



Training in Reproductive Health Research 2007 WHO 21 March 2007, Geneva

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),

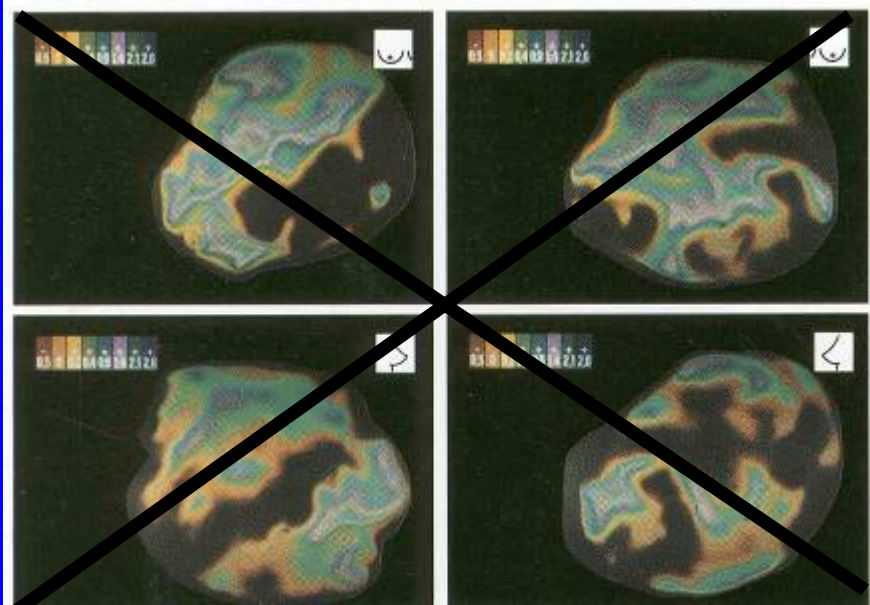
single photon emission computed tomography (SPECT),

thermography.

