

Thermo Mammogram as a Tool to Assess Response to Neoadjuvant Chemotherapy in Breast Carcinoma

Abstract

Introduction: Response to neoadjuvant chemotherapy (NACT) is predicted by clinical examination alone in locally advanced breast carcinoma. This study uses thermo mammogram (TMG) to assess the response. **Aim and Objectives:** The aim is to study TMG changes during NACT in breast cancer and predict response to NACT in locally advanced carcinoma and to compare clinical response with TMG response/changes in any form. **Patients and Methods:** All patients with locally advanced breast cancer who had treated with NACT were included in this study. Baseline TMG picture was taken using illumina360° (digital robotic rotational thermography device for 360 degree view of each breast) system before chemotherapy. TMG was repeated before next cycle. All patients were also assessed clinically during and after each cycle of chemotherapy. To assess the potential of TMG in predicting tissue response to chemotherapy, the precool, postcool, and the temperature difference between precool and postcool before every cycle were analyzed. **Results:** A total of 19 patients were analyzed. Eight patients had complete clinical response, six patients had partial response, and five patients had static disease. Median of precool, temperature difference between precool and postcool for patients between no response and complete response did not show statistically significant difference. However, the median of postcool spot temperature showed statistically significant difference. Median of postcool temperature difference for patients between partial response and complete response showed statistically significant difference. The median of postcool spot temperature for patients with no response and partial response did not show statistically significant difference. Precool temperature difference for all the visits showed no statistically significant difference. **Conclusion:** This preliminary study suggests that the TMG has potential for monitoring NACT response in breast cancer patients. Postcool temperature measurement is an early indicator of response to NACT.

Keywords: Assessment of response, breast carcinoma, thermo mammogram

Introduction

Infrared imaging of the breast is commonly known as breast thermography, painless examination, and a noninvasive modality which mainly measures the temperature of the breasts and does not expose the subject to toxic ionizing radiation and tests a subtle changes of physiologic response of the breast.^[1-6] Thermographic imaging has already been clinically used as a screening and diagnosis tool to detect the breast cancer, where high blood flow and metabolic activity due to high vascularity of the tumor is warmer than the surrounding normal functioning tissue. Thermographic or thermo mammogram (TMG) imaging can examine both tumor growth and vasculature changes.^[7] Recently, breast thermograms are widely applied for the precise detection of breast cancer worldwide.^[8-14]

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Most of the patients diagnosed with advanced breast cancer undergo preoperative neoadjuvant chemotherapy (NACT).^[15] Patients with pathological complete response for the NACT are associated with longer disease-free survival.^[16-18] Unfortunately, between 8% and 20% of breast cancer patients will not benefit from NACT and will be treated without clinical or pathologic response.^[16,19] Diagnostic methods to predict early response during therapy would help physicians to decide evidence-based changes on treatment strategies and potentially minimizing side effects and maximizing therapeutic outcome.

At present, most commonly used assessment of response to NACT is by clinical examination alone which is subjective in nature. Many other methods that are in practice to monitor the NACT response include ultrasonography, mammography

How to cite this article: Shanmugam S, Govindasamy G, Susikar S, Palaniyandi M. Thermo mammogram as a tool to assess response to neoadjuvant chemotherapy in breast carcinoma. Indian J Med Paediatr Oncol 2019;40:S25-32.

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_144_17

Quick Response Code:



and contrast-enhanced magnetic resonance imaging (MRI), magnetic resonance spectroscopy, and functional imaging technologies such as 18F-fluorodeoxyglucose positron emission tomography. Mammography is currently the most efficient imaging method for the detection of breast cancer with an accuracy of around 90% for screening. Although many treatment guidelines recommend mammography, the difficulty in assessing the tumor size is problematic when mammography is used for an application in chemotherapy response evaluation in chemotherapy response evaluation.^[20-22] Even, some of the recent methods including functional imaging technologies require exogenous contrast agents that may be poorly tolerated by some patients and are performed at significant expense.^[23,24] Hence, practical limitations include preventing many of these methods from being applied in clinical practice for the use.^[23]

This study aims to analyze the temperature variations for the response to NACT in locally advanced breast carcinoma using TMG by the following:

1. Whether thermography is useful to monitor the neoadjuvant therapy
2. Is there any possibility of using information obtained from thermography to predict the response to therapy?
3. What is the prediction model? Or proposed prediction model?

