Risk of breast cancer based on thermal tomography characteristics

Si Sun[1#], Xin Yu[2#], Juanjuan Li[2], Zhiyu Li[2], Shan Zhu[2], Lijun Wang[2], Juan Wu[3], Kaiyang Li[4], Qi Wu[2], Shengrong Sun[2]

[1]Department of Clinical Laboratory, [2]Department of Breast and Thyroid Surgery, [3]Department of Pathology, Renmin Hospital of Wuhan University, Wuhan 430060, China; [4]Department of Electronic Science and Technology, School of Physics and Technology, Wuhan University, Wuhan 430072, China

Contributions: (I) Conception and design: S Sun, X Yu; (II) Administrative support: S Sun; (III) Provision of study materials or patients: J Li, S Zhu, Z Li, K Li, L Wang; (IV) Collection and assembly of data: S Zhu, J Wu; (V) Data analysis and interpretation: S Sun, X Yu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Dr. Shengrong Sun; Dr. Qi Wu. Department of Breast and Thyroid Surgery, Renmin Hospital of Wuhan University, 238 Ziyang Road, Wuhan 430060, China. Email: sun137@sina.com; waiwai@whu.edu.cn.

Background: There is no uniform standard for the diagnosis of breast lesions by thermal tomography (TT). This study aimed to widely analyse the predictive value of TT in patients with breast cancer and establish a uniform standard for the diagnosis of breast lesions.

Methods: We retrospectively analysed data from women who suffered from non-inflammatory unilateral single breast lesion and underwent TT from January 2014 to July 2016. Changes in TT parameters were correlated with the pathologic diagnosis, and its predictive value was assessed.

Results: A total of 407 patients underwent TT examinations during the study period, including 196 subsequently diagnosed with breast cancer. Several characteristics were found to be significantly correlated with breast cancer: age $\geq$60 years [odds ratio (OR) =109.296, P<0.001], age $\geq$35 and <60 years (OR =25.720, P<0.001), q-r curve as an angle of 30°–45° (OR =14.895, P<0.001), ΔTs (surface temperature difference between the neoplastic side and the healthy side) $\geq$0.65 ℃ (OR =4.129, P<0.001), ΔTn (nipple temperature difference between the neoplastic side and the healthy side) $\geq$0.45 ℃ (OR =2.683, P=0.006), isotherm asymmetry (OR =2.297, P=0.035), and vascular plentiful (OR =3.333, P=0.004). Q value as a novel predictive indicator based on the multiple predictor modelling improved the diagnostic rate for breast cancer, and the accuracy in this study was up to 86.7%.

Conclusions: Age, q-r curve, ΔTs, ΔTn, isotherm, and vascular features were independent predictors of breast cancer. Q value could be used to assess the risk of breast cancer as an additional diagnostic tool for breast cancer screening and diagnosis.

Keywords: Thermal tomography (TT); breast cancer; diagnosis

Introduction

Breast cancer is currently the most common malignant tumour in Chinese women (1). Since there is no good strategy for primary prevention of breast cancer, early diagnosis of breast cancer is a pivotal method to increase the survival rate and improve the prognosis of the patients (2). The development of breast cancer screening is one of the most important reasons that the mortality rate of breast cancer has been decreasing while its incidence has been increasing (1). Therefore, the development of high-

efficiency screening methods is critical to improving the prognosis of the patients.

Current screening methods for breast cancer include mammography, ultrasonography and magnetic resonance imaging (MRI). Breast cancer screening must be done with mammography and ultrasonography, while MRI represents a second level instrumental examination to be reserved for those with an inherited susceptibility to breast cancer (3). Mammography is currently the preferred imaging examination method for breast cancer screening. However, it exposes patients to ionizing radiation, and its false negative rates range from 4% to 34% (4,5). In addition, it is less accurate for those with dense breast lesions or young women. Ultrasonography can be applied to patients who cannot be examined by mammography, such as young women and pregnant women, and it is convenient, safe and non-invasive, and easy to accept. However, it is less sensitive to micro-calcifications, ductal carcinoma *in situ*, and small invasive carcinomas, and its results are easily influenced by subjective factors (6). MRI is suitable for patients with a high risk of breast cancer due to its being highly sensitive (3,7). However, it is expensive and difficult to operate, it is not suitable for large-scale screening of populations for breast cancer.