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

QUANTITATIVE vs. QUALITATIVE



Old Contact Thermography

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



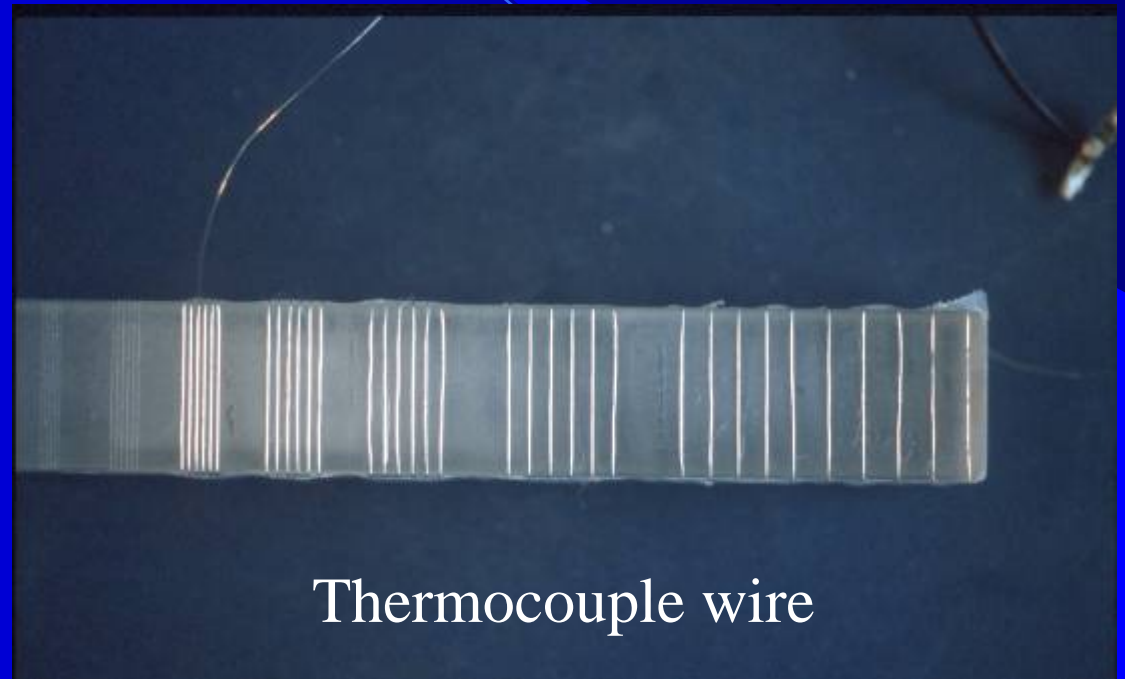
Dynamic Angiothermography -DATG

- Qualitative method
- Based on the detailed patterns of functional blood flows

TEST 1



- 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 1

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

Separate
lines

Our plate

TEST 1 A

Lines not
separate

Commercial plate

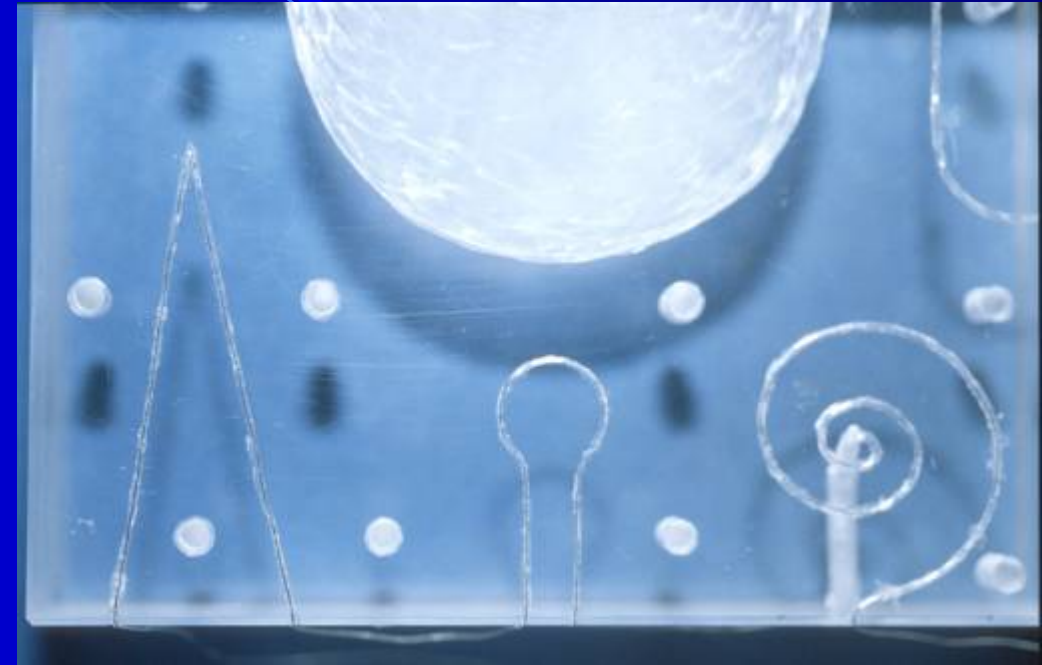
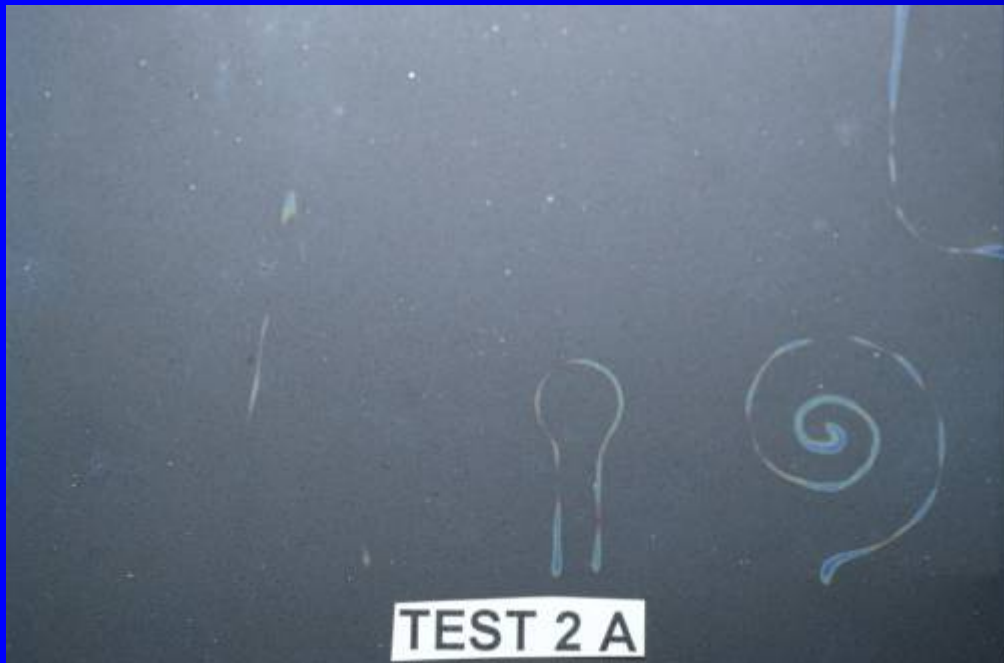
TEST 1 B

