ROLE OF CTLM IN EARLY DETECTION OF VASCULAR BREAST LESIONS

MOHAMMED EMAD E. EID, MD* HASSAN MANSOUR H. HEGAB, MD** ADOLF E. SCHINDLER, MD, PHD***

*Department of Radiology, Alexandria University, Egypt
**Department of Gynecology and Obstetrics, Alexandria University, Egypt
*** Institute for Medical Research and Education, Essen, Germany

Work has been performed in the department of Radiology, Saqr hospital, RAK, UAE.

ABSTRACT

**Purpose:** To target early detection of breast masses using CTLM as a tool for road-mapping the breast angiogenesis. To assess the high risk patients with micro-calcifications, bizarre breast architecture, mammography dense breasts, and patients who have family history of breast cancer.

**Methods and Materials:** The material was conducted on 250 patients with a total of 450 breasts evaluated. These patients attended the breast clinic in SAQR hospital, RAK, UAE. The symptoms varied between mastalgia +/- bleeding per nipple, breast masses, family history of breast cancer and/or HRT. The age range was between 18-65 years. All patients had Ultrasound, CTLM, Mammography (patients>35 years) or when indicated. Magnetic resonant imaging (MRI) was done in equivocal cases. Positive cases where followed by fine needle biopsy (FNA), true-cut biopsy or surgical excision with pathology confirmation.

**Results:** Among the 450 examined breasts CTLM was sensitive in early detection neovascularization process. CTLM was sensitive for small malignant masses less than 1 cm, as well as bizarre micro-calcifications; 100% specific in malignant breast masses more than 1 cm. False positive results were encountered in some fibro-adenomas with only focal high vascularity with no engorged adjacent vascularity as well as in the sclerosing adenosis.

**Conclusion:** CTLM with its 3-D capabilities is a very good non-invasive breast imaging tool to road-map the development of early neovascularity within the breast parenchyma. Our aim was to narrow the field in order to focus on the breast regions that are suspicious during US, and biopsy examination. This is very effective in mammography dense breasts, where DCIS localizations is difficult as well as in micro-calcifications and in studying the breasts with strong family history.

**Keywords:** Breast Cancer, Computed Tomography, Laser Mammography, Mammography.

INTRODUCTION

Early detection of breast lesions has been the aim since the introduction of all diagnostic modalities used for diagnostic examinations of the breast. Breast masses and/or lesions were thoroughly investigated and examined by several imaging modalities. Mammography to date is the modality of choice and the golden standard in any screening breast examination \(^{(1,2)}\).

Some difficulties have been encountered that hindered our ability to interpret mammography. First, age factor where screening programs start at certain age variable in different countries, with a mean age of 35 years. Consequently, not all females either with a breast lump or not are examined by mammography. Second, dense breast is an additional factor that makes the interpretation difficult. On the other hand, the multiplicity and distribution of micro-calcification foci with either benign or bizarre pleomorphic shapes in the breast, need to be thoroughly scrutinized to know which of these clustered foci are dormant or active regarding their vascular behavior for further selection purposes \(^{(3,4)}\).

For all of the above mentioned reasons and may be more, CTLM has been introduced to verify or exclude the topographic vascular behavior of the breast and the breast lesions in a 3-D pattern, reconstructed from sectional laser 2-D orthogonal sectional planes with both surface and volume capabilities \(^{(5)}\).
The early development of breast vascular lesions (mostly the malignant behavior changes), will express itself to become a palpable mass within 1-2 years from the initial diagnosis if left without any interference. CTLM utilizes the fact that any tumor 2 mm or more, can only survive if it is able to attract new blood vessels (neo-vascularization). This can be done by elaborating an angiotactic factors (6).

Tuning the imaging laser beam to a frequency that matches the absorption coefficient of both the oxy and de-oxymoglobin, (waving the low absorption coefficient of water), we are able to image only the vascular pole pattern of the breast including any neovascularization that might be present (6).

Using the CTLM near the infrared laser beam with an adjusted wave length between 600-900 nm (that of oxy & de-oxy Hb WL), will produce a fluorescent image. As both have a fluorescent behavior once that becomes accentuated and accumulated in the targeted focus (e.g. tumor). They express themselves by emitting that taken absorption energy to a fluorescent wave length in a background of breast soft tissue that lags that behavior (endogenous tissue contrast) (5,6).