Thermal tomography (TT) is a novel and non-invasive method for breast cancer screening and monitoring early treatment responses and has been used for early detection of breast tumours (8). It assesses breast lesions based on the angiectasis, angiogenesis and the change of temperature influenced by the metabolism of cells, which is closely related to pathological changes in the tissue (9-12). Compared to usual thermography, TT can not only detect surface temperature changes, but also generates a q-r curve to mine three-dimensional heat distribution data layer by layer based on the surface temperature distribution and reflect heat intensity varying with depth of tomography (8). In past trials we have concluded that the q-r curve for most breast cancer patients was between 30°–45°, while the q-r curve for most benign tumour patients was between 15°–30° (8). TT has the advantages of being convenient, fast, inexpensive, and objective, in addition to placing low demands on the operator and having a high sensitivity (13). As far as the large population of China is concerned, TT may be suitable for breast cancer screening. However, the correlation between the characteristics of TT and breast cancer is not clear, and there is no uniform standard for the diagnosis of breast lesions by TT (13). This may be one of the reasons why TT is not yet widely used at present.

This study is intended to clarify the correlation between TT characteristics and breast cancer, to establish the diagnostic criteria for breast lesions and define its value in distinguishing benign from malignant lesions in patients with known breast lump.

Methods

Patients

From January 2014 to July 2016, we conducted a retrospective case-control study including consecutive patients who underwent TT at Renmin Hospital of Wuhan University. The inclusion criteria were patients with a unilateral non-inflammatory single breast lesion. Patients who had undergone previous breast surgery or were pregnant were excluded. Moreover, the final diagnosis of the patient was determined by the pathological examination.

Characteristics of TT examinations

The TT system was supplied by Prof. Kaiyang Li (Department of Electronic Science and Technology, School of Physics and Technology, Wuhan University), as described previously (13). Before the examination, the patient was asked to enter the room where the temperature was 25±3 ℃ and had thermal source, then took off her coat and rested for 15 minutes. During this process, the patient's breasts could not be touched. During the examination, the patient raised her hands to expose the bilateral mammary glands, and we recorded the front, left anterior, and right anterior image of the patient at 2 metres from the patient's breast. The infrared thermal image was processed and analysed by the computer processing system. In this study, the parameters of TT were recorded, including age, q-r curve (type I: <15°, type II: 15° to 30°, type III: 30° to 45°, type IV: >45°) (8), ΔTs (surface temperature difference between the neoplastic side and the healthy side), ΔTn (nipple temperature difference between the neoplastic side and the healthy side), ΔTa (average temperature difference between the neoplastic side and the healthy side), isotherm (type I: symmetry, type II: asymmetry), vascular features (type I: normal, type II: vasodilation at the nodule, type III: discontinuity, type IV: plentiful).

Pathological diagnosis

In this study, standard pathology analysis of excised tissues

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was used to assess the subject's outcomes. The excised specimens were fixed, embedded in paraffin as tissue blocks and then serially sectioned at a thickness of approximately 5 mm before being stained with haematoxylin and eosin (HE). The final pathology examinations were evaluated by an experienced pathologist for grading of pathologic tumour response of the primary breast lesion using the 2003 version of the World Health Organization (WHO) to classify the breast lesions. Three criteria were used for grading: gland formation, nuclear morphology, and mitotic figures (14).

Statistical analysis

All statistical analysis was performed with SPSS 22.0 Statistical software (IBM Corporation, Armonk, NY, USA). For TT, changes in all parameters relative to baseline were compared between the two groups and analysed for significant differences using the *t*-test. For determining the cut-off of ΔTs, ΔTn and ΔTn, data were analysed by receiver operating characteristic curve (ROC curve) and taking the value corresponding to the maximum value of Youden's index (sensitivity + specificity –1) as the cut-off. For the single-predictor analysis, we used a χ^2 test and Fisher's exact test to determine which characteristics were statistically significantly associated with breast cancer. For the multiple-predictors analysis, we analysed the statistically significant predictors by using a stepwise regression, filtered the uppermost predictor, and calculated the regression coefficient per characteristic. Finally, the logic regression equation was obtained. ROC curve was used to estimate the effectiveness of the equation. The difference was significant if a two-sided P value <0.05.

