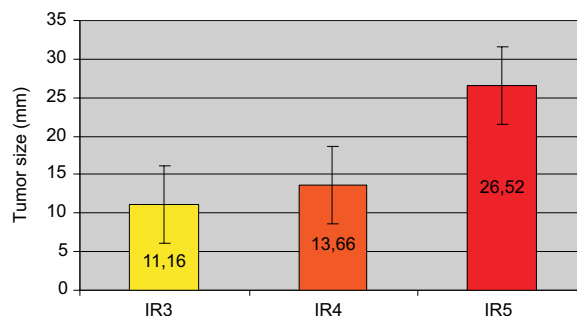


Figure 9. Mean tumor size according to the IR group (Ville Marie protocol).

Mean tumor size at pathohistologic evaluation was 21.7±13.2 (range = 2 to 58) mm. (Figure 9).

As seen in Figure 9. mean tumor size increased with number of pathological thermographic signs, with lowest size in IR 3 group and highest in IR 5 group.

Frequency and nature of pathological thermographic signs

Thermographic image sample for all three groups are shown at Figure 10 to 12.

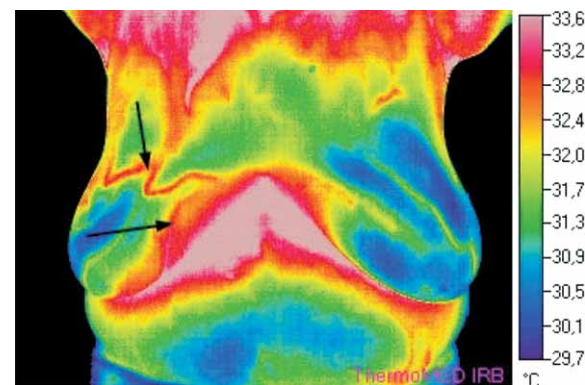


Figure 10. IR 3 group (according to ville marie protocol) one pathological thermographic sign: arrows point to pathologic vessel signs on the right breast.

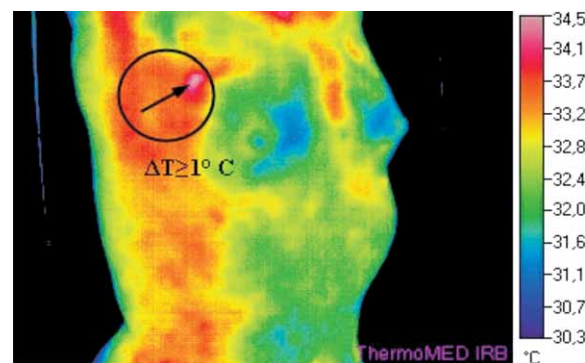


Figure 11. IR 4 group (according to ville marie protocol) two pathological thermographic signs: global heat (encircled area) and heat in area of finding (arrow) on the right breast.

TABLE 2

Number and percentage of pathological thermographic signs.

Type of pathological thermographic sign	n=262
Quantitative PTS (heat in area of finding, delta 3 sign, global heat, periareolar heat, nipple heat, hot spot sign)	195 (74%)
Descriptive PTS (vascular signs, contour signs)	67 (26%)

Total number of registered pathological thermographic signs was 262.

Mean number of pathological thermographic signs per patient was $3.5 \pm 1,72$ (range = 1 to 8). The most frequently noted singular signs were heat in area of finding (60) and vascular signs (54) (Figure 13).

DISCUSSION AND CONCLUSION

The results of this descriptive study clearly show that the method of IR thermography is capable to delineate malignant breast lesions. Furthermore, the size of detected lesion correlated with the number of thermographic signs indicating the existence of breast pathology.

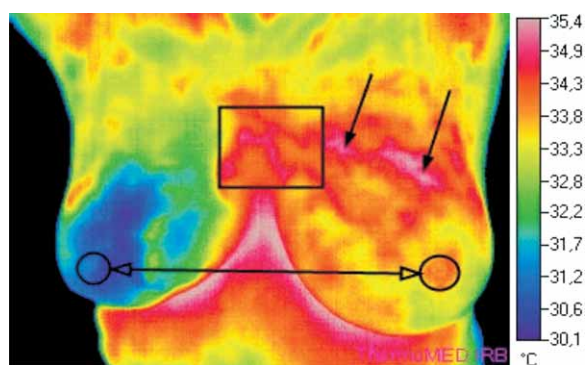


Figure 12. IR 5 group (according to ville marie protocol) three or more pathologic thermographic signs: right breast: global heat, periareolar and nipple heat (encircled areas), hot spot signs (arrows) and vascular signs (rectangle).

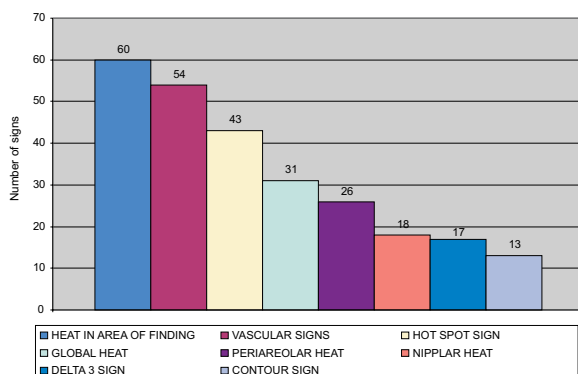


Figure 13. Distribution of pathological thermographic signs.