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)

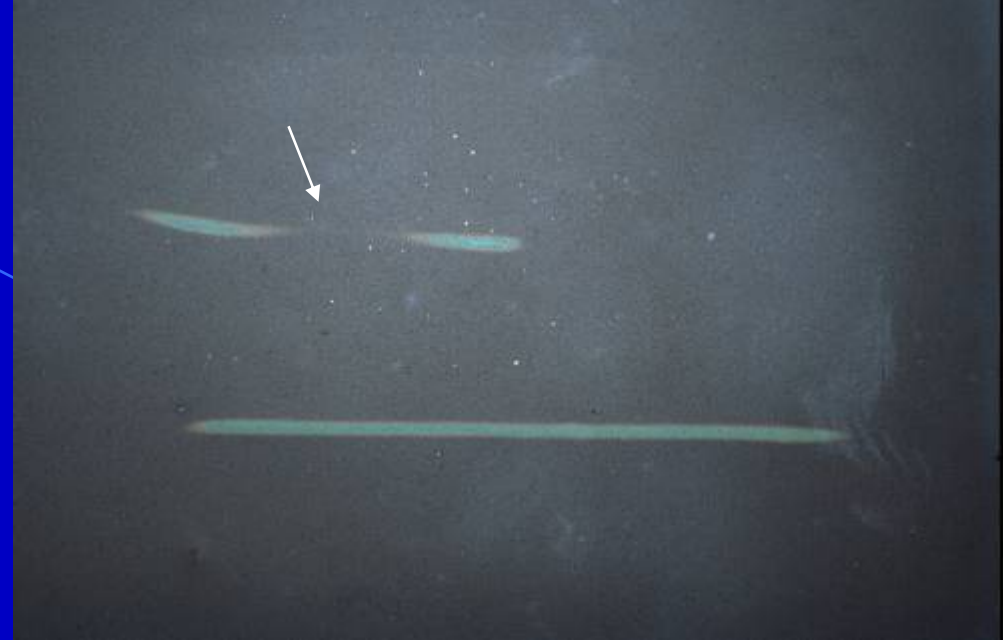
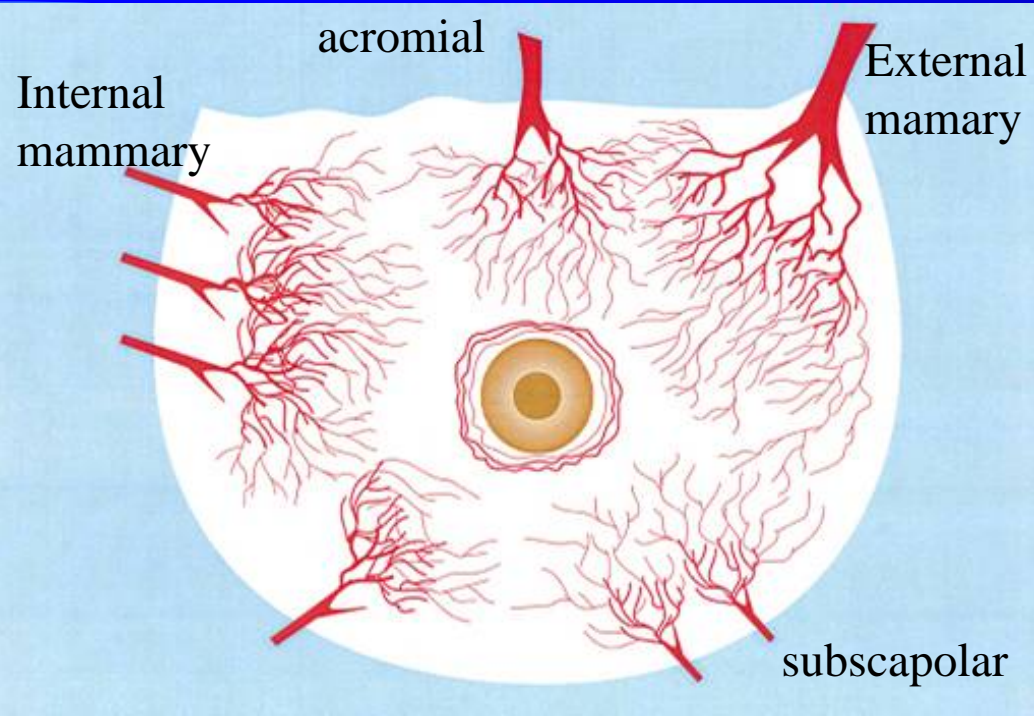


