

Training Course in Sexual and Reproductive Health Research Geneva, February 2009

Dynamic Angiothermography A new technology for breast cancer screening and diagnosis



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Dynamic Angiothermography (DATG)

New functional diagnostic tool

- Based on the imaging of mammary gland's normal vascularization and detection of its angiogenic micro-circulation
- 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







Breast Cancer:



Early Detection, Diagnosis, and Prognosis

<u>Imaging Technologies</u>.

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 21-2-09

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

QUANTITATIVE vs. QUALITATIVE



100 10 7171







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

University of Bologna's Department of Physics

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.



Thermocouple wire

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

University of Bologna's Department of Physics

TEST 1

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

Lines not separate

Our plate

Separate

lines

TEST 1 A

Commercial plate



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 2A after 3"

response time



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)





Scheme of vascular anatomy of left breast Cutaneous projection of the breast's main arteries.

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 endpointed, because they are ramifying and their signature flowlines reach a vanishing point



Fig. 8. — Dissection anatomique après injection de résine autopolymérisable intra-artérielle : mise en évidence de l'artère mammaire externe de type I majeur.

Fig. 8. — Anatomical dissection after intra-arterial injection of autopolymerisable resin : demonstration of a major type I external mammary artery.

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 contra lateral.



Fig. 10. — Dissection anatomique de l'artère acromio-thoracique après injection au latex : ici apparaît sa composante postérieure musculaire à destinée glandulo-cutanée (flèches rouges. La flèche noire indique l'origine de l'artère).

Fig. 10. — Anatomical dissection of the acromiothoracic artery after injection of latex, showing its posterior muscular component supplying the gland and the skin (arrows).

Normal flowlines

DATG







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.



10.3.

87

Bx4 Cx3 Dx3

Disgnosit

Pocolai multipli di carcinoma lobulare in situ con diffusi aspetti di diffusione intraduttale a tipo "pagetoid spreading".





SUSPICIOUS FLOWLINES

Deviations (all)
Non-pointed terminations (all)
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 patholagical 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)



Ultrasound normal

Breast Cancer in Family: Mother tested positive one year later

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.





Normal Progression of angiogenesis Hyperplasia In situ Cancer Invasive cancer





Visualizing the angiogenic switch

Neovascularization in a rat tumor model



Images reproduced with permission from Dr Judah Folkman.

Immunohistochemical expression of VEGF-A and its ligands in non-neoplastic lesions of the breast sampling-assisted by dynamic angiothermography

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Abstract. The aim of this 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 of the imaging method to recognize lesions with an enhaced vascular network of clinical importance in routine breast examination. The lesions were classified as non-proliferative, proliferative without atypia and proliferative with atypia. VEGF was diffusely expressed in the epithelial cells of proliferative lesions in almost all cases. Similarly, VEGFR-1 and -2 also exhibited epithelial positive reactions in the majority of cases. VEGF-A and its receptors were also present in blood vessels. CD31 showed an increase in vascular proliferation at the periphery of proliferative epithelial lesions, but not in non-proliferative lesions. Our results, showing marked expression of VEGF by the epithelial proliferative lesions and neoangiogenesis at their periphery, confirm that these lesions can be detected by dynamic angiothermography.

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?

Diagnosis	No.	%	% Group
Benign	143	13.43	00.74
Mastitis and/or ectasia	184	17.28	30.71
Simple ductal hyperplasia	182	17.09	
Florid ductal hyperplasia	243	22.82	39.91
Papillomatosis	48	4.51	4.51
Atypical duct hyperplasia	8	0.75	
Atypical lobular hyperplasia	23	2.16	4.13
Mixed atypical hyperplasia	13	1.22	
Ductal carcinoma in situ	16	1.50	
Lobular carcinoma in situ	28	2.63	5.54
Mixed carcinoma in situ	15	1.41	
Ductal microinvasive carcinoma	2	0.19	
Lobular microinvasive carcinoma	5	0.47	0.85
Mixed invasive carcinoma	2	0.19	
Ductal invasive carcinoma	130	12.21	
Lobular invasive carcinoma	16	1.50	14 <mark>.09</mark>
Mixed invasive carcinoma	4	0.38	
Malignant phyllodes	3	0.28	0.28
TOTAL	1.065	100%	100%

Microcirculation

"Naccarato A.G., Viacava P., Bocci G, Fanelli G., Lonobile A, Montruccoli G.C., and Bevilacqua G.