Patients and Methods

This is single-center, prospective cross-sectional study. The study included 19 consecutive locally advanced breast cancer patients who were undergoing NACT during the period from January 2016 to September 2016. Before the start of the study, signed informed consent was obtained from all patients, whose breasts were imaged by Illumina360° with minimum of 21-day interval up to minimum of three cycles of chemotherapy.

All patients were also assessed clinically and sonomammographically [Figure 1] before every chemotherapy cycle and imaging session. Data on grade, histologic subtype, size, and tumor response as per clinical assessment were recorded for all patients.

Patients were categorized as follows:

- Complete response: Complete disappearance of all disease
- Partial response: $\geq 30\%$ reduction in the sum of the longest diameter of target lesions
- Stable disease: Change not meeting criteria for response or progression
- Progression: $\geq 20\%$ increase in the sum of the longest diameter of target lesions
- Stable disease and progressive disease are considered as no response to chemotherapy.

Procedure for thermography technique

Thermography images were taken using Illumina360°, a medical device for breast imaging without involving any

radiation or contact with the patient breast. The subject lay prone on the imaging bed during the procedure with breast suspended through the opening in the top of the bed. Each breast was imaged individually. Infrared imaging began with a brief period of temperature stasis, after which a stream of cool air was circulated within the temperature conditioning chamber around the uncovered suspended breast. Multiple infrared images were taken one at every 15° angle by the infrared camera both before and after the cooling phase. After the first breast was imaged, the process was repeated for the contralateral breast. The entire session required approximately 15–20 min. Images were acquired in the affected side and the other side.

Statistical analysis

All baseline data (demographic and characteristics) and endpoint data are summarized with descriptive statistics – median and interquartile range (25%–75%). Normality violations for each parameter were checked using the Shapiro–Wilk test. We categorized the final disease status as a categorical variable, that is, no response, partial response, or complete response. Nonparametric Mann–Whitney test (two-sided, 95% confidence) was used to calculate for statistical significant changes in thermography temperature in cycle 1, cycle 2, and cycle 3 between no response, partial response, and complete response. Statistical significance level of $P < 0.05$ was used to assess statistical significance. Statistical analysis was performed using SPSS 20, (IBM, Armonk, NY, United States of America) software.

Results

Patients and tumor characteristics

The clinical characteristics of the patients and their tumors are summarized in Table 1. The median age of female patient was 50 years and seven patients were normally menstruating. Patients had a different combination of neoadjuvant treatment plans. Most of the patients had combined Adriamycin and paclitaxel-based chemotherapy. Of the 19 patients, three had tumor Grade 1, 12 patients had tumor Grade 2, and the rest, four patients had tumor Grade 3. Neoadjuvant treatment response is usually good for high-grade (2 or 3) tumors. However, in our study, only two patients had complete response. Estrogen/progesterone receptor (ER/PR) marker-positive patients responded very low for neoadjuvant treatment. As expected same in our study, among nine ER/PR-positive patients, seven patients were failed to get complete treatment responses. If HER2 biomarker is positive in histopathology, neoadjuvant treatment response is good. Even though seven patients had HER2-neu positive, only one patient had complete response.

Clinical and pathologic assessment of tumor response

Reduction in tumor volume has been widely used as the standard criterion for treatment response evaluation among solid tumors including a breast cancer. Three types of pathologic response patterns from the chemoresponsive