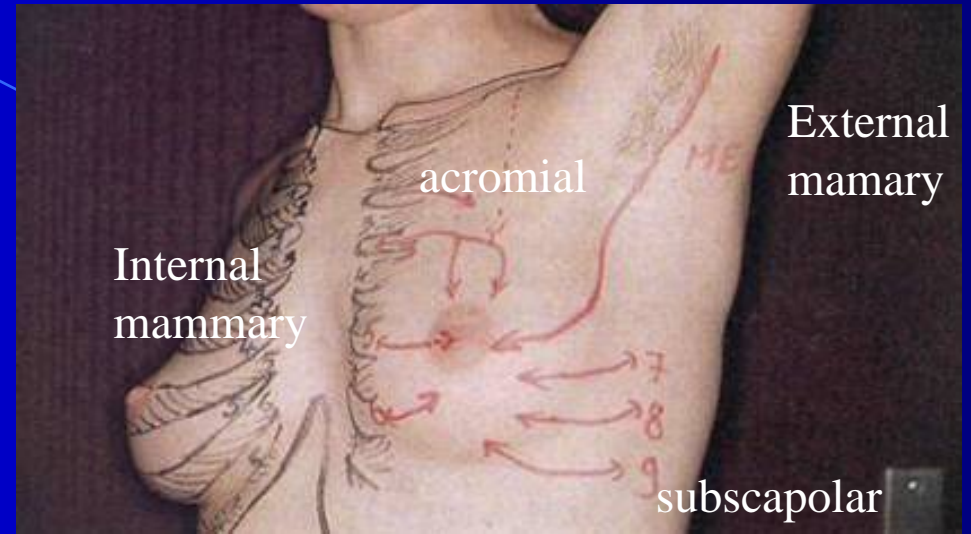
Plate sensitivity

- 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

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



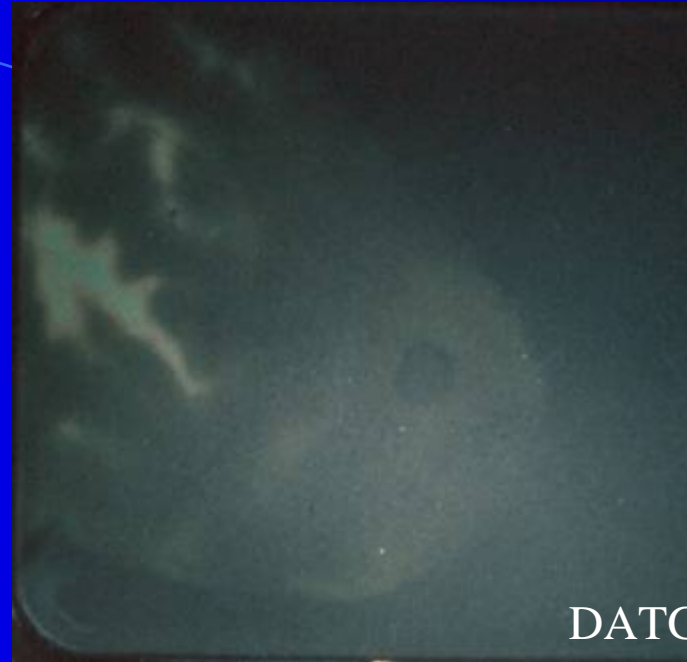
➤ Cutaneous projection of the breast's main arteries.

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



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 autopolymerizable resin : demonstration of a major type I external mammary artery.



Normal flowlines

DATG

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.

