Dynamic Angiothermography

A new technology for breast cancer screening and diagnosis

Prof. Gian Carlo Montruccoli
Prof. Daniele Montruccoli

Geneva Foundation for Medical Education and Research
Breast Cancer: Early Detection, Diagnosis, and Prognosis

**Imaging Technologies.**

NCI is funding research on a variety of technologies for breast imaging, including:

digital mammography,

elastography,
magnetic resonance imaging (MRI),
magnetic resonance spectroscopy,
ultrasound techniques, positron emission tomography (PET),
single photon emission computed tomography (SPECT),
thermography.

http://women.cancer.gov/planning/whr0001/breast.shtml  21-3-07
Dynamic Angiothermography (DATG)

- New functional diagnostic tool
- Based on the imaging of mammary gland’s normal vascularization and detection of its angiogenic microcirculation
- Morphological, qualitative images of the breast’s functional blood supply.
- Reproducible, non-invasive
- R&D with Dept Medical Physics, University of Bologna
- Clinical results for 7000 patients, 25-year Follow Up
- Excellent integration with other breast diagnostic techniques
QUANTITATIVE vs. QUALITATIVE

Old Contact Thermography
- Quantitative method
- Based on the measurement of thermal gradients (ΔT), evaluated by image coloration

Dynamic Angiothermography - DATG
- Qualitative method
- Based on the detailed patterns of functional blood flows
Experiments run at the University of Bologna’s Department of Physics tested the plate against the others on the market, especially as to spatial resolution (as high as a tenth of a millimeter) and response time. The results were excellent and the plate has now been patented in Europe and the United States.

From: “A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms” - Physica Medica - (Vol. XX, N. 1 January-March 2004 pp.27-31)
TEST 1

spatial resolution (as high as a tenth of a millimeter)

From: “A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms”

Physica Medica - (Vol. XX, N. 1January-March 2004 pp.27-31)
University of Bologna’s Department of Physics

From: “A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms”-

Physica Medica- (Vol. XX, N. 1 January-March 2004 pp.27-31)
Plate sensitivity

- We tried to reproduce blood flow lines in Dep. of Physics
- Insertion of the tube with warm water into the wax phantom
- Pointed terminations (normal flow lines)
Cutaneous projection of the breast’s main arteries.

Scheme of vascular anatomy of left breast

As vessels enter the breast, they get smaller and smaller, as they ramify.

When we put the DATG plate on the breast, it reveals normal vessels as end-pointed, because they are ramifying and their signature flowlines reach a vanishing point.
Normal angiothermographics flowlines reproduce the anatomy of the circulation of the breast.

- The flow-lines of each plexus should be centripetal, fade out as they terminate in their own area and be proportional to the contralateral.
Upper internal quadrant of the left breast showing a marked anomalous flow line formed by countless vessels activated by a Lobular and Ductal Carcinoma in Situ with intraductal diffusion.
SUSPICIOUS FLOWLINES

- Deviations
- Non-pointed terminations
- Flowlines that go beyond their own territory
MALIGNANT FLOWLINES

- Two or more flowlines that cross one another: these are called malignant crosses or stars
- Flowlines that converge towards a central hotspot
- Flowlines that converge from different territories
Menopausal patient

«Malignant star»

Infiltrating Lobular Carcinoma

Biopsy zone

Mammography: no pathological findings

The lesion is between skin and muscle perpendicular to the end of the angiothermographic flow line.

Diagnosi:

Carcinoma lobulare multifocale classico infiltrante associato a focolai di carcinoma lobulare in situ.
LCIS in pregnancy (8 weeks)

36 years old

• This 36-year-old patient, who said she was 8 weeks’ pregnant, can have the angiotest because it is harmless.
• The check-up showed a hot spot with flow lines from the acromial and the external mammary in the upper left external quadrant.
• An ultrasound was negative but the biopsy, performed under local anesthetics, returned LCIS as the histological result.
Progression of angiogenesis

Normal

Hyperplasia

In situ Cancer

Invasive cancer

DATG
Histological findings

We performed 1,065 biopsies on 693 out of a total 7,003 patients from 1975 to 2006.