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. False Positive 10%-15% False Negative 4 cases (1,065 biopsies)

> TO BE CONFERMED WITH A PROSPECTIVE STUDY

Screening or prevention?

18 years earlier...









□ Xray Mammography: 17-3-1994



□ DATG: 19-3-96

□ X-Ray Mammography: 15-3-96



After surgery

Comparison of Diagnostic Techniques



□ 5913 Mammography 20-2-97 □ 5913 left lateral 31-12-96

Pt 6128 Appearance of microcalcifications :LCIS 3 mm.



MAMMOGRAPHY LEFT 2-6-1998 MICROCALCIFICATIONS

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

GROUP A	No. of	No. of cases		Age (years)			Size				Rx			DATG	
	cases	Right	Left	Min	Max	Mean±SD	Min	Max	Mean±SD	Neg.	Susp	Positive	Neg.	Sosp	Positive
ALH	2	1	1	53	53	53.0				1	1			1	
ADH	3	1	2	35	58	46.7±11.5				2	1			1	2
MAH	5	3	2	16	66	47.0±19.0			and the second s	5					5
LCIS	10	2	8	41	72	49.6±10.3	3	3	3.0	8	2			2	8
DCIS	5	2	3	45	51	47.0±2.8	2	8	4.0±2.7	5				2	2
MCIS															
LMC	1	4		49	49	49.0				1				1	
DMC															
MMC	1		1	45	45	45.0	15	15	15.0	1					1
LIC	8	3	5	40	72	55.6±12.6	8	25	15.0±7.3	5		3			8
DIC	67	34	33	31	81	57.2±12.2	3	80	21.2±13.9	16	16	35		2	65
MIC	1	1	0	46	46	46.0				1				1	
Total	103	48	55	16	81	54.7±12.3	2	80	19.3±13.7	45	20	38			

Legenda:

ALH (athypical lobular hyperplasia)- ADH (athypical ductal hyperplasia)-MAH (mixed athypical hyperplasia)

LCIS (lobular in situ cancer)-DCIS (ductal in situ cancer)-MCIS (mixed in situ cancer)

LMC (lobular microinvasive cancer)-DMC (ductal microinvasive cancer)-MMC(mixed microinvasive cancer)

LIC (lobular invasive cancer) - DIC (ductal invasive cancer) - MIC (mixed invasive cancer)

Table 2. Overall diagnostic results by means of DATG toghether with RX Biopsy at first visit (group A)

GROUP B	No. of	No. of cases		Age (years)			Size				Rx			DATG	ÎÎ
	cases	Right	Left	Min	Max	Mean±SD	Min	Max	Mean±SD	Neg.	Susp	Positive	Neg.	Sosp	Positive
ALH	4	10	4	38	56	46.7±7.4		-		4			8	1	3
ADH	1	1		45	45	45.0	4	4	4.0	1				1	
MAH	5	1	4	47	83	62.0±13.7				5			1		5
LCIS	6	2	4	37	53	43.5±5.9				5	1			3	3
DCIS	2		2	51	65	58.0±9.9	5	5	5.0±0.0	1	1			1	1
MCIS	5	2	3	48	74	58.8±10.6			1	4	1			2	3
LMC	2	1	1	37	44	40.5±4.9				2			1	1	1
DMC	1	1	1	51	51	51.0				1				1 22	1
MMC								-		2					
LIC	3	3		42	62	50.7±10.3	6	20	13.0±9.9	2	1		1	1	2
DIC	8	3	5	45	77	56.6±10.1	8	38	19.5±12.8	3	2	3	3	1	4
MIC									- Second report of the				0.00	1 1	
Total	37	14	23	37	83	52.7±11.1	4	38	14.3±11.7	28	6	3			

Legenda:

ALH (athypical lobular hyperplasia)- ADH (athypical ductal hyperplasia)-MAH (mixed athypical hyperplasia)

LCIS (lobular in situ cancer)-DCIS (ductal in situ cancer)-MCIS (mixed in situ cancer)

LMC (lobular microinvasive cancer)-DMC (ductal microinvasive cancer)-MMC(mixed microinvasive cancer)

LIC (lobular invasive cancer) - DIC (ductal invasive cancer) - MIC (mixed invasive cancer)

Table 3. Overall diagnostic results by means of DATG toghether with RX Biopsy during follow-up (group B)

- 2°localization ?