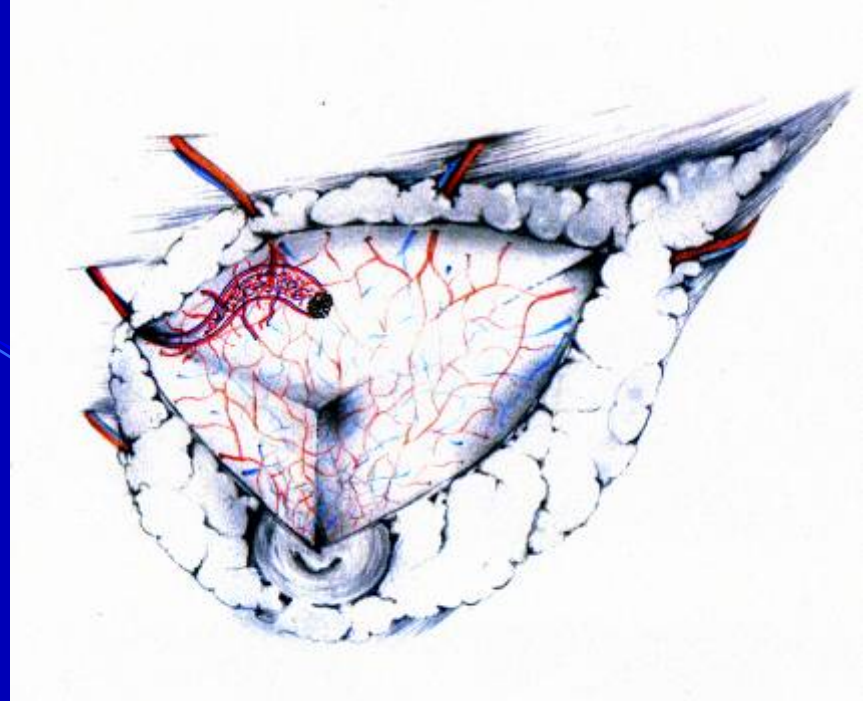


Fig. 10. — Dissection anatomique de l'artère acromio-thoracique après injection au latex : ici apparaît sa composante postérieure musculaire à destinée glandulo-cutanée (flèches rouges. La flèche noire indique l'origine de l'artère).

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



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.

ID.3. n. 87

Frammento di tessuto fibro-adiposo, riferibile a parenchima mammario, misurante cm 8 di asse maggiore.
 Al taglio appare costituito da un tessuto bianco-roseo, nodulare.

Ax3
 Em4
 Cx3
 Dx3

13 prelievi random

Diagnosi:

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

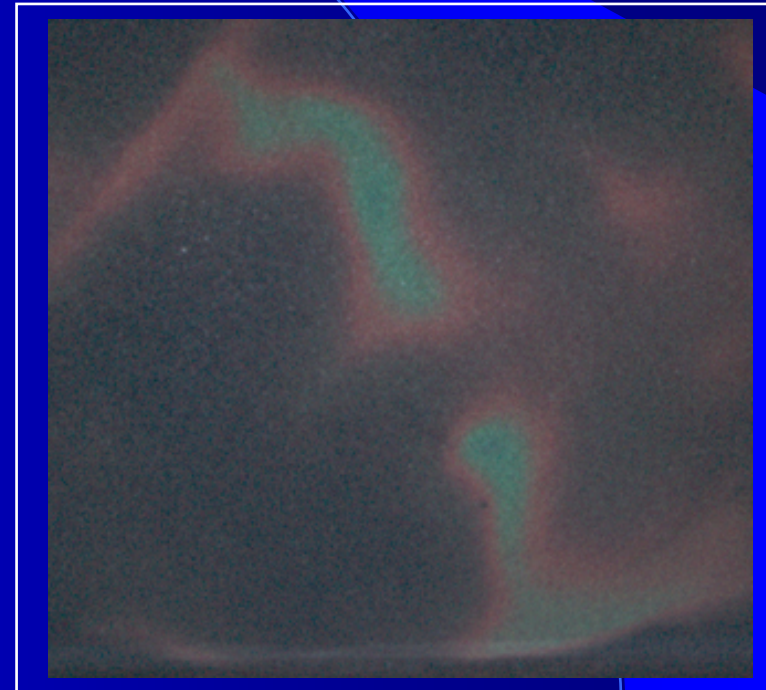
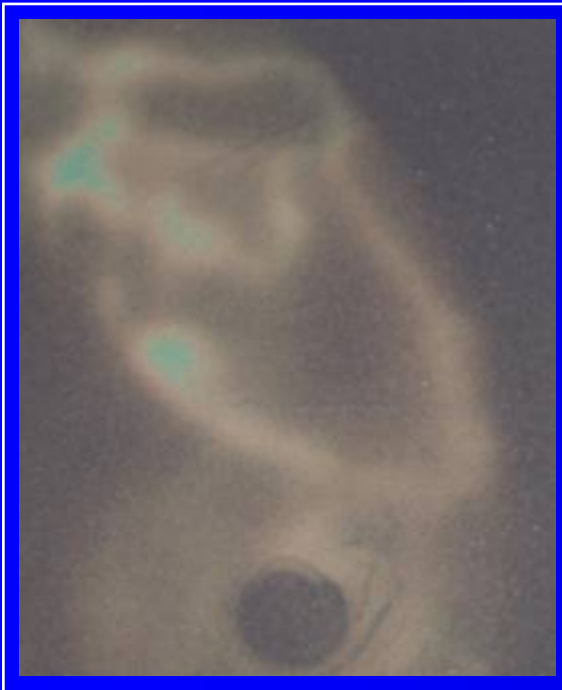
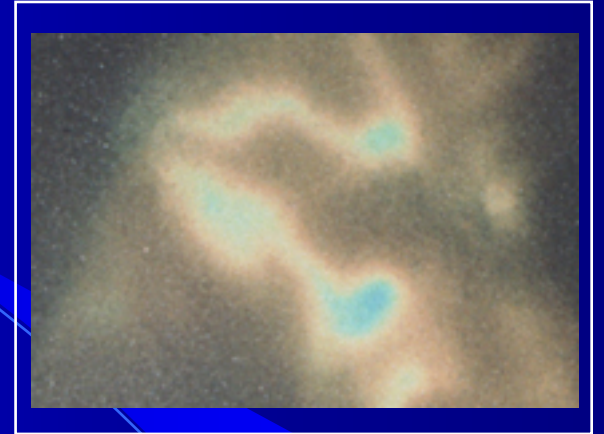
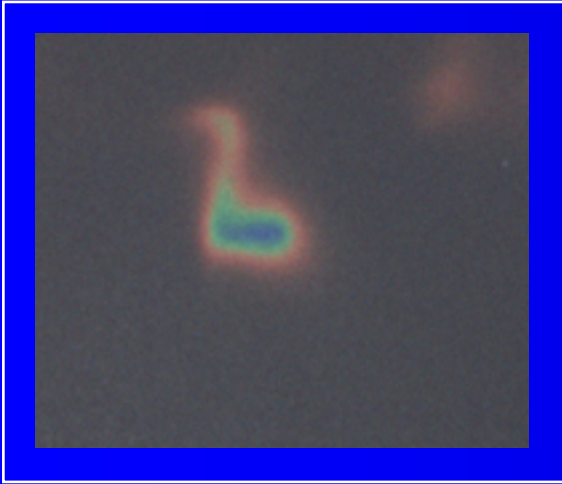
P. **Histological report**