Note first that the rate of epithelial lesions runs as high 70% if simple hyperplasia is considered. (Molecular tests showed a loss of heterozygosity in 90% of hyperplasia cases)

Note too that pre-invasive lobular lesions were more than double the ductal, contrary to what is reported in literature. Why?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>%</th>
<th>% Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastitis and/or ectasia</td>
<td>143</td>
<td>13.43</td>
<td>30.71</td>
</tr>
<tr>
<td></td>
<td>184</td>
<td>17.28</td>
<td></td>
</tr>
<tr>
<td>Simple ductal hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Florid ductal hyperplasia</td>
<td>182</td>
<td>17.09</td>
<td>39.91</td>
</tr>
<tr>
<td></td>
<td>243</td>
<td>22.82</td>
<td></td>
</tr>
<tr>
<td>Papillomatosis</td>
<td>48</td>
<td>4.51</td>
<td>4.51</td>
</tr>
<tr>
<td>Atypical duct hyperplasia</td>
<td>8</td>
<td>0.75</td>
<td>4.13</td>
</tr>
<tr>
<td>Atypical lobular hyperplasia</td>
<td>23</td>
<td>2.16</td>
<td></td>
</tr>
<tr>
<td>Mixed atypical hyperplasia</td>
<td>13</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>16</td>
<td>1.50</td>
<td>5.54</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>28</td>
<td>2.63</td>
<td></td>
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<tr>
<td>Mixed carcinoma in situ</td>
<td>15</td>
<td>1.41</td>
<td></td>
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<tr>
<td>Ductal microinvasive carcinoma</td>
<td>2</td>
<td>0.19</td>
<td>0.85</td>
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<tr>
<td>Lobular microinvasive carcinoma</td>
<td>5</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Mixed invasive carcinoma</td>
<td>2</td>
<td>0.19</td>
<td></td>
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<tr>
<td>Ductal invasive carcinoma</td>
<td>130</td>
<td>12.21</td>
<td>14.09</td>
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<tr>
<td>Lobular invasive carcinoma</td>
<td>16</td>
<td>1.50</td>
<td></td>
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<tr>
<td>Mixed invasive carcinoma</td>
<td>4</td>
<td>0.38</td>
<td></td>
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<tr>
<td>Malignant phyllodes</td>
<td>3</td>
<td>0.28</td>
<td>0.28</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td>1,065</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
DATG-detected Lobular and Ductal Pathology

Number of cases

AH: ATYPICAL HYPERPLASIA; CIS: CANCER IN SITU; MC: MICROINVASIVE CANCER; IC: INVASIVE CANCER

Definition of the microvascular pattern of the normal human adult mammary gland.

*Journal of Anatomy* vol. 203, pp. 599-603, 2003"

One finding in particular indicates that in the normal state the duct’s microcirculation has a smaller surface area than the lobule’s and that the latter’s circulation is represented by sinusoids and is hence notably slower.
IMMUNOHISTOCHEMICAL EXPRESSION OF VEGF-A AND ITS LIGANDS IN NON NEOPLASTIC LESIONS OF THE BREAST: CORRELATION WITH DYNAMIC ANGIOThERMography RESULTS

1 Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Portugal; 2 IPATIMUP, Porto, Portugal; 3 Department of Surgery Pietro Valdoni, University of Rome La Sapienza, Rome, Italy; 4 Department of Obstetric and Gynecology - Toniolo Private Clinic – Bologna, Italy; 5 Medical Faculty of Porto University, Porto, Portugal.

The aim of the study was to investigate the expression of angiogenic markers, vascular endothelial growth factor A (VEGF-A) ligand and its receptors, VEGFR-1 and -2, in a series of biopsy-proven non neoplastic lesions of the breast detected by dynamic angiothermography. We have also studied the vascular density demonstrated by CD31 immunoreactivity, in order to assess the potential impact of the imaging method to recognize lesions with enhanced vascular network of clinical importance in the routine of breast examination. The lesions were classified as non proliferative lesions, proliferative lesions without atypia and proliferative lesions with atypia. VEGF was diffusely expressed in the epithelial cells of proliferative lesions in almost all cases. Similarly, VEGFR-1 and R-2 have also exhibited epithelial positive reactions in the majority of cases. VEGF-A and its receptors also decorated angiogenic vessels. VEGFR-2 also decorated vessels with morphological profile of lymphatics. On the other hand, VEGFR-1 decorated more specifically small blood vessels. CD31 showed increased of vascular proliferation in the periphery of proliferative epithelial lesions. Our results, showing expression of VEGF by the epithelial lesions and neoangiogenesis at their periphery, can support that these lesions can be detected by this imaging technique.

Acknowledgements. This study was partially supported by grants from FIGO.
THREE FUNDAMENTAL CHARACTERISTICS OF DATG

- Each woman has her own strictly personal flowline pattern (like fingerprint)
- This pattern remains constant over decades in the absence of patho-physiological changes
- Pathological modifications are independent of tumor size and shape
Comparison of Diagnostic Techniques
5913

5913 Mammography 20-2-97

5913 left lateral 31-12-96
Pt 6128
Appearance of microcalcifications: LCIS 3 mm.
Pt 6128

Appearance of microcalcifications: LCIS 3 mm.