Results

The study consisted of 407 cases, including 196 patients with malignant tumours with an average age of 52.34 [95% confidence interval (CI), 51.00 to 53.68] and 211 patients with benign tumours with an average age of 38.96 (95% CI, 37.38 to 40.54) (*Table 1*). In this series of patients undergoing breast cancer, 74.0% (145/196) of patients were diagnosed with invasive ductal carcinoma while adenoma fibroma was the primary diagnosis among patients diagnosed with benign disease, accounting for 58.8% (124/211) (*Table S1*). Likewise, the age distribution was wide, with 145 (74.0%) diagnosed with a malignancy at 35–60 years and 47 (24.0%) at 60 years or older. Furthermore, the incidence of malignant tumour increases with age (*Table 1*). As shown in

Figures 1 and *2*, TT showed characteristics of breast lump different from other morphological examinations such as mammography. Patients with malignant tumours had a higher breast temperature, and the mean values of ΔTs, ΔTn and ΔTa of patients with benign tumours were 0.371, 0.157 and 0.110 ℃, while those of patients with malignant tumours were 0.989, 0.801, and 0.487 ℃ (P<0.001). The q-r curve of most patients with benign tumours was within 15–30°, while that of most patients with malignant tumours was within 30–45°. For patients with malignant tumours, their isotherm showed asymmetry, and their blood vessels were more plentiful compared to those with benign diseases.

To explore the correlation between TT parameters and cancer risk, we adopted a ROC curve to assess the predictive value of ΔTs, ΔTn and ΔTa (*Figure S1*). We took the value corresponding to the maximum value of Youden's index as the cut-off and found the cut-off of ΔTs, ΔTn and ΔTa were 0.65, 0.45 and 0.35 ℃. Furthermore, several TT factors were significantly associated with the odds of a lesion harbouring cancer as estimated by the single-predictor model (*Table 2*). In terms of age, the risk of patients aged between 35 and 60 was 22.330-fold (95% CI, 7.947 to 62.748, P<0.001), and the risk of patients over 60 was 100.528-fold (95% CI, 29.313 to 344.756, P<0.001) compared with that of patients younger than 35, indicating that age had the strongest association with breast cancer. Moreover, the q-r curve also had a strong association with breast cancer, and the odds ratio (OR) of the q-r curve between 35° and 45° was 26.254 (95% CI 15.274 to 45.129, P<0.001), and the OR of the q-r curve greater than 45° was 13.385 (95% CI, 1.356 to 132.127, P=0.024). In addition, ΔTs, ΔTn, ΔTa, isotherm and vascular features were also each associated with cancer, but the magnitude of the association was smaller, with ORs ranging from 0.592 to 8.817.

Ultimately, a total of seven characteristics were significantly associated with the risk of cancer in the multiple predictor modelling: age ≥60 years (OR =109.296, 95% CI, 21.227 to 562.763, P<0.001), age ≥35 and <60 years (OR =25.720, 95% CI, 7.129 to 92.786, P<0.001), q-r curve at an angle of 30°–45° (OR =14.895, 95% CI, 7.535 to 29.441, P<0.001), ΔTs ≥0.65 ℃ (OR =4.129, 95% CI, 2.030 to 8.399, P<0.001), ΔTn ≥0.45 ℃ (OR =2.683, 95% CI, 1.327 to 5.424, P=0.006), isotherm asymmetry (OR =2.297, 95% CI, 1.059 to 4.981, P=0.035), and vascular plentiful (OR =3.333, 95% CI, 1.455 to 7.633, P=0.004) (*Table 3*). The remaining characteristics were not significantly associated with cancer.

Since our main aim was to establish a uniform standard for thermal imaging diagnosis of breast cancer, we

Table 1 Patient and thermal tomography characteristics.