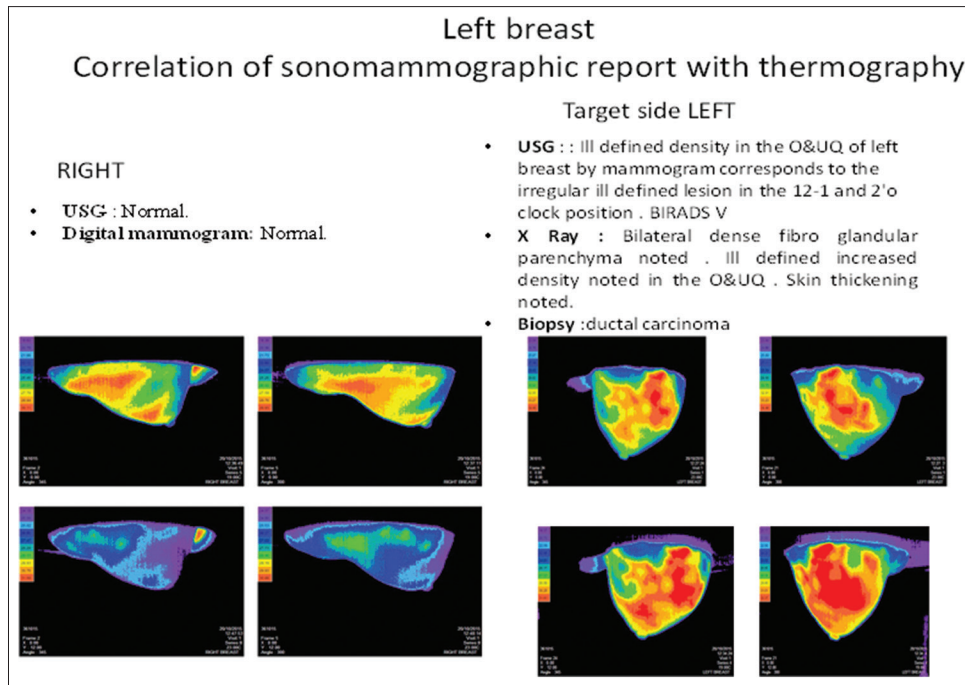


Figure 1: Correlation of sonomammogram with thermo mammogram

Table 1: Summary of clinical characteristics of the patients and their tumors

| Patient ID | Age | Menopause status (pre/post) | Tumor size (at V1) | Histology | Grade | ER/PR | HER2 | Neoadjuvant treatment | Tumor size (at V3) |
|--------------------------|-----|-----------------------------|------------------------|-----------|-------|-------|------|-----------------------|--------------------|
| Complete response | | | | | | | | | |
| 65 | 51 | Post | 5.8 cm × 2.4 cm | IDC | 1 | -/- | - | (A) (P) | Nil |
| 44 | 55 | Post | 4 cm × 3 cm | IDC | 3 | +/+ | - | (D) (P) | Nil |
| 83 | 56 | Post | 6 cm × 5 cm | IDC | 2 | -/- | + | (P)(A) | Nil |
| 92 | 58 | Post | 6 cm × 5 cm | IDC | 3 | +/+ | + | (A)(C) | Nil |
| 108 | 40 | Pre | 8 cm × 6 cm | IDC | 2 | -/- | + | (P)(A) | Nil |
| 118 | 58 | Post | 6 cm × 5 cm | IDC | 1 | +/- | + | (D) (A) (C) | Nil |
| 136 | 48 | Pre | 2.6 cm × 1.8 cm | IDC | 2 | -/- | - | (A) (P) (C) | Nil |
| 138 | 46 | Post | 6 cm × 4 cm | IDC | 2 | +/- | - | (A) (P) | Nil |
| Partial response | | | | | | | | | |
| 6 | 33 | Pre | 8 cm × 5 cm | IDC | 1 | +/+ | + | (A)(C) | 2 cm × 2cm |
| 45 | 58 | Post | 8 cm × 7 cm | IDC | 2 | -/- | - | (A) (C) | 2 cm × 2cm |
| 47 | 42 | Pre | Enlarged entire breast | IDC | 2 | +/+ | - | (A) (C) (P) | Reduction noticed |
| 105 | 55 | Post | 6 cm × 4 cm | IDC | 2 | -/- | + | (A)(P) | 3 cm × 2 cm |
| 129 | 47 | Pre | 8 cm × 6 cm | IDC | 2 | -/- | - | (A) (C) | 3 cm × 3cm |
| 142 | 57 | Post | 7 cm × 6cm | IDC | 2 | +/+ | - | (A) (P) | 5 cm × 4cm |
| No response | | | | | | | | | |
| 25 | 48 | Post | 8 cm × 6 cm | IDC | 3 | +/+ | - | (A) (C) | 8 cm × 6 cm |
| 67 | 56 | Post | 5 cm × 4 cm | IDC | 2 | -/- | - | (A) (P) | 6 cm × 5 cm |
| 91 | 52 | Post | 8 cm × 6cm | ILC | 2 | -/- | - | (A) (C) | 8 cm × 6 cm |
| 114 | 42 | Pre | 15 cm × 12 cm | IDC | 3 | -/- | + | (D) (A) (C) | 12 cm × 10 cm |
| 147 | 36 | Pre | 8 cm × 6 cm | IDC | 2 | +/+ | - | (A) (C) (P) | 5 cm × 5 cm |

Where the neoadjuvant treatment markings are as mentioned below: (A)–Adriamycin; (C)–Cyclophosphamide; (D)–Docetaxel; (P)–Paclitaxel. IDC – Infiltrating ductal carcinoma; ILC – Invasive lobular carcinoma; ER – Estrogen receptors; PR – Progesterone receptors

group were observed. Among the 19 patients, the tumor was undetectable at cycle 3 of treatment in 8 patients and they were categorized as complete [Figure 2] responders,

6 patients had partially [Figure 3], and only 5 patients had poor response and they were categorized no response group [Figure 4].