- MAMMOGRAPHY LEFT 2-6-1998
- Pz. 6128 Left Lateral Pre-op
Pt.6128 after surgery: Normal

- Pz.6128 Mammography 25-10-1999
- Pz.6128 lateral left 18-10-2000
A 40-year-old woman operated elsewhere for Ductal Infiltrating Carcinoma with radiotherapy. MRI shows a local relapse that is supported by DATG.
2° localization ?
DATG Applications
Hormone Replacement Therapy
604 Long follow-up with HRT
Long follow-up with HRT and biopsy (Hyperplasia lobular and ductal)

With HRT

Without HRT

After surgery
Genetics
4779 after surgery:
“Atypical lobular Hyperplasia”
Young Patient
17 year old: “papillary duct hyperplasia of the breast”
17 year old: “papillary duct hyperplasia of the breast”

-pre-op-

3634-front left 23-6-87
Pre-op.

3634-front left 2-12-02
Post-op.
Integrated Diagnosis
5647

Cancer

Normal

Fibrosis
34 year old patient
Hormonal stimulation for infertility

Patient with fine needle aspiration (elsewhere) positive for infiltrating ductal carcinoma.  

The DATG shows a second neoplastic localization

A: Ductal Infiltrating Carcinoma G3

B: Ductal Infiltrating Carcinoma with intraductal G2

Controlateral is normal
Pre-operative Chemotherapy
1661 front. Sin 6-6-80

1661 front. Sin 19-6-80
1661 mammografia
29-5-80

1661 mammografia
22-8-80
2423
B.C.
2423

After two course of pre-op chemotherapy
Screening
DATG pattern remains the same over 16 years (in absence of pathology)

DATG is useful for screening
DATG pattern remains the same over 20 years (in absence of pathology)

DATG is useful for screening
DATG pattern remains the same over 25 years (in absence of pathology)

DATG is useful for screening
The two flow-lines (white arrow) of the external mammary are initially normal.

15 months later one remains the same and the other disappears to form a new line with the acromial. (red arrow) Both go on to feed a lobular in situ carcinoma (1 mm. in diameter).

This new flowlines (12-15 cm. long) feed such very small tumor.
Dramatic change: Mixed lobular/duct CIS
Naccarato AG, Viacava P, Vignati S, Fanelli G, Bonadio AG, Montruccoli G., Bevilacqua G.
Bio-morphological events in the development of the human female mammary gland from fetal age to puberty.
VIRCHOWS ARCHIV-AN INTERNATIONAL JOURNAL OF PATHOLOGY,

Bevilacqua G.
Definition of the microvascular pattern of the normal human adult mammary gland.,
JOURNAL OF ANATOMY,
vol. 203, pp. 599-603, 2003

G.C. Montruccoli, D. Montruccoli Salmi, F. Casali
A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms.
PHYSICA MEDICA
Vol.XX, N.1, January-March 2004 pp.27-31

Daniele Montruccoli, Franco Casali, Stefano Brusori, Paolo Barillari,
Corrado Scipioni et Gian Carlo Montruccoli
“L’angiothermographie dynamique : un avenir ?”
L’AGENDA GYNECOLOGIE, Mars 2005 pag.42-43

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Thermography fiction or reality?
INTERNATIONAL JOURNAL OF OBSTETRICS AND GYNAECOLOGY
Vol. 83 Supplement N.3 pag.18 November 2-7 2003

G. C. Montruccoli, D. Montruccoli, F. Casali, S. Brusori, W. F. Grigioni, A. G.
Naccarato, P. Viacava, N. Decarli, A. Cavazzana, G. Bevilacqua.
Clinical application of a new thermographic plate: histopathological findings of 1027 breast lesions.
95TH AMERICAN ASSOCIATION FOR CANCER RESEARCH
AACR ANNUAL MEETING 27-31 MARCH 2004

Viacava P., Naccarato A.G., Bocci G., Fanelli G., Aretini P., Lonobile A.,
Montruccoli G.C., Bevilacqua G.
Angiogenesis and VEGF expression in pre-invasive lesions of human breast.
JOURNAL OF PATHOLOGY
2004; 204: 140-146
COLLABORATIVE GROUPS IN DATG CLINICAL AND RESEARCH

- A. Campana
  Geneva Foundation for Medical Education and Research
- M. Merialdi
  World Health Organization. Department of Reproductive Health and Research.
- J.A. Pinotti; M. Pinotti; F. Carvalho
  State University S. Paolo-Brasil
- G. Lindeque
  University of Pretoria-South Africa
- D. Vanel
  Institut Gustave Roussy-Villejuif- France
- F. Schmitt-M. J. Cardoso
  University of Porto-Portugal
- G. Bevilacqua; A. Cavazzana
  University of Pisa-Italy
- D. Generali, A. Bottini
  Breast Unit - Cremona Hospital
- E. Lifrange
  Università de Liege -Belgique
- J. Bojages
  National Breast cancer center – Sydney
- D. Montruccoli
  University of Rome La Sapienza-Italy
Next step

**International clinical protocol coordinated by**

Geneva Foundation for Medical Education and Research

&

World Health Organization (WHO).