Characteristics	Benign N=211 (%)	Malignancy N=196 (%)
Age (year)		
<35	77 (36.5)	4 (2.0)
≥35 and <60	125 (59.2)	145 (74.0)
≥60	9 (4.3)	47 (24.0)
ΔTs (℃), average (95% CI)	0.371 (0.319, 0.423)	0.989 (0.882, 1.097)*
ΔTn (℃), average (95% CI)	0.157 (0.094, 0.220)	0.801 (0.661, 0.941)*
ΔTa (℃), average (95% CI)	0.110 (0.07, 0.149)	0.487 (0.403, 0.571)*
Q-r curve		
<15°	10 (4.7)	1 (0.5)
15°–30°	174 (82.5)	39 (19.9)
30°–45°	26 (12.3)	153 (78.1)
>45°	1 (0.5)	3 (1.5)
Isotherm		
Symmetry	93 (44.1)	20 (10.2)
Asymmetry	118 (55.9)	176 (89.8)
Vascular feature		
Normal	4 (1.9)	0 (0.0)
Vasodilation at the nodule	104 (49.3)	89 (45.4)
Discontinuity	71 (33.6)	36 (18.4)
Plentiful	32 (15.2)	71 (36.2)

ΔTs, tumor surface temperature difference between neoplastic side and healthy one; ΔTn, nipple temperature difference between neoplastic side and healthy one; ΔTa, average temperature difference between neoplastic side and healthy one; *, two-tailed *t*-test P values estimate significance of the differences between the two groups (P<0.001).

constructed a regression equation based on the regression coefficients of each characteristic referring to the previous method (15). In this study, the regression equation based solely on the characteristics of TT is: $P=1.418 \times A+0.987 \times B+0.832 \times C+2.701 \times D+1.204 \times E$. The regression equation based on the characteristics of TT and age is: $Q=1.418 \times A+0.987 \times B+0.832 \times C+2.701 \times D+1.204 \times E+3.247 \times F1+4.694 \times F2$ (A: ΔTs ≥0.65 ℃, B: ΔTn ≥0.45, C: isotherm asymmetry, D: q-r curve at an angle of 30°–45°, E: vascular plentiful, F1: age ≥35 and <60, F2: age ≥60). The ROC curve for the P and Q value is shown in *Figure 3*; the area under the curve (AUC) of the P and Q value are 0.914 and 0.943. Taking the value corresponding to the maximum value of Youden's index as the cut-off, we found the cut-off of P and Q value were 3.4935 and 5.943. In this study, the sensitivity, specificity and accuracy of diagnosis of breast cancer by P values were

80.6%, 88.6% and 84.8%. The sensitivity, specificity and accuracy of diagnosis of breast cancer by Q values were all 86.7% (*Table 4*). Compared with P value, Q value has slightly lower specificity but higher sensitivity and accuracy, which is more suitable for breast cancer screening. Taken together, Q value is offered as a guideline to quantify the risk of breast cancer diagnosed by TT.

