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Infrared Imaging for Screening Breast Cancer Metastasis Based on Abnormal Temperature Distribution

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Medical infrared imaging is obtained by measuring the self-emitted infrared radiance from the human body. Infrared emission is related to surface temperature and temperature is one of the most important physiological parameters related to health. Though recent applications such as security identification and oriental medicine have provided new fields of biomedical applications, infrared thermography has had ups and downs in its usages in cancer detection. Some of the main difficulties include finding proper applications and efficient diagnostic algorithms. In this study, infrared thermal imaging was used to detect regional metastasis of breast cancer. Our measurements were done for 110 women. From 63 individuals of a Healthy Group and a Benign Breast Disease Group, we developed algorithms for differentiating malignant regional metastasis based on temperature difference and asymmetry of temperature distribution. Testing with 47 cancer patients, we achieved a positive predictive value of 87.5% and a negative predictive value of 95.6%. The results were better than for mammogram examination. A proper analysis of infrared imaging proved to be a highly informative and sensitive method for differentiating regional cancer metastasis from normal regions.

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I. INTRODUCTION

Temperature is one of the most important physiological parameters that indicate the status of health. Radiation thermometry measures the radiant electromagnetic wave that is emitted from the surface. Radiant power is related to the surface temperature. Human body at 36.5° C emits the strongest radiation at 9.36 μm that lies in the mid-infrared region. Infrared (IR) thermometry or thermal imaging has become attractive and useful in biophotonics from the '90s when high-resolution fast scanning cameras and fast focal plane array IR sensors were available. Various biomedical applications of thermal imaging have been called to attention [1-9]. Blood perfusion is one of the main mechanisms that control body temperature. Thus blood circulation related applications are of particular interest for infrared imaging. For example, cancerous tissue tends to develop more vascularization with higher blood circulation, which, in turn, increases temperatures. Infrared imaging has been used to detect abnormality of breast cancer [3, 4]. Visualizing subcutaneous veins was investigated for the purpose of gaining venous access or vascular surgery [5]. Vein patterns on palm-dorsa were analyzed for security identification [6]. Minute energy propagation along the meridian channels in oriental medicine was studied using infrared emission and propagation [7, 8]. Sleep and body temperature are temporally associated. Thermoregulatory changes associated during sleep were reported by measuring infrared imaging [9].

Breast cancer detection is one of the most intriguing and challenging areas in infrared imaging [1-4]. Cancerous cells are very active drawing more oxygen and nutrition through blood vessels and higher temperature is shown in the cancerous region. One of the important parameters for the prognosis of breast cancer is the regional metastasis into axillary and clavicular regions of lymphatic nodes [10]. Five-year survival rate for patients without metastasis was 82-90%, but it dropped to 50-70% with the presence of metastasis [11]. But there have been difficulties in determining this propagation or diffusion of diseased cells. Nowadays one of the most popular methods to detect the metastasis into axillary, subclavicular and supraclavicular lymph nodes is a fine needle biopsy. But many researches reported that negative results did not guarantee the absence of metastasis since only 33% of metastases were verified during biopsy [11]. Moreover, biopsy, as an invasive method, can increase the risk of tumor dissemination. This circumstances demanded doctors to apply more strict criteria for its administration [12].

X-ray or ultrasound examination of axillary area provides a poor quality of information due to anatomic features of this area and small sizes of lymph nodes. Infrared imaging had not been widely practiced as a diagnostic tool for breast imaging especially before the mid 90's. The reasons might be poor imaging quality and the lack in proper measurement protocol or diagnostic algorithm. But in the last decade a new generation of infrared devices was introduced and a powerful data processing using a computer was used. These technical developments make thermographic prognoses more optimistic than before [3, 4]. Another important point to be mentioned is how to choose which type of imaging modality to be used. No one imaging modality can be superior for every type of cancer. To our knowledge, infrared imaging has not been applied for diagnosing regional metastases of breast cancer. Our literature review showed that there has been no one published article devoted to this problem though there were several publications with a brief mention of the possibility of using thermal imaging [13, 14]. The aim of our research is to fill this gab shown in screening regional metastasis.

II. BACKGROUND AND METHODS

Every object that is above the absolute zero radiates electromagnetic waves. The amount of radiation, W_λ [W/cm^2-μm], at a wavelength λ, depends on temperature and physical properties and is described by Plank's law.

$$W_\lambda = \frac{\varepsilon C_1}{\lambda^5[\exp(C_2/\lambda T)-1]} \tag{1}$$

where $C_1 = 3.74\times10^4$ [W-μm^4/cm^2], $C_2 = 1.44\times10^4$ [μm-°K], T= temperature [°K], ε = emissivity. Emissivity is defined as the ratio of the radiant emission of object to that of black body. Skin emissivity is about 0.97- 0.98 and close to that of black body [15]. Wien's displacement law gives the wavelength where emitted radiation is the maximum. It can be derived by differentiating Eq. (1) and setting this to zero.

$$\lambda_m = 2898/T \qquad [\mu\text{m}] \tag{2}$$

Human body at 36.5°C emits the strongest radiation at 9.36 μm that lies in the mid-infrared region. 3～12 μm wavelength band has been used in measuring surface temperature.

