PRELIMINARY EVALUATION OF PREOPERATIVE CHEMOHORMONOTHERAPY-INDUCED REDUCTION OF THE FUNCTIONAL INFRARED IMAGING SCORE IN PATIENTS WITH LOCALLY ADVANCED BREAST CANCER

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Abstract: 20 successive patients who received preoperative chemohormonotherapy (PCT) for locally advanced breast cancer underwent high resolution digital Infrared imaging (IR) both before and after PTC and prior to surgery. The images were graded using a new scale. Initial pre-PCT IR imaging revealed obvious and often dramatic angiogenesis-related findings in all our patients. Following PCT, there was a significant decrease in both the IR score and in the clinical size of those with measurable disease. Four of the six patients with complete pathological response also saw their IR revert to normal. In nine patients, the elevated pre-PCT IR score lingered longer than the clinical findings. IR provides a very safe and convenient alternative functional imaging modality to monitor PCT. Further study and follow-up is required to assess whether the IR changes that reflect the effect of PCT on tumor vascularity also provide an additional valuable prognostic indicator for this subset of patients with aggressive tumors.

I. INTRODUCTION

Approximately 10% of our current breast cancer patients present with sufficient tumor load to be classified as having locally advanced breast cancer.. This heterogeneous subset of patients, usually diagnosed with either stage 3 or T4 lesions without evidence of metastasis, and thus judged as potential surgical candidates, constitutes a formidable therapeutic challenge. Preoperative or neo-adjuvant chemotherapy, hormonotherapy or both, preferably delivered within a clinical trial, is the current favored treatment strategy.

PCT offers a number of advantages, including ensuring improved drug access to the primary tumor site by avoiding surgical scarring, the possibility of complete or partial tumor reduction that could downsize the extent of surgery and also the ability to better plan breast reconstruction when the initial tumor load suggests the need for a possible total mastectomy. In addition, there is sufficient data to suggest that the absence of any residual tumor cells in the surgical pathology specimen following PTC confers the best prognosis, while those patients achieving at least a partial clinical response as measured by at least a 50% reduction in the tumor's largest diameter often can aspire to a better survival than non-responders [1] While current clinical parameters do not always reflect actual PCT induced tumor changes, there is sufficient correlation to make measuring the early clinical response to PTC an important element in assessing the efficacy of any chosen regimen. Unfortunately the currently available conventional monitoring tools, such as palpation combined with structural/anatomic imaging such as mammography and ultrasound, have a limited ability to precisely measure the initial tumor load, and even less to reflect the effect of PCT. [2]

These relatively rudimentary tools are dependant on often imprecise anatomical and structural parameters. A more effective selection of often quite aggressive therapeutic agents and ideal duration of their use could be enhanced by the introduction of a convenient, safe and accessible modality that could provide an alternative and serial measurement of their therapeutic efficacy.

There is thus currently a flurry of interest to assess the potential of different functional imaging modalities that could possibly monitor tumor changes looking at metabolic and/or vascular features to fill the void. Detecting early metabolic changes associated early tumor initiation and growth using Positron Emission Tomography [3], MRI and Sestamibi scanning [4] are all potential candidates to help monitor PCT-related effects. Unfortunately, they are all hampered by limited access for serial use, duration of the exam, costs and the need of intravenous access. High resolution digital Infrared imaging, on the other hand, is a convenient functional imaging modality that requires neither radiation, nuclear material, contact nor compression and can be repeated frequently without safety issues. There is ample data indicating its ability to effectively and reliably detect, in a multi-imaging strategy, neoangiogenesis related to early tumor growth [5,6]. The premise of our review is that this same phenomenon should even be more obvious when using IR as a monitoring tool in patients with tumors associated with extensive vascular activity as seen in LABC.

II. METHODOLOGY

To evaluate the ability of our high resolution digital infrared (IR) imaging station and our new scoring system to monitor the functional impact of PCT, 20 successive patients with locally advanced breast cancer underwent prospective IR imaging, both prior to and after completion of PCT, usually lasting between 3 to 6 months, which was then followed by curative-intent surgery. Ages ranged between 32 and 82 with a mean 55. Half of the patients were under 50. Patients presented with T2, T3 or inflammatory carcinoma and were all free of any distant disease, thus remaining post

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PCT surgical candidates. IR was done at the initial clinical evaluation and prior to core biopsy, often ultrasound guided to ensure optimal specimen harvesting, which was used to document invasive carcinoma,.