Discussion

Thermography has been extensively used in many medical fields, including for diabetes (16,17), influenza (18), eye diseases (19), tumours, (8) digestive disorders (20), pain diagnosing and treatment monitoring (21). And there have been many studies on thermal images of breast masses (22,23). On the basis of usual thermography, TT further
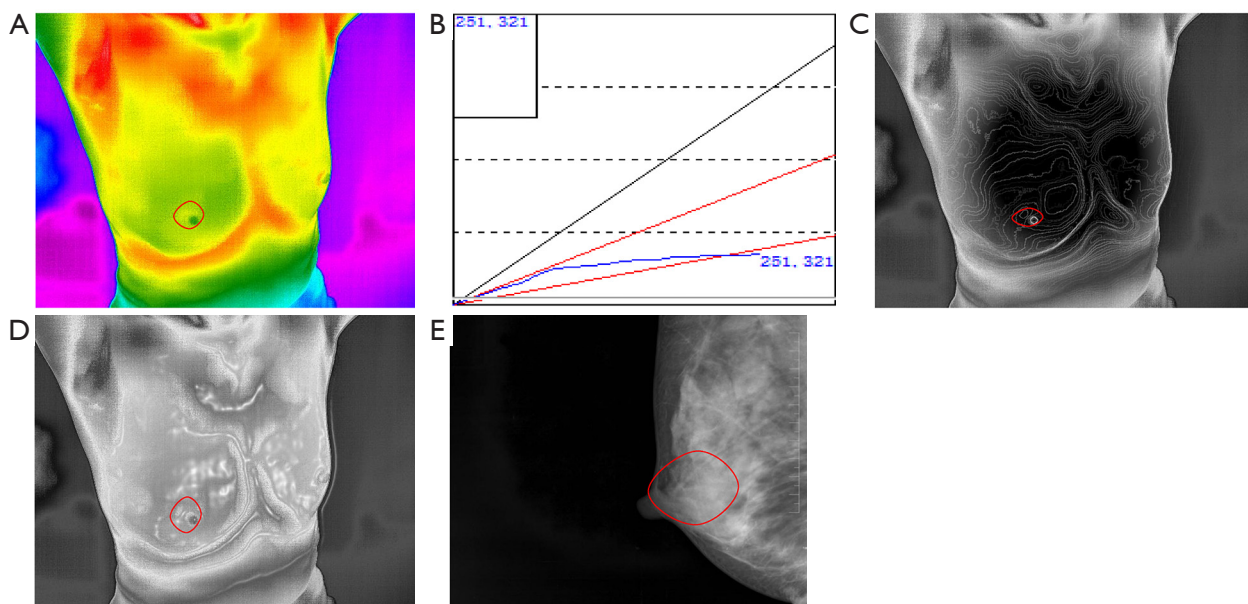
Figure 1 Case 1: adenoma fibroma. (A) Far-infrared thermography revealed left and right breast temperatures were almost the same. (B) q-r curve as an angle of 15°–30° (the blue line is q-r curve). (C) Normal isotherm of tumor site. (D) Normal blood vessels at the tumor site. (E) Mammography showed no obvious abnormality. The circle indicates the location of the patient's breast mass.
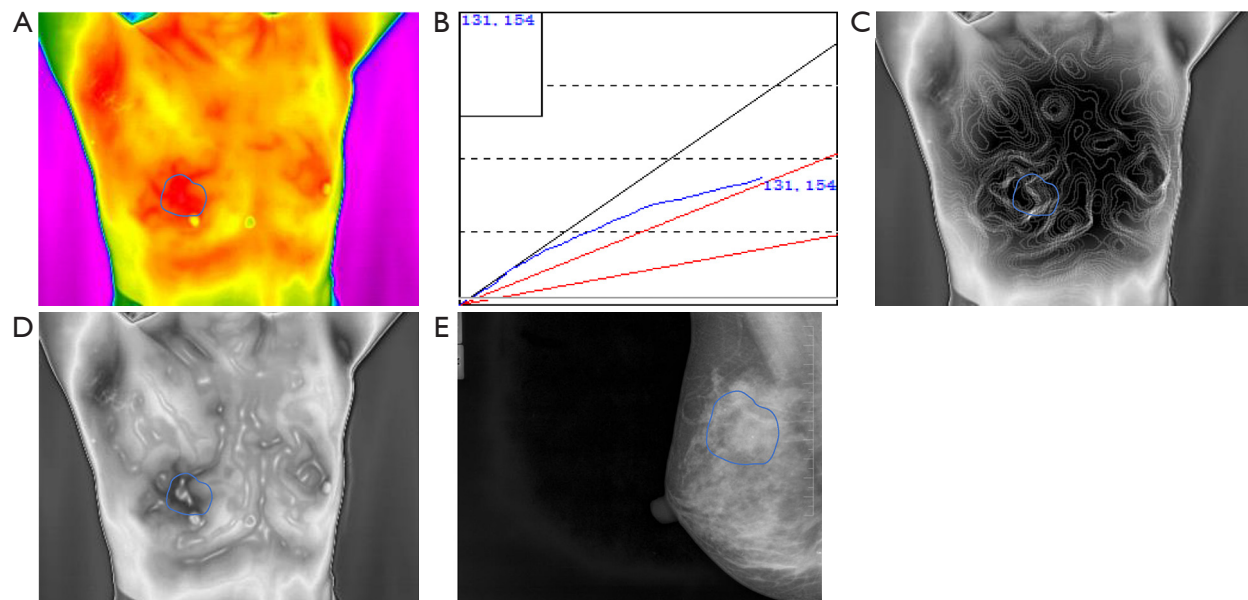

Figure 2 Case 2: invasive ductal carcinoma. (A) Thermograph obtained with far-infrared thermography. The temperature of the right breast was significantly higher than that of the left breast. (B) q-r curve as an angle of 30°–45° (the blue line is q-r curve). (C) The isotherm of tumor sites was disordered and the isotherms of bilateral breasts were asymmetric. (D) Tumor site blood vessel was plentiful. (E) Mammography showed small calcifications in breast lump. The circle indicates the location of the patient's breast mass.