We used TV-03K^{TM} medical thermal camera made in Russia. This device can measure relative temperature of the object with 8-bit resolution in the range of 30-45° C. The infrared sensor used in the thermal camera was a single $C_dH_gT_e$ detector. Liquid nitrogen cooling was applied to reduce the thermal noise of the detector. Measured infrared images are converted into temperature and temperature distribution can be analyzed in various modes. Temperature images are displayed either in gray scale or pseudo-colored. The bottom part in the software display contains a color palette with the value of temperature diapason in Celsius. The temperature difference (i.e. relative temperature) between any two points may be calculated according to Eq. (3):

$$dT = (T_a - T_b)\times T_s/255 \tag{3}$$

where T_a and T_b - values of infrared emission in 'a' and 'b' points, measured by thermograph, Ts - width of temperature scale in Celsius, measured by a special setup procedure. This relative temperature distribution is more important to diagnose abnormally warm or cool area on human body.

The present research was performed from January to May 2001 at the Regional Center of Oncology (Nyzhny Novgorod, Russia). 110 women were examined. Three groups were assigned; Healthy Group consisted of 36 women from 17 to 48 years old with a median of 37 years old, Benign Breast Diseases Group of 27 women from 18 to 63 (a median age of 37) and Malignant Breast Disease Group of 47 women from 30 to 71 (a median age of 51). Several methods were applied to verify the diagnosis or health condition. They were mammography, ultrasound breast examination and fine needle biopsy. Then infrared imaging was obtained. All patients with breast cancer were surgically treated by breast amputation with axillary lymph nodes removal and histological examination on the tumor and lymph nodes was followed. Each infrared image was measured according to the following steps. First, patient undressed to the waist and stood at 1.5 m distance from the infrared camera. Secondly, 7 - 10 minutes waiting period were allowed for thermal adaptation. Thirdly, three infrared images of front, right and left semi-side postures were taken. For the semi-side exposures, the patient lifts her arm to show axillary area.

Verification of the presence or absence of metastasis into axillary lymphatic nodes was done by mammography and histological examination. This verification was made for each patient. Pre-operation diagnosis of subclavicular lymph node metastasis was performed by routine palpation. In the suspected cases (five women) these nodes were removed surgically and examined. Sentinel lymph node biopsy in pre-operational period was not performed because all patients were subjected to surgical operation with removing of axillary nodes. Statistics was made on the principles of Evidence-based medicine using statistic functions of Microsoft® Excel 2000.

III. RESULTS

To compare quantitatively, a parameter was introduced. This parameter was proportional to the difference between the maximal value of temperature in the axillary area (Fig.1, area A) and the average temperature at the reference area (Fig. 1, area R). An example of healthy woman was given in Fig. 2. Infrared images of axillary area in Healthy Group (36 women) showed two typical features. First, temperature distributions had individual features (it may be warm, cold or isothermal), but revealed symmetry between the right and left axillary areas. Secondly, the difference between maximal temperature in the axillary area and the area of 5-7 rib on the medial axillary line (reference area) varies from -1 to +2°C, but right-left difference (hereinafter referred to as RLD) of these values in each healthy person is no more than 0.6°C. Fig. 3 shows a typical image where high RLD is measured. Fig. 4 shows an image with clear asymmetry.

Metastasis into subclavicular lymph nodes is a less-frequent complication in breast cancer. We found only five cases of this disease (10.6%) in our patient's group. Pre-operational diagnosis of subclavicular lymph node metastasis is usually not based on needle biopsy since biopsy on this area can be complicated due to technical difficulties and potential complications such as contamination. Fig. 5 shows typical abnormal temperature distributions with subclavicular and supraclavicular lymph node metastasis.

For the Healthy Group of 36 women, asymmetry in the infrared image for axillary area was found only in two cases (5.5%). The highest temperature difference in the axillary area was 2.5°C and the smallest one was 0.12°C. The maximal RLD was 0.39°C and the minimal was 0°C. The average RLD value was 0.21°C (δ±0.13, $p<0.05$). It was found that the right axillary area was

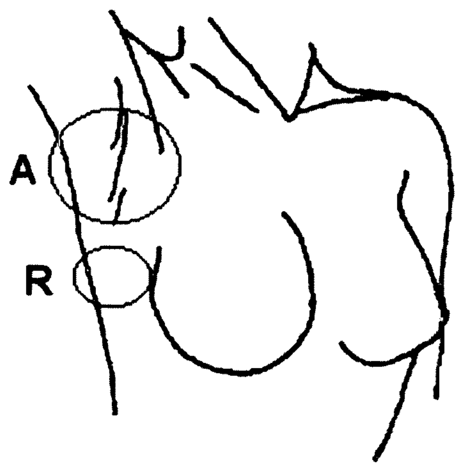

FIG. 1. Location of axillary (A) and reference (R) areas.