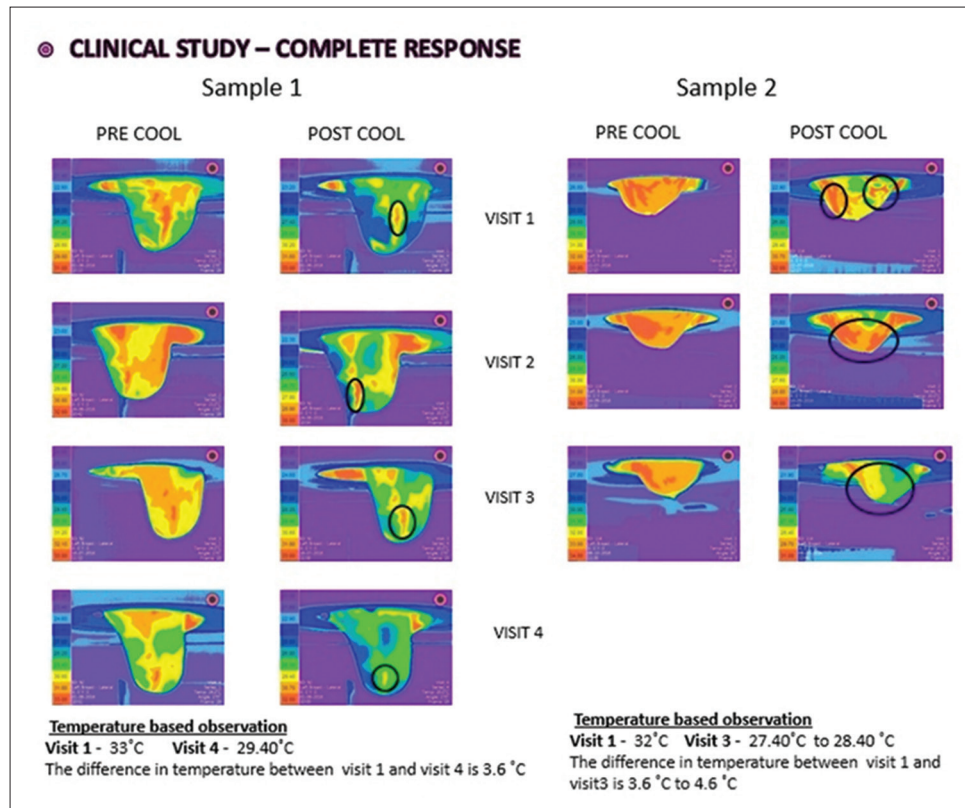


Figure 2: Thermo mammographic images of complete response sample cases

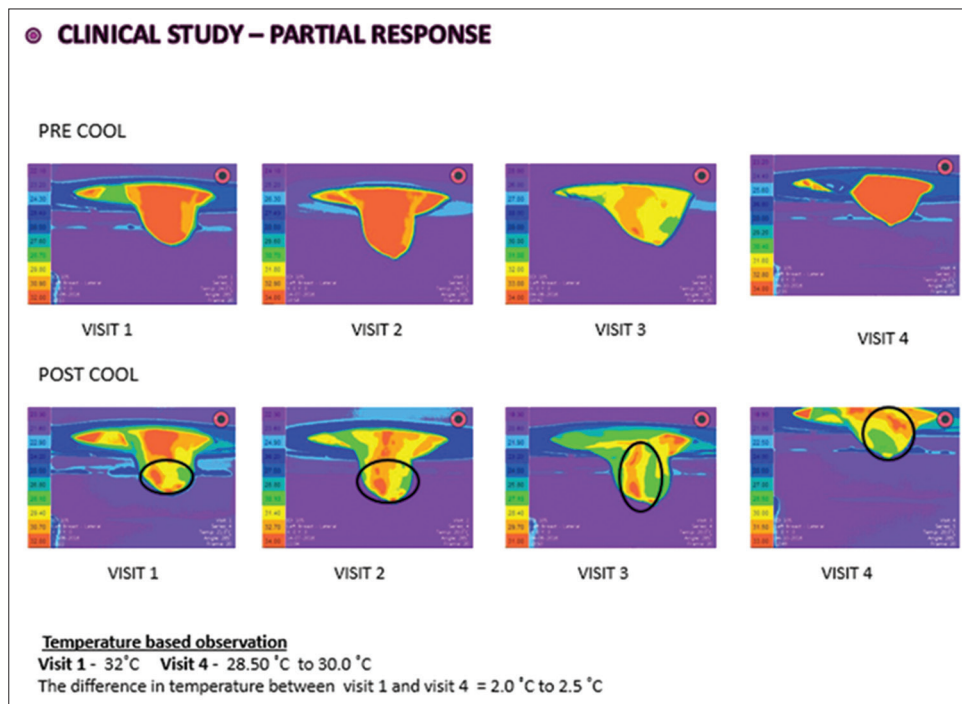


Figure 3: Thermo mammographic images of partial response sample case

Thermo mammogram assessment of tumor response

Overall, 19 patients’ thermography details were collected for three cycles of neoadjuvant treatment. To assess the