Table 2 Comparison of characteristics between benign and malignancy lesions

Characteristics	OR (95% CI)	P value
Age (year)		
<35	1 (reference)	
≥35 and <60	22.330 (7.947, 62.748)	<0.001
≥60	100.528 (29.313, 344.756)	<0.001
ΔTs (℃)		
<0.65	1 (reference)	
≥0.65	8.817 (5.590, 13.907)	<0. 001
ΔTn (℃)		
<0.45	1 (reference)	
≥0.45	6.395 (4.116, 9.936)	<0.001
ΔTa (℃)		
<0.35	1 (reference)	
≥0.35	5.313 (3.349, 8.430)	<0.001
Q-r curve		
<15°		0.694
15°–30°	1 (reference)	
30°–45°	26.254 (15.274, 45.129)	<0.001
>45°	13.385 (1.356, 132.127)	0.024
Isotherm		
Symmetry	1 (reference)	
Asymmetry	6.936 (4.056, 11.859)	<0.001
Vascular feature		
Normal		0.128
Vasodilation at the nodule	1 (reference)	
Discontinuity	0.592 (0.363, 0.968)	0.036
Plentiful	2.593 (1.566, 4.293)	<0.001

ΔTs, tumor surface temperature difference between neoplastic side and healthy one; ΔTn, nipple temperature difference between neoplastic side and healthy one; ΔTa, average temperature difference between neoplastic side and healthy one.

obtains the relationship between heat source intensity and depth through three-dimensional reconstruction and layer-by-layer scanning. However, there is currently no uniform diagnostic criteria for the diagnosis of breast cancer by TT. In the presented study, we retrospectively analysed the results of 407 patients with non-inflammatory, unilateral, and single-breast lesions assessed by TT and established a new diagnostic standard to determine the diagnostic value of breast cancer.

Age was the most important factor. Our results indicated that patients with an older age had a higher risk of having a malignant tumour. The ages of the majority of patients with breast cancer were between 35 to 60 years old, but patients over 60 had the highest risk of getting breast cancer (OR = 109.296). This conclusion is consistent with the previous research (1,24). However, the prognosis of elderly patients with breast cancer is better than that of younger patients (25,26). Therefore, age is an important consideration in the

Table 3 Multivariate association between characteristics and the likelihood of cancer, chosen using a stepwise logistic regression

Characteristics	B	OR (95%CI)	P value
Age			
≥35 and <60	3.247	25.720 (7.129, 92.786)	<0.001
≥60	4.694	109.296 (21.227, 562.763)	<0.001
ΔTs ≥0.65	1.418	4.129 (2.030, 8.399)	<0.001
ΔTn ≥0.45	0.987	2.683 (1.327, 5.424)	0.006
Q-r curve: 30°–45°	2.701	14.895 (7.535, 29.441)	<0.001
Isotherm asymmetry	0.832	2.297 (1.059, 4.981)	0.035
Vascular plentiful	1.204	3.333 (1.455, 7.633)	0.004

ΔTs, tumor surface temperature difference between neoplastic side and healthy one; ΔTn, nipple temperature difference between neoplastic side and healthy one.
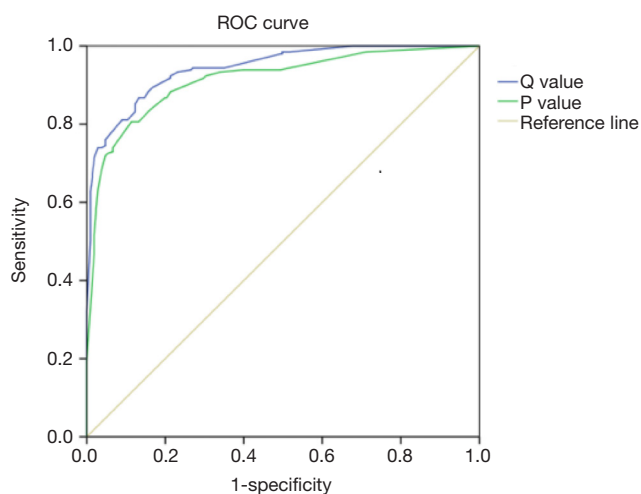