Il Responsabile
 del Laboratorio

PER CONFERENZA
 PROF. W.F. GRIGNONI

SUSPICIOUS FLOWLINES

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

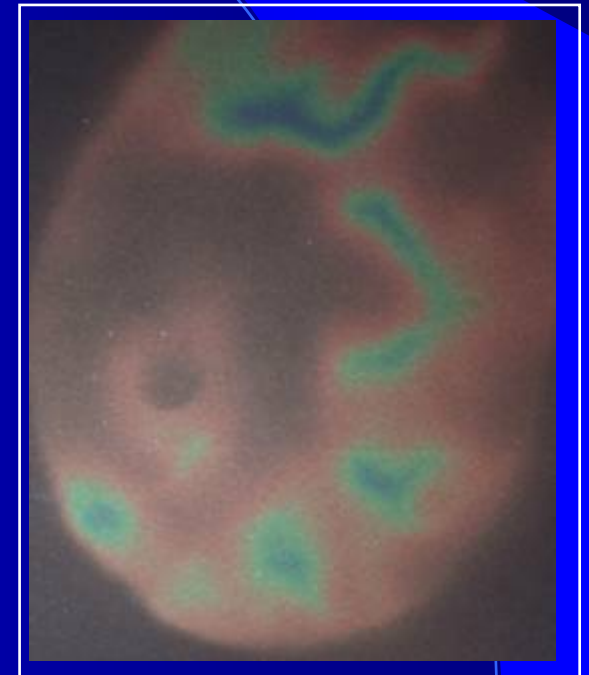
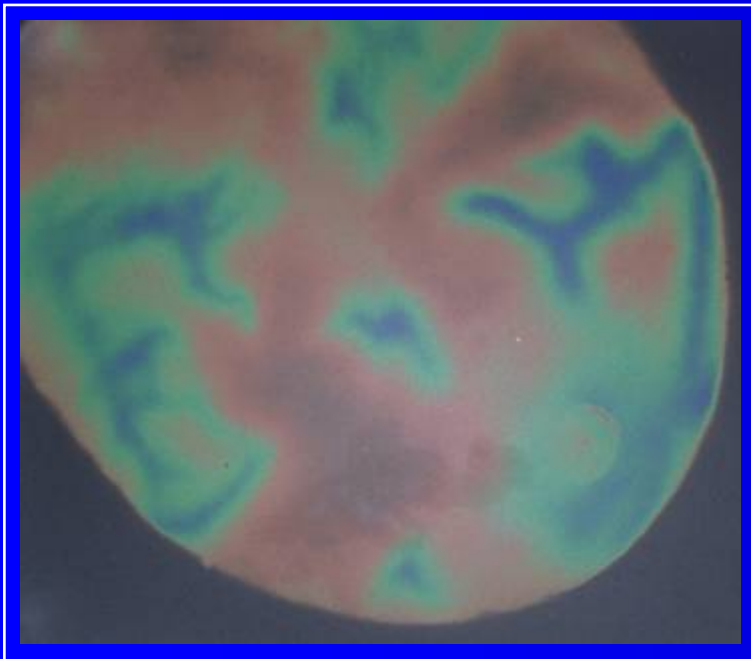
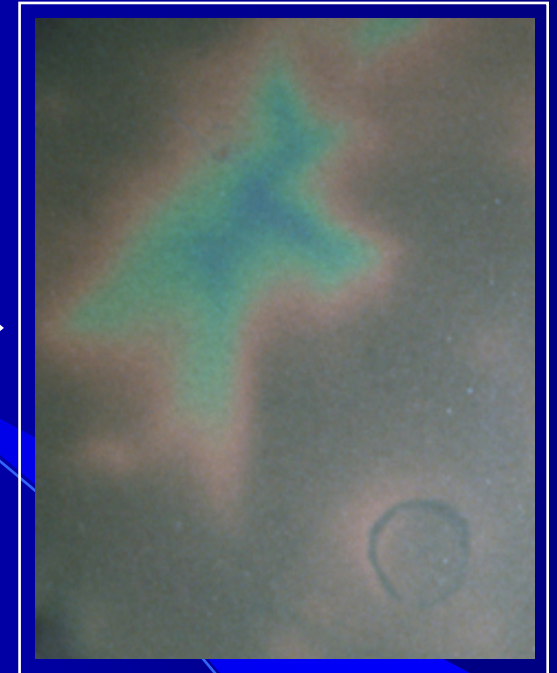


