

Breast Thermography Is a Noninvasive Prognostic Procedure That Predicts Tumor Growth Rate in Breast Cancer Patients

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INTRODUCTION

The Breast Cancer Detection and Demonstration Projects (BCDDP) that were carried out by the American Cancer Society and National Cancer Institute (USA) between 1973 and 1981 evaluated breast thermography as a diagnostic procedure for breast cancer. From the results of the BCDDP study the American Radiology Society concluded that thermography was ineffective as a diagnostic procedure in breast cancer. However, with the abandonment of breast thermography in the United States further large-scale studies to determine its value in predicting the risk of breast cancer and as a prognostic indicator were not pursued. This study demonstrates the prognostic significance of breast thermography for the breast cancer patient and further relates the thermal characteristics of the breast to the growth rate of the breast cancer patient's tumor.

MATERIAL AND METHODS

Two groups of patients were chosen to do the two parts of this study. The first group consisted of 126 deceased breast cancer patients (all women who had died of causes other than breast cancer were eliminated from the study), 100 randomly selected surviving breast cancer patients, and 100 randomly selected normal or noncancer patients, all of whom had undergone breast thermography in conjunction with mammography and clinical examination as part of their breast examination at The Elliott Mastology Center since 1973. The second group consisted of breast cancer patients that had thermography,

clinical/pathological staging, and laboratory testing of known prognostic indicators done since the beginning of 1989. Thermography was interpreted as abnormal when asymmetric heat patterns (focal hot spots, areolar and/or periareolar heat, vessel discrepancy, diffuse global heat, or thermographic edge signs) were found during routine thermographic exam. In the process of clinical/pathological staging the following information was obtained: tumor size (clinical and pathological), nodal status (clinical and pathological), presence of metastatic disease, age and location of tumor (left or right breast). Laboratory testing included the determination of the following prognostic indicators: estrogen and progesterone receptors by both the DCC-cytosol (DuPont; Billerica, MA) and immunocytochemical (Abbott Laboratories; Abbott Park, IL) methods, tumor tissue ferritin (Hybritech Inc.; San Diego, CA), ploidy and cell cycle analysis (S, G₂M) by flow cytometry, and Ki-67 by immunocytochemical method (Cell Analysis Systems; Lombardi, IL).

RESULTS AND DISCUSSION

In TABLE 1 are presented the results of thermography by patient disease status. Patients without cancer that came through the clinic for routine breast exams including clinical exam, thermography, and mammography had a high false-positive rate of 28%, when the results of thermography were compared to mammography. However, these false positives occurred in a population that is at a higher risk than the normal risk of approximately 10%. Gautherie and Gros,¹ and Stark² have shown that this group of patients with abnormal thermograms are at significantly higher risk for breast cancer, with occurrence rates of 38% (298/784) in the 4-year period following thermography and 23% (346/1499) in the 10-year period following thermography, respectively.

The prognostic significance of thermography is also demonstrated in TABLE 1, as the 126 deceased patients included a significantly higher proportion (88%) of patients with abnormal thermograms than the 65% for surviving cancer patients, a large proportion of which should have been cured by stan-

TABLE 1. Thermographic Results for Normal, Cancer, and Deceased Cancer Patients

Thermographic Results	Patients		
	Normal	Cancer	Deceased
Normal	72	35	15
	72%	35%	12%
Abnormal	28	65	111
	28%	65%	88%

NOTE: $p < 0.0001$, chi-square analysis for independence.

dard surgery, radiotherapy, and chemotherapy. This is in agreement with a study of 70 patients by Isard *et al.*³ that clearly demonstrated the prognostic significance of thermography in breast cancer: 30% five-year survival of patients with abnormal thermograms compared to 80% survival with normal thermograms.

To determine if thermographic findings are an independent prognostic indicator, comparisons were made to the components of the TNM classification system. No significant differences were found in the pathological size of the tumor, clinical nodal status, pathological nodal status (number or % of positive nodes) between patients with normal and abnormal thermograms. There were not enough patients with extension of tumor to chest wall or skin, or with metastatic disease to evaluate thermography in relationship to these prognostic indicators. Breast cancer patients with abnormal thermograms had significantly ($p = 0.006$) larger tumors clinically than patients with normal thermograms. TABLE 2 shows the distribution of these patients' thermographic results by clinical size classification and clearly shows the increase in the percentage of patients with abnormal thermograms as the tumor size increases by T classification, so that all patients in this study with T3 tumors (tumors with diameters greater than 5.0 cm in diameter) had abnormal thermograms. Also, it is interesting to note that 53% (10/19) of patients with T1 tumors (less than 2.0 cm in diameter) had abnormal thermograms. Additional studies will be needed to determine if thermography is an effective prognostic indicator for stage I patients (54% of stage I patients had abnormal thermograms), and to see if thermography is useful in determining which stage I patients should be treated with adjuvant chemotherapy. Thermographic results were found to be unrelated to other information of prognostic significance (age, menopausal status, estrogen receptor status, and progesterone receptor status).