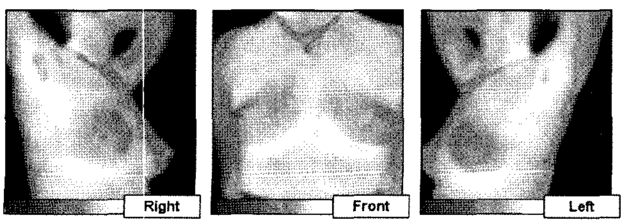

FIG. 2. Infrared images for breast and axillary area for a healthy woman.

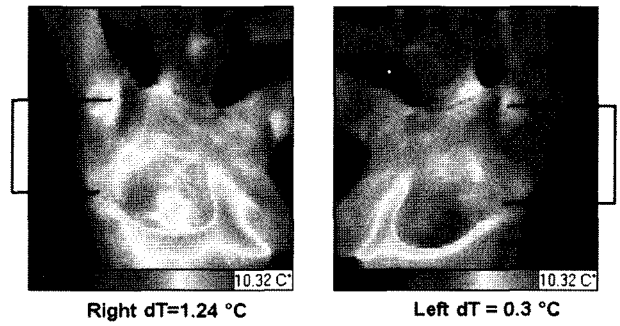

FIG. 3. An example high right-left difference (RLD) value.

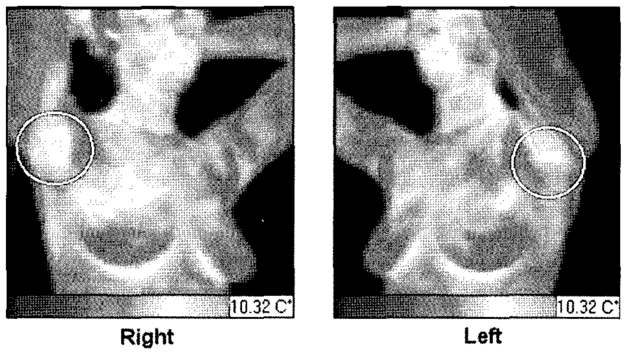

FIG. 4. An example of clear asymmetry in the axillary areas.

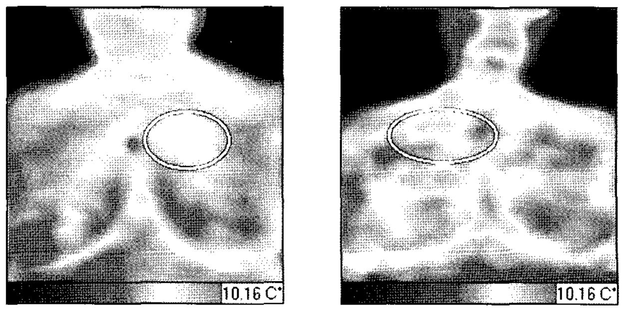

FIG. 5. Typical abnormal temperature distributions with subclavicular and supraclavicular lymph node metastases.

warmer for 12 women (33%) and that the left side was warmer for 19 (53%) women. For the remaining five cases (14 %), there was no substantial difference where the difference was smaller than 0.1˚C. Temperature resolution of the thermal camera was about 0.06 ˚C.

We applied the same procedures for the Benign Breast Diseases Group (27 women) with the following results. Asymmetry in the infrared image for axillary area was found in three cases (11.1 %). Maximal temperature difference in the axillary area was 2.86˚C and minimal temperature was 0.23˚C. The maximal RLD was 0.64˚C and the minimal RLD was 0˚C. The average RLD value was 0.27˚C (δ±0.18, p<0.05). The right axillary area was warmer for 12 women (44%) and the left side was warmer for 12 women (44%). For the remaining 3 cases (12%), temperatures of the left and right areas were less than 0.1flC. In the case of tumor located in one side, the temperature of this axillary area was higher than that of the healthy side. This was so for 16 out of 18 one-side tumor cases.

Then we put Healthy and Benign Groups (total 63 women) together as one group, five cases (8%) showed asymmetry for the axillary area and RLD was within 0.64˚C with an average of 0.23 (δ±0.16, p<0.05). To increase reliability, the "+ 2δ deviation" was set as the high limit for normal RLD. This gave 0.55˚C. Therefore, for screening method to detect axillary lymph node metastasis based on infrared imaging, two criteria were used. They were RLD>0.55˚C and observed asymmetry between the axillary areas.