Sc 9.1/15 T1FFE / FFE/M Dt 01:31 min

R

Scan 5 T2 Spair SENSE TSE

0 #





Scan 5 T2 Spair SENSE TSE

DATG Applications
Detection of Breast Cancer











Breast tumor during pregnancy



6389 right lateral
 23-6-2000
 26° week of pregnancy



6389 right lateral
2-8-2000
after biopsy





4779 after surgery: "Atypical lobular Hyperplasia"



Breast Cancer Familiarity: close follow-up Appearence of disease



Young Patient

17 year old: "papillary duct hyperplasia of the breast"



17 year old: "papillary duct hyperplasia of the breast" post-op.



3634-front left 23-6-87 Pre-op. 3634-front left 2-12-02 Post-op.

Monitoring the Therapy

Hormone Replacement Therapy

604 Long follow-up with HRT





Long follow-up with HRT and biopsy (Hyperplasia lobular and ductal)

h911- 12.79h







В

Without HRT

Antiblastic Therapy



At diagnosis

A 54-year-old woman. The external upper quadrant of the right breast shows an incomplete malignant ring composed of numerous short flowlines of external mammary, acromial and internal mammary origin, all ending in spatula terminations.



□ 3583 Right lateral 21-4-87

3583

After 2 cycles of preoperative chemotherapy, the DATG pattern has become negative. All the abnormal flowlines have largely disappeared. The subsequent biopsy revealed a 1 cm invasive ductal carcinoma.

After preoperative chemotherapy



□ 3583 Right lateral 2-6-87

1661 After antiblastic therapy





□ 1661 Left frontal 6-6-80

□ 1661 Left frontal 19-6-80

1661 Monitoring antiblastic therapy



1661 Left XRM 29-5-80At diagnosis

1661 Left XRM 22-8-80 After antiblastic therapy





□ 2423 Left frontal 1-10-82

□ 2423 Left lateral 1-10-82

2423 After 2 months of Tamoxifen



□ 2423 Left frontal 2-12-82

□ 2423 Left lateral 2-12-82

Benign: mastitis (after 14 days of antibiotics)





Integrated Diagnosis





34 year old patient Hormonal stimulation for infertility

A Ductal Infiltrating Carcinoma G3



<mark>3N+/15</mark>

B: Ductal Infiltrating Carcinoma with intraductal G2 Controlateral is normal Patient with fine needle aspiration (elsewhere) positive for infiltrating ductal carcinoma. A The DATG shows a second neoplastic localization B

Other Interesting Cases

2125 von Recklinghausen's disease



□ 2125 Right lateral

□ 2125 Right lateral

2125 von Recklinghausen's disease



□ 2125 Left lateral

□ 2125 Left lateral

4797 Angioma without heat transmission



□ 4797 Left: angioma 21-3-91

□ 4797 Left lateral 21-3-91

3786 Herpes zoster



□ 3786 Left frontal 1-3-88

3786 Left frontal 1-3-88
 DATG "cool"



DATG pattern remains the same over 16 years (in absence of pathology)





□ 1041 15-3-79 □ 1041 9-11-95

DATG is useful for screening

DATG pattern remains the same over 20 years (in absence of pathology)





□ 114 27-12-79 □ 114 9-3-99

DATG is useful for screening

DATG pattern remains the same over 25 years (in absence of pathology)





□ 657 14-3-78

□ 657 27-11-03

DATG is useful for screening
DATG pattern changes in presence of pathology



2° Visit : suspect



•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



в

D





NEXT STEP

 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

<u>International clinical protocol coordinated by</u> Geneva Foundation for Medical Education and Research & World Health Organization (WHO). Department of Reproductive Health and Research

Geneva Foundation for Medical Education and Research

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Dynamic angiothermography A new technology for breast cancer screening and diagnosis



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EQUIPMENT







Equipment 2009











Equipment 2009















CAD – Computer Aided Diagnosis



Comparison with the other technique

The entire history of the patient



Classificationsof Diseases and Functioning&Disability

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)

International Classification of Disease rev.2002

2007 ICD-9-CM is here! (effective 10/1/06)

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Procedures

>> Tabular Index >> Alphabetic Index

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88.89 Thermography of other sites Lymph gland thermography Thermography NOS

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Immunohistochemical expression of VEGF-A and its ligands in non-neoplastic lesions of the breast sampling-assisted by dynamic angiothermography

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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

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Prof.Gian Carlo Montruccoli

Thank You



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