Figure 3 ROC curve for the P and Q value. The green diagonal shows a completely random classification result of ROC whose AUC is 0.5. P value:AUC =0.914, Q value:AUC =0.943. ROC, operating characteristic; AUC, area under the curve.

diagnosis and treatment of breast cancer.

For breast cancer, in addition to being used as a screening tool, TT can also be used to monitor tumour responses to neoadjuvant chemotherapy (27). The q-r curve is a curve that reflects heat intensity varying with depth of tomography and the difference in temperature between the lesion and the surrounding tissue. The patient's q-r curve distribution in this trial conformed to our past conclusions (8). In this study, patients with a q-r curve of 30°–45° had the highest risk of breast cancer (OR =14.895). Q-r curves are the most important factors. Meanwhile, this might suggest in the present study that the patient was likely to suffer from breast cancer when ΔTs was greater than 0.65 ℃ and ΔTn was higher than 0.45 ℃. Although univariate analysis showed that ΔTa was associated with breast cancer, multivariate analysis showed it was not. Many researchers have different opinions on how much the difference in breast temperature can be used as a diagnostic indicator. Head *et al.* (28)

Table 4 The distribution of P and Q value of patients

Variables	All patients (N=407) (%)	Benign (N=211) (%)	Malignancy (N=196) (%)
P value			
Average (95% CI)	3.09785 (2.87020 to 3.32549)	1.45535 (1.26145 to 1.64294)	4.86605 (4.61788 to 5.11423)
≥3.4935	182 (44.7)	24 (11.4)	158 (80.6)
<3.4935	225 (55.3)	187 (88.6)	38 (19.4)
Q value			
Average (95% CI)	5.89773 (5.58904 to 6.20643)	3.57914 (3.28829 to 3.87000)	8.39377 (8.11667 to 8.67088)
≥5.943	198 (48.6)	28 (13.3)	170 (86.7)
<5.943	209 (51.4)	183 (86.7)	26 (13.3)

believed that ΔTa >0.5 ℃ indicated that patients were more likely to have breast cancer. In contrast, Garduño-Ramón *et al.* (29) believed that it was more appropriate to use 1 ℃ as the dividing line of ΔTs while Ng *et al.* (30) thought that 2 ℃ was suitable. This bias may be due to the differences in body temperatures. Temperature is closely related to breast disease, and an abnormal breast temperature can indicate the possibility of breast cancer in patients.

As for TT imaging, vascular and isotherm were also factors in the diagnosis of breast cancer. In most malignant tumours, tumour angiogenesis factor (TAF) stimulates tumours (31) into forming a rich vascular network in the tumour area. With the growth of the tumour, the distribution of blood vessels and the increase in the number of blood vessels are constantly increasing. Therefore, most malignant tumours have an abundant arterial blood supply, and the OR of vascular plentiful was 3.333, close to the results of ultrasonography examination (32). Although there have been few studies in the past that have mentioned the association between isotherm and breast cancer, the isotherms of the malignant tumours in this study were disorderly and dense due to the abnormal metabolism of malignant tumours, and the OR of the isotherm asymmetry was 2.297. Both vascular and isotherm abnormalities note the possibility of breast cancer.

Compared to mammography, ultrasonography and MRI (5-7,33), TT is objective and rapid and involves no contact, no radiation, and no contrast agent injection, has high repeatability and is suitable for any age group. In addition, because the changes in cell metabolism in pathological tissues occurs earlier than its functional and morphological changes, TT can detect diseases earlier (8,13). However, TT also has a few shortcomings. It is not effective for small breast cancers with a deep location. For patients with obesity or large breasts, the diagnostic results of TT are inaccurate. At the same time, TT has a poor ability to locate lesions. These shortcomings remain to be improved.