Department of Reproductive Health and Research

- Double –blind prospective study comparing DATG, US, X-Ray and MRI.
- Sensitivity & specificity of DATG / X-Ray against Histology as “gold standard”.
- DATG sensitivity to young BRCA 1&2 carriers
FLOW CHART (draft)

TRAINING OF INVESTIGATION IN DATG
in Bologna or Rome-Italy
Time 15 days

INTRA–INSTITUTIONAL TRAINING AND VALIDATION:
COMPARATIVE STUDY OF 100 CASES SCHEDULED FOR BIOPSY
DUE TO POSITIVE MAMMOGRAPHY (BiRads 5)

**Advantage**: training with the technique in the local centre
in comparison with positive mammography

**Disadvantage**: all cases were already considered positive
for the traditional technique and will be operated anyway

**time**: 3 MONTH

This first step will be object for a first publication
<table>
<thead>
<tr>
<th>PROJECT 1 (PROT.1)</th>
<th>PROJECT 2 (PROT.2)</th>
<th>PROJECT 3 (PROT.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time:</strong> 6 month to 1 year</td>
<td><strong>Time:</strong> 6 month to 1 year</td>
<td><strong>Time:</strong> 6 month to 1 year</td>
</tr>
<tr>
<td>- MAMMOGRAPHY</td>
<td>- MRI SUSPICIOUS OR POSITIVE IN BRCA1-2 POSITIVE PATIENTS</td>
<td>- CLINICAL, MAMMOGRAPHICAL AND HISTOLOGICAL PROUVED BREAST CANCER SELECT FOR NEO-ADJUVANT CHEMOTHERAPY</td>
</tr>
<tr>
<td>- BIRADS 1-2-3-4-5</td>
<td>- DATG</td>
<td>- TUMOUR ASSESSMENT BY MAMMOGRAPHY (SIZE), US (SIZE), DATG (VASCULAR PATTERN)</td>
</tr>
<tr>
<td>- DATG</td>
<td>- BIOPSY</td>
<td>- NEO-ADJUVANT CHEMOTHERAPY FOR 3-6 COURSE</td>
</tr>
<tr>
<td>- BIOPSY</td>
<td>- MRI SUSPICIOUS OR POSITIVE IN BRCA1-2 POSITIVE PATIENTS</td>
<td>- TUMOR RESPONSE ASSESSMENT BY MAMMOGRAPHY, ULTRASOUND, DATG AND HISTOLOGY</td>
</tr>
<tr>
<td>N. Patients included: to discuss with the statisticians</td>
<td>N. Patients included: to discuss with the statisticians</td>
<td>N. Patients included: to discuss with the statisticians</td>
</tr>
</tbody>
</table>

**EXPECTED RESULTS:**

**IN CANCER:** AT LEAST THE SAME SENSITIVITY AND SPECIFICITY WITH MAMMOGRAPHY

**IN PRE-INVASIVE LESION:** DATG MORE ACCURATE WITH MAMMOGRAPHY

**EXPECTED RESULTS:**

DATG CAN HAVE AT LEAST THE SAME SENSITIVITY AND THE SPECIFICITY OF MRI WITH LOW COST

**EXPECTED RESULTS:**

DATG CAN BE MORE ACCURATE THAN MAMMOGRAPHY OR US IN ASSESS TO TUMOUR RESPONSE TO CHEMOTHERAPY
Dynamic angiothermography
A new technology for breast cancer screening and diagnosis

Prof. Giancarlo Montrucchi
Gynaecologist, member of the Gynaecology and Oncology Committee of the International Federation of Gynaecology and Obstetrics (FIGO)
Member of the International Society of Sonology (S.I.S.) Committee of Experts

Prof. Daniele Montrucchi
Oncologist and Gynaecologist
Fellow in Oncology at the Institute Gustave - Roussey Villejuif - Paris
Adjunct Professor in Oncology, University of Rome “La Sapienza” Department of Thoracic Surgery
Member of the Geneva Foundation for Medical Education and Research
Office: Via F. Bolognese 27/3a – 40137 Bologna-Italy

daniele@montruccoli.it
EQUIPMENT
DATG: 
practical considerations

- DATG is:
  - Rapid
  - Economical: (limited equipment and maintenance costs)
  - Completely non-invasive

- Can be used at any age
- Very good compliance
- Breast cancer prevention (even detection of lobular neoplasia)
- No radiations, No chemical, No pain
- Repetitive and Reproducible
- Rapid performance time, immediate response
Prof. Gian Carlo Montruccoli

F.I.G.O. Oncological Committee
S.I.S. Expert Member

Thank You