potential of thermography in predicting early response, the precool, postcool, and temperature difference before every cycle were analyzed.

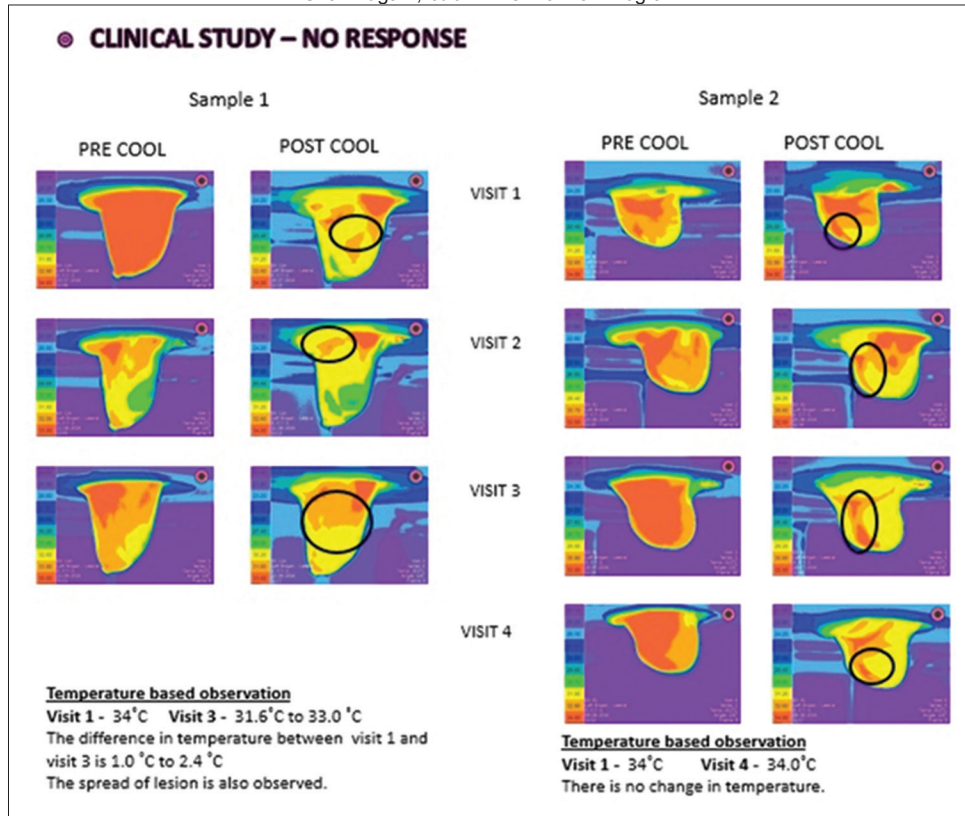


Figure 4: Thermo mammographic images of no response sample cases

Table 2: To assess the potential of thermography in predicting early response, the precool, postcool, and temperature difference before every cycle were analyzed