A correlation between the growth rate of tumors and their metabolic heat pattern has been demonstrated, and this results in patients with faster-growing tumors being more likely to have abnormal breast thermograms.⁴ In TABLE 3 are the growth rate-related tissue ferritin concentrations for patients with normal and abnormal thermograms. There was a significantly higher ($p =$

TABLE 2. Chi-Square Analysis for Independence of Clinical Tumor Size and Thermographic Results

Thermographic Results	Clinical Size Classification		
	T1	T2	T3
Normal	9	14	0
Abnormal	10	31	10
% Abnormal	53	69	100

NOTE: $p = 0.0323$, chi-square analysis for independence.

TABLE 3. Comparison of Proliferation-Related Parameters to Thermographic Results

	Thermographic Results		
	Normal	Abnormal	Significance
Ferritin	762 ± 620 (21) ^a	1512 ± 2027 (50)	<i>p</i> = 0.021 ^b
Ploidy, % diploid	41 (7/17)	41 (9/22)	NS ^c
S-phase			
Diploid or aneuploid	2.90 ± 0.94 (11)	6.05 ± 4.13 (20)	<i>p</i> = 0.004 ^b
Diploid and aneuploid	4.18 ± 2.27 (11)	9.35 ± 5.96 (20)	<i>p</i> = 0.002 ^b
S-phase + G ₂ M-phase			
Diploid or aneuploid	5.63 ± 3.35 (11)	10.45 ± 6.65 (20)	<i>p</i> = 0.012 ^b
Diploid and aneuploid	7.63 ± 4.15 (11)	14.65 ± 7.61 (20)	<i>p</i> = 0.002 ^b

^a Mean ± standard deviation (number of patients).

^b Probability from Student's *t*-test.

^c NS, not significant; chi-square analysis for independence.

0.021) concentration of ferritin in the tumors from patients with abnormal thermograms, which supports the concept that patients with abnormal thermograms have faster-growing tumors and poorer prognosis.⁵ Ploidy analysis by flow cytometry showed no relationship to thermographic findings. Both the percent of cells in DNA synthesis (S-phase) and the percent of cells dividing (proliferative index = % S-phase + % G₂M-phase) were strongly associated with thermographic results (TABLE 3), and this was true when the S-phase and proliferative index were calculated by two different methods. In one method the percentages of S-phase and G₂M-phase cells were determined either from the diploid or aneuploid population, whereas in the second method the percentages from both the diploid and aneuploid populations were added together in aneuploid tumors. The results of immunocytochemical determination of Ki-67, a third method for determining cell proliferation,⁶ are found in TABLE 4. The expression of this proliferation-associated antigen is related to thermographic results: patients with abnormal thermograms had a significantly higher proportion of tumors that were highly proliferative (greater Ki-67 expression). The association of all three of these proliferation-related prognostic indicators with thermographic results suggests that thermography is a noninvasive prog-

TABLE 4. Chi-Square Analysis of Ki-67 and Thermographic Results

Thermographic Results	Ki-67	
	Low	High
Normal	8	2
Abnormal	3	8

NOTE: *p* = 0.021, chi-square analysis for independence.

nostic procedure that is able to predict the growth rate of breast tumors, and could be useful for determining which stage I breast cancer patients would benefit from adjuvant chemotherapy.

SUMMARY

Our recent retrospective analysis of the clinical records of patients who had breast thermography demonstrated that an abnormal thermogram was associated with an increased risk of breast cancer and a poorer prognosis for the breast cancer patient. This study included 100 normal patients, 100 living cancer patients, and 126 deceased cancer patients. Abnormal thermograms included asymmetric focal hot spots, areolar and periareolar heat, diffuse global heat, vessel discrepancy, or thermographic edge sign. Incidence and prognosis were directly related to thermographic results: only 28% of the noncancer patients had an abnormal thermogram, compared to 65% of living cancer patients and 88% of deceased cancer patients. Further studies were undertaken to determine if thermography is an independent prognostic indicator. Comparison to the components of the TNM classification system showed that only clinical size was significantly larger ($p = 0.006$) in patients with abnormal thermograms. Age, menopausal status, and location of tumor (left or right breast) were not related to thermographic results. Progesterone and estrogen receptor status was determined by both the cytosol-DCC and immunocytochemical methods, and neither receptor status showed any clear relationship to the thermographic results. Prognostic indicators that are known to be related to tumor growth rate were then compared to thermographic results. The concentration of ferritin in the tumor was significantly higher ($p = 0.021$) in tumors from patients with abnormal thermograms (1512 ± 2027 , $n = 50$) compared to tumors from patients with normal thermograms (762 ± 620 , $n = 21$). Both the proportion of cells in DNA synthesis (S-phase) and proliferating (S-phase plus G₂M-phase, proliferative index) were significantly higher in patients with abnormal thermograms. The expression of the proliferation-associated tumor antigen Ki-67 was also associated with an abnormal thermogram. The strong relationships of thermographic results with these three growth rate-related prognostic indicators suggest that breast cancer patients with abnormal thermograms have faster-growing tumors that are more likely to have metastasized and to recur with a shorter disease-free interval.

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