MALIGNANT FLOWLINES

• 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)

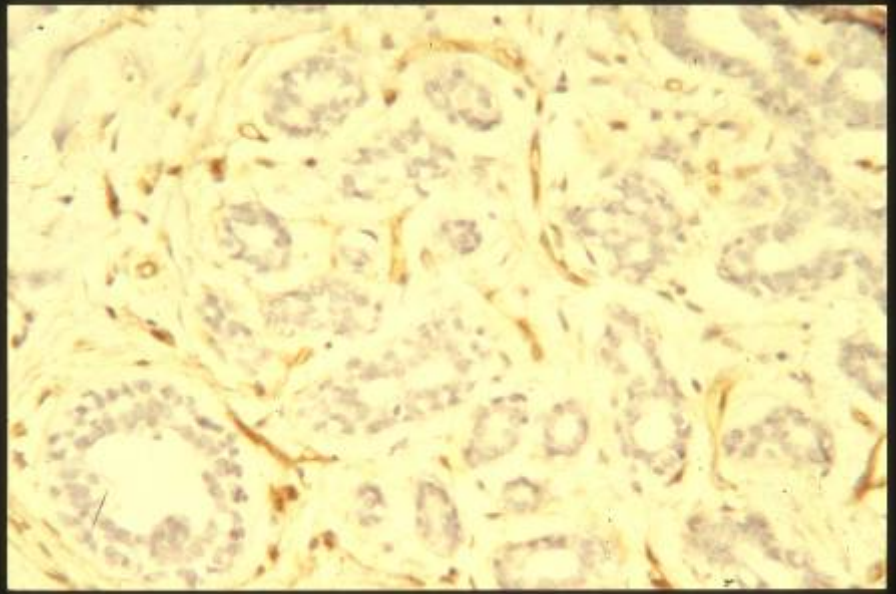


36 years old

Ultrasound normal

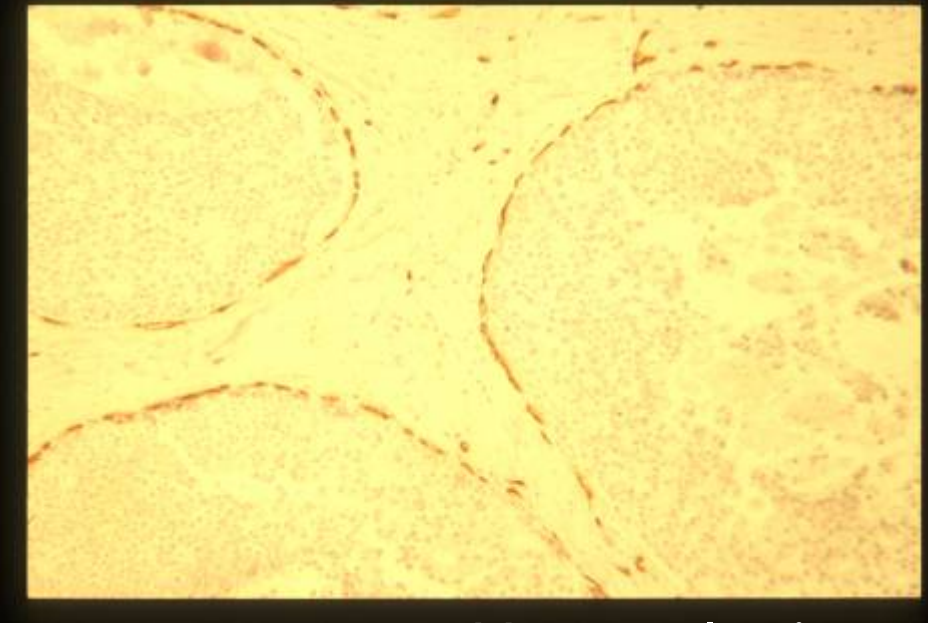
Breast Cancer in Family:
Mother tested positive
one year later