Both sets of IR images were acquired according to our published protocol [6] using our integrated infrared station which consisted of a scanning mirror optical system containing a mercury-cadmium-telleride detector (Bales Scientific, CA) with a spatial resolution of 600 optical lines, a central processing unit providing multi-tasking capabilities, and a high resolution color monitor capable of displaying 1024 X 768 resolution points and up to 110 colors or shades of grey per image. Infrared imaging took place in a draft-free, thermally controlled room maintained at between 18°C and 20°C, after a five minute equilibration period. We requested the patients refrain from coffee, smoking, exercise, deodorant and lotions three hours prior to testing. Four images were generated, evaluated and stored by the treating physician who then scored the findings using a modification of our previously published grading system [6]

We used the following modified IR scale (Table 1) where IR-1 reflects the absence of any significant vascular pattern to minimal vascular symmetry; IR-2 encompasses symmetrical to moderately asymmetrical vascular patterns, including focal clinically-related significant vascular asymmetry; IR-3 implies a regional significant vascular asymmetry (SVA) while an extensive SVA, occupying more than a third of the involved breast, constitutes an IR-4. Mean temperature difference (ΔT) in degrees centigrade between the area of focal, regional or extensive SVA and the corresponding area of the non-involved breast is then added, resulting in the final IR score.

TABLE I
MODIFIED VILLE MARIE INFRARED (IR) SCORING SCALE

IR1 =	Absence of any significant vascular pattern to minimal vascular symmetry.
IR2 =	Symmetrical vascular pattern to moderate vascular asymmetry, particularly if stable or due to known non-cancer causes (eg: infection, abscess, recent or prior surgery or anatomical asymmetry). Focal clinically related significant vascular asymmetry.*
IR3 =	Regional significant vascular asymmetry (SVA).*
IR4 =	Extensive SVA, involving at least 1/3 or the breast area.*

*Add the temperature difference (ΔT) in degrees centigrade between the involved area and the corresponding area of the non-involved contralateral breast to calculate final IR score.

Conventional clinical response to PCT was done by measuring the maximum tumor size in centimeters, both before beginning and after completion of PCT.

Induction PCT in ten patients, 8 on a clinical trial (NSABP B-27 or B-57) consisted of 4 cycles of Adriamycin (A) 60mg/m2 and Cyclophosphamide (C) 600mg/m2, with or without additional Taxotere (T) 100mg/m2, or six cycles of AT every 21 days. Eight other patients received AC with additional 5 FU (1000mg/m2) and Methotrexate (300mg/m2). Tamoxifen, given to select patients along with the chemotherapy, was used as sole induction therapy in two elderly patients.

Values in both clinical size and IR scoring both before and after chemotherapy were compared using a paired t-test.

III. RESULTS

All 20 patients in this series with locally advanced breast cancer presented with an abnormal IR image (IR $\geq$ 3). The pre-induction PCT mean IR score was 5.5 (range: 4.4 to 6.9). Infrared imaging revealed a decrease in the IR score in all our patients following PCT, ranging from 1 to 5.4, with a mean of 3.1 ($p < 0.05$). This decrease following PCT reflected the change in the clinical maximum tumor dimension, which decreased from a mean of 5.2 cms. prior to PCT to 2.2 cms ($p < 0.05$) following PCT in the two-thirds of our series who presented with a measurable tumor. Four of the six complete pathological responders in this series saw their IR score revert to normal following PCT and an additional seven patients had a final post PCT IR score that reflected the final tumor size as measured at surgery. However, in nine patients, the elevated pre PCT IR score remained slightly higher following PCT than did the final surgical pathology tumor size.

IV. CONCLUSIONS

LABC is considered an aggressive process that is typically associated with extensive neo-angiogenesis required to sustain rapid and continued tumor growth [7] Functional IR imaging provided a vivid real-time visual reflection of this invasive process in all our patients. The dramatic IR findings associated with LABC, often occupying more than a third of the breast, are further emphasized by the comparative absence of any significant vascular findings in the uninvolved breast. These images thus provided a new parameter and base-line to complement the traditional structurally-based imaging, particularly for the 7 patients with clinically non-measurable LABC.

The significant reduction in the mean IR score following PCT is primarily an indication of its effect on neo-angiogenesis. While this reduction can sometimes correspond to tumor size, as it did in half of this series, IR's main contribution concerns functional parameters that can both precede and linger after structural tumor-induced changes occur. Because IR-detected regional angiogenesis responded slightly slower to PCT than did the anatomical parameters in nine patients underscores the fundamental difference between functional imaging such as IR and structural dependant parameters such as clinical tumor dimensions currently used to assess PCT response. IR has the advantage of not being dependant on a minimal tumor size but rather on the tumor's very early necessity to develop an extensive network to survive and proliferate. This would be the basis of IR's ability to sometimes detect tumor growth earlier than can structurally-based modalities. The slight discrepancy between the resolving IR score and the anatomical findings in nine of our patients could suggest that this extensive vascular network, most evident in LABC, requires more time to

dismantle in some patients. It could reflect the variable volume of angiogenesis, the inability of PCT to affect it, and thus possibly constitute a prognostic factor. This feature could also result from a deficiency in our proposed scoring scale.

Further study and follow-up are needed to better evaluate whether the sequential utilization of this practical imaging modality, requiring neither contact, radiation nor intravenous access, can provide additional pertinent information regarding the efficacy of our current and new therapeutic strategies, particularly in view of the increasing number with anti-angiogenesis properties, and whether lingering IR-reflected neo-angiogenesis following PCT ultimately reflects on prognosis.

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