| | Median (25 th and 75 th percentile) | | | P* | | |
|--|---|-------------------|--------------------|--------------------------------------|-------------------------------------|---|
| | No response | Partial response | Complete response | No response versus complete response | No response versus partial response | Partial response versus complete response |
| Visit 1 | | | | | | |
| Precool spot temp | 35.0 (34.036.0) | 35.0 (33.0-35.0) | 32.5 (32.0-33.0) | NS | NS | NS |
| Postcool spot temp-no response | 34.0 (32.0-34.0) | 33.0 (32.0-34.0) | 31.5 (30.0-33.0) | P<0.003 | NS | P<0.040 |
| ΔTemp (precool, postcool) spot temp -no response | 2.0 (1-2.5) | 2.0 (0-2.0) | 1.5 (-1-3.75) | NS | NS | NS |
| Visit 2 | | | | | | |
| Precool spot temp | 34.0 (32.5-36.0) | 34.0 (34.0-35.0) | 32.0 (32.0-33.75) | NS | NS | NS |
| Postcool spot temp | 33.0 (32.5-34.5) | 33.0 (32.0-34.0) | 30.0 (29.17-32.55) | P<0.030 | NS | P<0.021 |
| ΔTemp (precool, postcool) spot temp | 1.00 (-0.5-2.5) | 1.00 (0-3.0) | 2.00 (1.1-2.75) | NS | NS | NS |
| Visit 3 | | | | | | |
| Precool spot temp | 35.00 (32.0-36.0) | 34.00 (34.0-34.0) | 33.00 (32.38-34.0) | NS | NS | NS |
| Postcool spot temp | 33.00 (30.5-35.0) | 32.00 (32.0-33.0) | 30.60 (28.80-31.0) | P<0.039 | NS | P<0.001 |
| ΔTemp (precool, postcool) spot temp | 1.00 (0-3.00) | 2.00 (1-3.00) | 2.95 (1.4-5.03) | NS | NS | NS |

*Mann-Whitney test. NS: Not significant

Median of precool, temperature difference for patients show statistically significant difference. However, between no response and complete response did not median of postspot temperature for patients in Visit 1

(34.0 vs. 31.5) $P < 0.003$; visit 2 (33.0 vs. 30.0) $P < 0.030$; visit 3 (33.00 vs. 30.60) $P < 0.039$ did show statistically significant difference [Table 2].

Similarly, median of precool, temperature difference for patients between partial response and complete response did not show statistically significant difference. However, median of postspot temperature for patients in Visit 1 (33.0 vs. 31.5) $P < 0.040$; visit 2 (33.0 vs. 30.0) $P < 0.021$; visit 3 (32.00 vs. 30.60) $P < 0.001$, respectively, did show statistically significant difference [Table 2].

Median of postspot temperature for patients with no response and partial response: Visit 1 (34.0 vs. 33.0) $P < 0.876$; Visit 2 (33.0 vs. 33.0) $P < 0.755$; Visit 3 (33.00 vs. 30.60) $P < 0.432$ did not show statistically significant difference. Same results were also obtained for precool, temperature difference that temperatures did not show statistically significant difference for any visit [Table 2].

Discussion

In this study, the application of the thermographic infrared imaging technique to detect the response of NACT in carcinoma breast tumor has been demonstrated, expanding on previously published studies which focused solely on screening of breast cancer. For the first time, we demonstrate the utility of thermographic infrared imaging for the response to neoadjuvant chemotherapies to breast cancer.

Thermography is a technique for assessing the body surface temperature and is widely implemented in medical applications. Infrared imaging procedure is a physiological test that measures the subtle physiological changes in the body such as cancer.

These conditions are commonly related with local hyperthermia, vasodilation, hypermetabolism, hyperperfusion, and hypervascularization, which generate a high-temperature heat source. Unlike imaging techniques such as ultrasound, X-ray, MRI, and other structural-based imaging techniques that largely provide information on the

anatomical structures, infrared imaging technique provides functional physiological information which is otherwise not easily measured by other techniques.

The important discovery of our work projected here is that thermographic imaging technique can be applied to noninvasively monitor the breast tissue response expected to have triggered by anticancer agents administered in chemotherapy to breast cancer patients. Crucially, we have shown that this monitoring is possible in the first 3 cycles after treatment, a period in which the patient does not show a significant clinical physical response to treatment. This will bring significant benefits since monitoring can be carried out in the treatment over the entire treatment procedure rather than having not benefited for the treatments.