We measured infrared images for 47 women for Breast Cancer Group. Each cancer patient had histological examination using removed nodes to find out the type of cancer. 22 (47%) out of 47 patients had the metastases into axillary lymph nodes. Metastasis was found on the right side for 12 cases (54 %), on the left side for 8 cases (36 %). Two cases (10%) had infiltration on both sides. 25 out of 47 did not have metastasis. We applied the two criteria on infrared images in order to check the ability of diagnosing metastasis. The results were analyzed according to the classical four-cell quadrate method and were summarized in Table 1. TP is true positive, FN is false negative, FP is false positive and TN is true negative. Calculations were made by Sensitivity=TP/(TP+FN), Specificity=TN/(FP+TN), Positive Predictive Value (PPV) =TP/(TP+FP) and Negative Predictive Value (NPV) =TN/(FN+TN). Asymmetry criterion was better than RLD criterion. RLD/Asymmetry combined criteria provided the best results. Using the combined criterion, we could achieve a positive predictive value of 87.5% and a negative predictive value of 95.6% (Table 1).

IV. DISCUSSIONS

When the RLD criterion was applied, metastases for 16 out of 22 patients could be diagnosed. For asymmetry criterion, 18 out of 22 were successfully found. When both RLD and asymmetry criteria were employed, 21 out 22 were correctly diagnosed. In this case, the successful diagnosis of no metastasis was 22 out of 25 (88%). When the same patient group was screened by mammography, only seven cases were diagnosed as metastasis out of 22 patients. It shows that infrared imaging is particularly successful for differentiating regional metastasis. In all cases, the increased temperatures on the disease-affected lymph nodes were detected. False negative was diagnosed for only one case where a 48 year woman with II stage cancer where both breasts had metastasis into both axillary lymph nodes.

For a healthy person, temperature distribution on clavicular area was isothermal. In the case of metastasis affection this area became warmer and the temperature gradients between this area and symmetrical one were from 0.8 to 1.6˚C (Fig. 5). Very often one can see an additional symptom - hyperthermia in the lower part of front neck and upper part of the chest. We found

TABLE 1. Infrared image diagnosis of metastasis for 47 breast cancer patients using right-left difference (RLD) value, observed asymmetry and RLD/asymmetry combined parameters.

diagnostic criteria	metastasis (total 22)	no metastasis (total 25)	sensitivity [%] specifity [%]	PPV [%] NPV [%]
RLD	16 (TP)	3 (FP)	72	84
	6 (FN)	22 (TN)	88	78.6
asymmetry	18 (TP)	3 (FP)	82	85.7
	4 (FN)	22 (TN)	88	84.6
RLD or asymmetry	21 (TP)	3 (FP)	95	87.5
	1 (FN)	22 (TN)	88	95.6

TP: true positive, FN: false negative, FP: false positive, TN: true negative
Sensitivity=TP/(TP+FN), Specificity=TN/(FP+TN)
Positive Predictive Value (PPV)=TP/(TP+FP)
Negative Predictive Value (NPV)=TN/(FN+TN)

metastatic infiltration of the clavicular lymph nodes from seven women. Diagnosis for clavicular lymph node metastasis was 100% successful, which was confirmed by histological examination.

Theoretical background of using infrared imaging in diagnosis of metastatic disease of the lymph nodes is cancer-induced blood vessel formation [16]. Hyperplasia and formation of new vessels take place not only in primary tumor nodes, but also in metastatic areas [17]. Those processes lead to the increase of blood circulation into cancer nodes. But new vascular net changes the structure and cannot maintain the normal temperature balance. This produces formation of a pathological local area with elevated temperature. The value of the temperature gradient formed is relatively high and may reach, according to theoretical calculations, up to 3°C. One has to perform invasive measuring using thermocouples to detect local temperature more precisely, however. Most axillary lymph nodes are located near the skin, which allows detecting their radiation temperature directly. In our research the temperature gradient between the center of thermal abnormal area and surrounding skin was up to 2.4°C.

Infrared imaging passively detects radiation emission from human body. It does absolutely no harm unlike other imaging modality. For example, X-ray mammogram uses ionizing radiation and provokes concerns to regular users. No one imaging modality alone can detect breast cancers in various stages and locations. We have found that infrared thermal imaging is particularly effective in differentiating regional cancer metastasis. Temperature difference between right and left regions (RLD) and asymmetrical temperature distribution were parameters from which abnormality could be predicted. Using simple analysis algorithms, we achieved a sensitivity of 95%, a specifity of 88%, a positive predictive value of 87.5%, and a negative predictive value of 95.6 % in screening regional metastasis cancer. Infrared imaging does not give any inconvenience to a patient and can be a method for frequent screening for regional metastasis. Screening can make early detection possible, a very important feature. Infrared imaging may be used also as a method for locating the point for fine needle biopsy of the lymph node.

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