Hence, the authors' interpretation of thermographic findings was based on combination of temperature and »morphological and descriptive« signs and previously published protocols for interpretation of pathologic IR images of the breast (8, 12).

In our study, the most frequently noted pathological thermographic sign was heat in area of finding that offers a possibility to decrease the number of biopsies and FNA in areas that do not show temperature disturbances. However, this observation should be evaluated in future controlled studies. Another frequently seen pathologic thermographic sign was combination of various vascular signs. The thermographic visualization of »blood vessels« in thermograms is a consequence of a need for abundant supply of nutrients to maintain the tumor growth. Nitric oxide (NO) is produced by tumor cells in order to increase circulation, keeping the existing blood vessels open, recruiting dormant vessels and creating new ones (neoangiogenesis) (20).

In spite of the existence of established diagnostic protocols for thermography of breast disease, these protocols do not inevitably offer the ideal tool to meet the challenges of IR (infra red) images interpretation. In many situations ordinal and/or nominal scales have been used in different published studies with equivocal results. Furthermore, some studies still use different combinations or modifications of current interpretation protocols, including the unsuccessful attempt of interpretative model based on simply visual color interpretation (10).

Some studies (7, 8, 9, 10, 13, 14, 21, 22) use interpretative models that try to improve existing protocol and their interpretation with innovations in different software solutions and attempt to integrate artificial neural networking. Results and experiences of different authors with the use of thermographic technology in the diagnosis of breast disease are very difficult to compare (7, 9, 10, 13, 14, 21, 22) because the initial objectives of these studies were entirely different.

To illustrate this observation, three thermographic studies, conducted preoperatively on patients with breast cancer deserve our attention.

On a sample of 875 biopsies Parisky (7) highlighted the high sensitivity of the method of 97% and specificity of 14%, while in a sample of 92 patients Arora (9) reported sensitivity of 97% and specificity of 44%. In contrast, a study carried out by Kontos (10) noted on a sample of 63 patients a low IR method sensitivity of 25%, and a significantly higher specificity of 85%.

Given such highly contradictory results in regard to interpretation of IR imaging in breast cancer there is a constant need for improvement in the field.

In our study, based on preoperative imaging of woman with histopathologically confirmed breast cancer, we have established simplified and grouped criteria for interpretation of thermography findings.

The authors' proposal for thermographic evaluation of breast disease designs the interpretation of IR images in three steps:

1. Interpretation of quantitative thermographic signs on each breast, separately
2. Comparison of observed quantitative signs between the breasts
3. Recognition of descriptive and vascular signs by characteristics and number in both breasts.

Finally, the thermogram should be denoted as pathologic if one or more pathologic signs are identified (categories IR 3 to IR 5, according to Ville Marie protocol).

Our study clearly demonstrates that:

1. all of the surgically treated patients have had positive thermography findings.
2. the number of thermographical pathological signs varies between 1 and 8 (average 3.5 signs) per patient.
3. there is a clear correlation between the size of the tumor and number of thermographical pathological signs (IR3 group mean tumor size 11, 2 mm, IR4 group mean tumor size 13, 7 mm, and IR 5 group 26, 5 mm / IR 3 vs. IR 4 = NS, IR 3 and IR 4 vs. IR 5, $p < 0.05$)
4. the most common pathological thermographical sign is heat in the area of the finding, which means that the site was detected as pathological by clinical methods (mammography, US, MRI or Fine Needle Aspiration (FNA)).
5. appearance of high percentages (20 % 54/262) of pathological thermographical vascular signs indicates possible visualization of angiogenesis in development of neoplastic process
6. although thermographical method itself is not morphological method, high percentage of appearance of heat in the area of finding offers a possibility to decrease the number of biopsies and FNA in areas that do not show temperature disturbances. However, this observation should be evaluated in future controlled studies.

Establishing standardized diagnostic-interpretative protocol for mammography findings (BI RADS) (23) has enabled simpler and faster interpretation of the findings and worldwide comparison of the results. Standardized diagnostic-interpretative protocol for mammography helped setting the mammography as a standard method in clinical practice as well as in screening programs. Hence, considering current protocols and interpretative models we have tried to contribute to standardization of thermography findings interpretation by grouping and simplifying current criteria.

Unfortunately, many clinicians still hesitate to consider infrared imaging as a useful tool in spite of the steady improvements in both infrared technology and image analysis. The reason for this observation could be the fact that most clinicians are unfamiliar with the physical and biological basis of infrared imaging.

Conclusively, thermography of the 21st century represents a noninvasive and biologically safe diagnostic method that has a significant clinical potential for early breast cancer detection: it detects early lesions, the method is available to all age groups of the population, it is inexpensive and reproducible and it is characterized by high sensitivity and high negative predictive values (7, 18).

However, we should keep in mind the learning curve of medical teams involved and ethical aspects as well. As we have seen in the past (17), the introduction in clinical use of every new diagnostic method must be in tune with the ethical and scientific principles of medicine and healthcare, including the right of the patients to be involved in the process of diagnosis and therapy of the disease.

According to the results of this study and previously published data in the literature, we firmly believe that a widely adopted standard and simplified protocol for diagnosis of breast lesions by thermography will facilitate introduction of this promising diagnostic tool in every day clinical practice and screening programs, as well.

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