There were some limitations to this study. First, we did not classify breast cancer results by histological type. Second, there is a selection bias because we selected patients who had undergone pathological examination while some patients with an obviously low risk of breast cancer at ultrasonography did not undergo pathological examination. Third, because some patients were not examined by mammography, ultrasonography and MRI, there is no direct comparison between TT and these three modalities. Finally, the results obtained in this study are only applicable to patients with a unilateral non-inflammatory single breast lesion. Therefore, it is necessary to conduct further prospective studies to allow for longer follow-up of larger cohorts to confirm our findings.

Conclusions

Our main findings are as follows: (I) age, q-r curve, ΔTs, ΔTn, isotherm, and vascular features were independent predictors of breast cancer; (II) the Q value calculated by the logistic regression equation could be used to assess a patients' risk of breast cancer and its accuracy was 86.7%. Based on the results of this trial, in the follow-up trials we will (I) use the equation to diagnose other patients with breast lumps to verify the results of this study; (II) use the equation to distinguish breast cancer patients sensitive to TT from insensitive patients in order to monitor the former response to neoadjuvant chemotherapy by using TT; (III) assessing the relationship between local temperature elevation of breast cancer and thermogenic proteins UCP1 and UCP2, which are highly expressed in a variety of cancer cells including breast cancer (34), make molecular probes targeting UCP1 and UCP2 to combine molecular diagnostics and TT to improve the evaluation effect of lesion size, location and depth.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.29). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

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appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and with approval from the Ethics Committee of Renmin Hospital of Wuhan University (No. 2013-081). Informed consent was obtained from all individual participants included in the study.

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Table S1 The pathological results of this study

Types of pathology	All patients (N=407)
Malignant	196
Invasive ductal carcinoma	145
Ductal carcinoma *in situ*	35
Invasive lobular carcinoma	5
Mucinous adenocarcinoma	3
Invasive neuroendocrine carcinoma	2
Encapsulated papillary carcinoma	1
Invasive tubule carcinoma	1
Apocrine carcinoma	1
Squamous cell carcinoma	1
Basaloid cell carcinoma	1
Invasive cribriform carcinoma	1
Benign	211
Adenoma fibroma	124
Adenosis of mammary glands	30
Fibrocystic changes	22
Cysts	13
Intraductal papilloma	10
Hyperplasia of mammary glands	7
Lipoma	2
Phyllodes tumor of the breast	2
Mammary duct ectasia	1
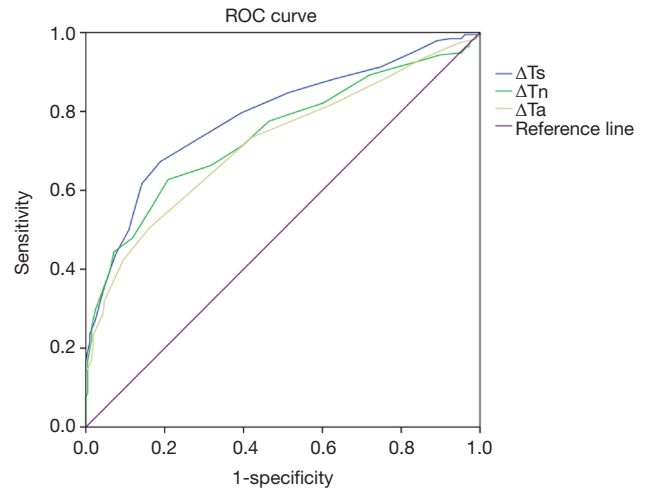
Figure S1 ROC curve for ΔTs, ΔTn and ΔTa. The purple diagonal shows a completely random classification result of ROC whose AUC is 0.5. Q value:AUC =0.943. ΔTs, surface temperature difference between the neoplastic side and the healthy side; ΔTn, nipple temperature difference between the neoplastic side and the healthy side; ΔTa, average temperature difference between the neoplastic side and the healthy side. ΔTs:AUC=0.787, ΔTn:AUC = 0.741, ΔTa:AUC =0.719.