The change of the temperature parameters measured by thermography on the pathological response status was compared as shown in Figure 5. An additional observation was that the median temperature change measured by thermography decreased more in complete responders ($\Delta = 1.9$) than in nonresponders ($\Delta = 1$) and partial responders. However, the difference was not found to be statistically significant.

Among all the methods, there was a trend that the postcool temperature was adequate that this temperature information can be used for monitoring the therapy. We assumed that the combined use of precool and postcool temperature modalities may provide valuable insight to predict treatment response better than separate modality alone. However, results confirm that the postcool temperature can be used for accurate measurement of the treatment response. Hence, assessment of response to chemotherapy in breast carcinoma during neoadjuvant setting can be monitored using TMG.

Although this study was not specifically focused on the application of thermographic imaging to monitor drug toxicities, the relationship between body weight losses would suggest that thermographic imaging could also be utilized to monitor overt treatment toxicity.

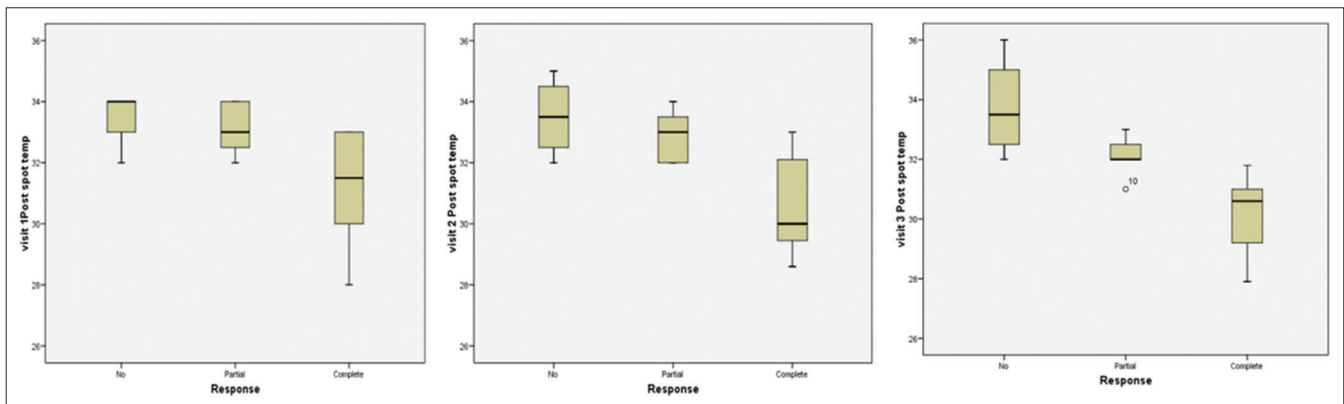


Figure 5: Change of the temperature parameters measured by thermography on the clinical response status was compared

Infrared imaging is hazard free, noninvasive method, patient-friendly, and the cost is very low. These features, together with its early detection capability, have enabled infrared imaging to be a strong candidate as a complementary imaging modality to traditional mammography. There was no standard pattern or reporting system developed in TMG as like digital X-ray mammogram. However, for the individual patient, TMG picture was same and was reproducible. Hence, any subtle changes in temperature during the course of chemotherapy were monitored.

The main limitation of this study is the small sample size. Studies are ongoing so that future work can assess the relationship between temperature with different neoadjuvant setting and clinical outcomes in a larger patient population.

Conclusion

This preliminary study suggests that the thermography infrared technique has a potential for monitoring neoadjuvant treatment response in breast cancer patients. In addition, postcool temperature measurement may offer an early indication of the physiological changes happening in the breast tissue in response to neoadjuvant therapy. These findings combined with the improved thermography infrared technique support further for monitoring breast cancer treatment response.

Acknowledgements

The authors wish to thank the patients who participated in the study. We are grateful to Tuscano equipments private limited, a subsidiary of CURA Healthcare for creating this research opportunity by building an innovative product, MAMRIT, now referred as illumina360°. Our sincere thanks to the entire team for their technical support and a special mention to the product team Ms. Aarthee M and Mr. Senthil A for their outstanding contribution in thermography analysis and data collation and Dr. R. Karthick for statistical analysis of the data. This work was supported by grants from BIRAC (Biotechnology Industry Research Assistance Council, A Govt. of India enterprise) through their Biotechnology Industry Partnership Programme (BIPP).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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