PATIENTS AND METHODS

This study was conducted in 250 female patients. 450 breast examinations were included in the study. These patients were examined in the Radiology Department, Saqr Hospital, RAK-UAE. Patients have been forwarded from the breast surgery clinic, gynaecology department, HRT-, or during breast screening-clinics.

Fifty patients had unilateral breast examination, 20 patients had unilateral mastectomy, and the other 30 patients refused to complete both breast examinations and wanted to have only examined the affected breast. The examined patients have been collected over a period of 2 years (Aug. 2003 - Aug. 2005). The age of the examined patients ranged between 18-65 years.

All patients within the studied material where subjected to CTLM® (Model 1020) with sections ranged between 1-4 mm (according to the breast size). Breast ultrasound examinations using a superficial probe (5-12 MHz) of an ATL 5000 were done in all of the studied patients. Patients above 35 years were subjected to conventional mammography (Philips); in standard cranial-caudal and medio-lateral views. Magnification views were resorted to if necessary. Few cases were also subjected to MRI (1.5 T version) examination using breast coil (Philips Intera). Fine needle aspiration (FNA), true cut (both by US guidance) or total surgical excision after US needle localization wiring, with cytological or pathological correlation, were done in doubtful cases. All patients presenting with signs of inflammatory breast changes were excluded from the study.

RESULTS

The numbers of females included in the study were 250, with 450 breasts examined. Fifty patients (20% of total patients) had unilateral examination, out of those 20 patients (8% of total patients) had previous unilateral mastectomy secondary to a breast cancer. The age ranged between 18 years to 65 years with an average mean age of 41.5 years.

The 250 patients included in the study attended the clinics with a variety of indications, which are shown in (table I)

CTLM was done in all of the examined 450 breasts as in initial study (Fig 1-3), followed by ultrasound examination (Fig 4-5). Patients’ ≥ 35 years, mammography was done in 350 (77.8%) breasts from the examined 450 breasts. Table I:

From the studied population, 5 patients were subjected to MRI, 3 patients were below the age of mammography and had doubtful CTLM with a lump in one breast. The other 2 patients had a family history of breast cancer. Those 3 breasts in women below 35 years with a lump, turned out to be fibroadenomas (0.7% from 450 examined breasts) Fig. 4 (A-C). However, the other 2 with strong family history of breast cancer and below the 35 years, one of them turned out to have a focus 4-5 mm of DCIS grade 0 (0.2% from 450 B.) Fig. 1(A-D).

Tissue characterization was done by fine needle aspiration, true-cut biopsy, or surgical lumpectomy in 22 (4.9%) breasts among the studied 450 breasts depending on the analysis of the diagnostic signs achieved by the examined different modalities with BIRAD opinion given before
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the intervention process. In 9 breast lumps (2%), they proved to be malignant from the 50 breast lumps examined, 5 (1.1%) where vascular active from the abnormal micro-calcification, proved to be malignant out of the 30 breasts found with bizarre micro-calcifications.

Table I: The 250 patients included in the study attended the clinics with a variety of indications, which are shown:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mastalgia +/- Bleeding per nipple.</td>
<td>50</td>
<td>20%</td>
</tr>
<tr>
<td>2. Family history of cancer breast.</td>
<td>40</td>
<td>16%</td>
</tr>
<tr>
<td>3. Breast lumps +/- nipple discharge.</td>
<td>50</td>
<td>20%</td>
</tr>
<tr>
<td>4. Hormonal replacement therapy (HRT).</td>
<td>70</td>
<td>28%</td>
</tr>
<tr>
<td>5. Unilateral treated previous breast cancer.</td>
<td>20</td>
<td>8%</td>
</tr>
<tr>
<td>6. Regular breast screening doubt.</td>
<td>20</td>
<td>8%</td>
</tr>
<tr>
<td>Total</td>
<td>250</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table II shows the above findings in the examined modalities within the 450 breasts done CTLM& US and those 350 breasts also standard mammography was done:

<table>
<thead>
<tr>
<th>Findings</th>
<th>CTLM(n=450)</th>
<th>Ultrasound (n=450)</th>
<th>Mammography (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ve</td>
<td>-ve</td>
<td>+ve</td>
</tr>
<tr>
<td>Lumps (n=50)</td>
<td>47(94%)</td>
<td>3(6%)</td>
<td>39(78%)</td>
</tr>
<tr>
<td>D.B.* (n=35)</td>
<td>34(97.1%)</td>
<td>1(2.8%)</td>
<td>25(71.4%)</td>
</tr>
<tr>
<td>Abnormal M.Cal. V.A*</td>
<td>5(16.7%)</td>
<td>25(83.3%)</td>
<td>15(50%)</td>
</tr>
<tr>
<td>HRT* (n=70)</td>
<td>5(7.1%)</td>
<td>65(92.9%)</td>
<td>2(2.9%)</td>
</tr>
</tbody>
</table>


Table III: Detailed CTLM signs among the gathered and detected lesions in the studied population either with or without mammogram are represented:

<table>
<thead>
<tr>
<th>CTLM Signs</th>
<th>Lumps (n=50)</th>
<th>AMCVA* (n=30)</th>
<th>D.B. (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. High I.Q.*</td>
<td>7(14%)</td>
<td>3(10%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>2. H.I.F.R.*,</td>
<td>10(20%)</td>
<td>2(6.7%)</td>
<td>1(2.9%)</td>
</tr>
<tr>
<td>3. V. E. *</td>
<td>9(18%)</td>
<td>5(16.7%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>4. Normal V*</td>
<td>4(82%)</td>
<td>25(83.3%)</td>
<td>34(97.1%)</td>
</tr>
<tr>
<td>5. V. D. *</td>
<td>5(10%)</td>
<td>0(0%)</td>
<td>1(2.9%)</td>
</tr>
</tbody>
</table>

AMCVA*=abnormal micro-calcification vascular activity, HIQ*=high intensity quadrant, HIFR*=high intensity focal region, V.E.*=vessel engorgement, Normal V*=normal vascularity, V.D.*=vessel displacement.
Fig. 1(A-D): Case of family history of breast cancer with FNA result proved to be DCIS grade 0. A) 3-D CTLM image depicted: high intensity NV at the inferior outer quadrant of the breast. B) 3-D Surface-Shaded Display CTLM image revealed: high intensity neo-vascularization that involves the inferior outer quadrant of the breast with more pectoral base engorged vessels at the pectoral side. C) MRI STIR: outer high intensity signals are seen in the outer mid-section of the breast, extending to the pectoral fascia. D) SPIR T1 MRI (Post-IV GAD fat suppressed sequence) appreciable focal signal of contrast uptake is seen at the outer mid-section of the breast, matching the CTLM high signal breast excitation region of NV.

Fig. 2(A-B): Base-line study for HRT patient revealed; A) Distorted breast architecture is seen in the mid-section at the sub-areolar region, advised CTLM in the report. B) 3-D CTLM image revealed: significant moderate intense fluorescence of neo-vascularization is seen at the sub-areolar region with ectatic to mildly dilated 2 O’clock draining vein reaching the pectoral region. True-cut biopsy revealed lobular carcinoma grade 1, with multiplicity in the contra-lateral breast.
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Fig. 3 (A-E); Patient 35 yrs old, presented with a lump, felt in the past 1 month, painless, immobile, minimally
tender by palpation A) CC mammogram showed Satellite-shaped dense mass lesion of ill-defined outlines
with radiating streaks infiltrating the adjacent breast parenchyma. B) US showed ill-defined mass lesion,
immobile, not tender, hypo-echoic, invading the pectoral fascia. C) CTLM 3D Surface-Shaded Display re-
vealed: Mass lesion of neo-vascular fluorescence is seen with markedly excited and dilated breast vascular
system extending to the pectoral fascia. D) STIR MR, revealed high intensity mass extending to the skin and
areola with nipple retraction. High signal alteration of the rib bone marrow denotes BM high vascularization
as seen by CTLM. E) MRI 3D Subtracted Post GAD. SPIR T1 sequence showed; high intensity contrast
uptake along the previously mentioned mass and its extension.

Fig. 4 (A-C); Patient aged 36 years, presented with a mobile mass lesion, not tender, painless. A) Mammogram
showed dense breast with a denser (about 1.5 cm) mass lesion having a faint hallow hypo-dense rim (mesh-
effect). B) US showed A well-defined kidney shaped mass lesion of hypo-echoic nature, displacing the breast
parenchyma C) 3D CTLM image revealed: Significant displacement & stretch of the breast vessels around
a potential space occupying parenchymal mass lesion. FNA revealed the pattern of fibro-adenoma mass.
DISCUSSION

The group of females that had been chosen in our prospective study was free from any signs of apparent breast inflammatory changes. This was an important issue in our initial study to assess the value of the new CTLM modality. Any conflict that can be raised from the developed neovascularity from the inflammatory process was waived during this study.

Female patients attended with various breast complaints. They fulfilled the different breast imaging modalities according to the age or the availability of the modality in their clinics, yet, the final diagnosis was still not reached. They needed further invasive breast biopsy or intervention. Those breast cases were the best candidates for our prospective study. They need another complimentary non-invasive modality, e.g. CTLM, which either waive the possibility of active neovascular lesions or certify their presence, and then move to the next invasive step. So, the aim was decrease the incidence of invasive procedures in the breast. (7)

In our initial study in this field, which must be followed by other investigations, using only ultrasound in patients less than 35 years was not a sufficient procedure in patients suffering from mastalgia with advanced fibrocystic disease. Possibility of small masses less than 4mm could be easily missed in the back ground of ductal dilatations and more ramifications with possibility of associated variable sized cysts in a fibro-glandular stroma. Also, patients above 35 years, having mammograms with architectural breast alteration with no definite visible masses. Dense breast mammograms, was another problem, to evaluate either an inside denser lesion or bizarre micro-calcifications, was greatly difficult. (8)

The bizarre micro-calcifications before was a reason for biopsy. Those foci being active regarding vascularity or not was not an issue in selecting those cases. (9)

Researcher believe that a 1-2mm focus of ductal carcinoma in situ (DCIS) might or might not progress to a malignant lesion within the next 2 years, and present as a palpable clinical 1-2 cm mass lesion. So, our believe is to see those lesions very early and get familiar with their vascular behavior, as well as their ability to retain and form certain substances that are chemo-tactically of fluorescent nature. (8, 10)

In our study with the usage of CTLM, not all of the detected lumps were malignant. Out of the examined 50 breast lumps, 7 breast lumps were proven to be malignant. Depending on the above criteria, were any malignant lesion will not flourish except with the development of neovascularity, and retention of a high fluorescent substance, so, BIRAD opinion was given before the biopsy and was matching the biopsy results in the examined cases.

Also, not all CTLM focal high intensity signal (colouration) must be malignant, the adjacent engorged vessels must be present. This was seen in 2 breast patients in our study, where focal high intensity focus plus engorged vessels were seen. The first was one patient with a strong family history of cancer breast (fig.1). The other patient was starting to have a base-line mammogram with a focal altered breast architecture to start HRT with few faint bizarre micro-calcifications (fig.2). The rest of the examined cases with only focal high intensity were proven to be fibro-adenomas and fibro-adenosis (fibro-cystic disease), that gave false-positive results, where no adjacent breast vascular engorgement could be seen. Also CTLM was able to detect the volume of hypo or non intensity masses, through the 3-D software capabilities, by only deflection and displacement of the surrounding breast parenchymal vascularity (fig.4).

CONCLUSION

The golden standard in breast screening is and will continue to be mammography. However, an adjunct complimentary noninvasive CTLM study is as much important as to road-map the breast vascular system to point-out in a functional way any development of early abnormal angiogenesis within the breast parenchyma. This will discover breast masses as early as possible, down to 4mm in size as found in one of our silent cases with family history of cancer breast and proved by both MRI and biopsy results.

Age was not a factor in this study as we were dealing with laser light beam adjusted to hemoglobin wave length. Filtering abnormal cases either
from the screening or “complaining” patients are the material of the CTLM cases.

In spite of that screening the breast with CTLM narrows the field of research for the radiologist to the segments or quadrants with odd high intensity sites of angiogenesis or neovascularization before to progress to the other breast imaging modalities as this was our experience from the study.

Reducing the number of biopsy cases was achieved in our study by implementing the criteria of CTLM experienced through the cases by time.

Dense breast in mammograms, due to hormonal changes or affinity of the breast to fluid accumulation, is waived by adequate laser light penetration of the CTLM machine.

False-positive segments in CTLM study is forgivable in cases thought to be malignant and turned out to be benign. On the contrary, the reverse is a disaster without the usage of CTLM with the routine other breast modalities usage only.

Further studies are needed for optical imaging modality to reduce the false positive cases, and by usage of the recently ongoing projects of coupling fluorescent tumor marker dye (ICG; Indocyanin Green) in conjugation with examination, sensitivity of early tumor detection will be magnified.

REFERENCES