- 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

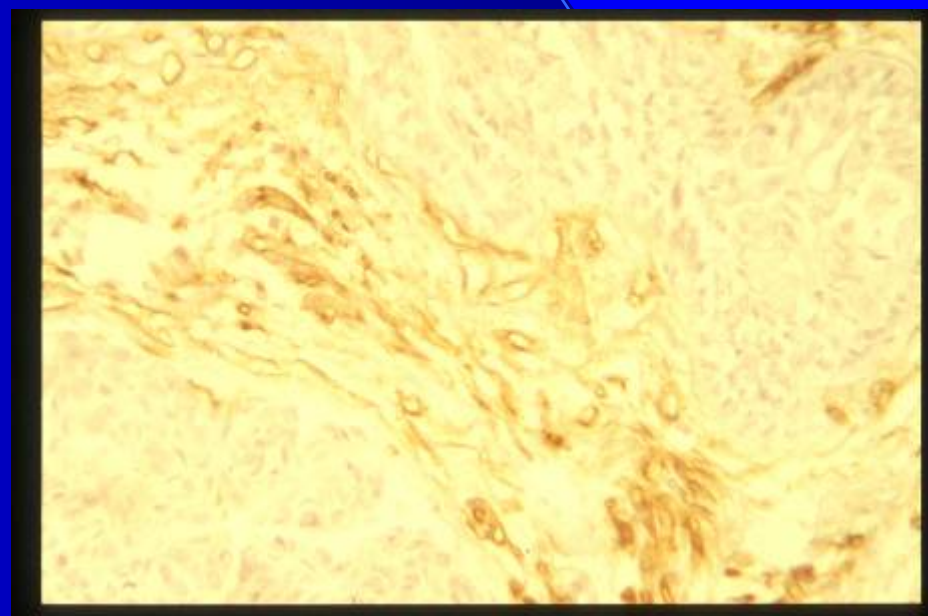
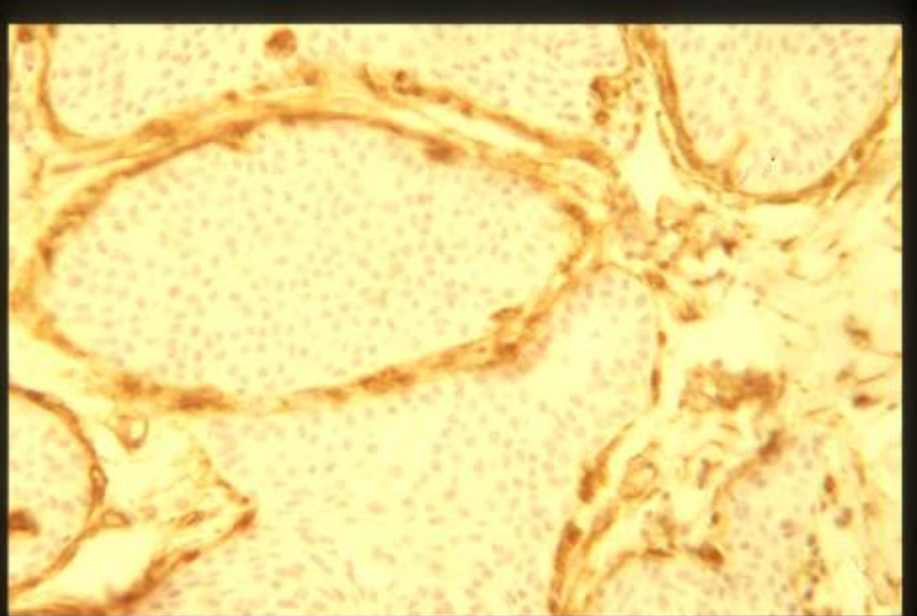
In situ Cancer



Hyperplasia

Progression of angiogenesis

Invasive cancer



Histological findings

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

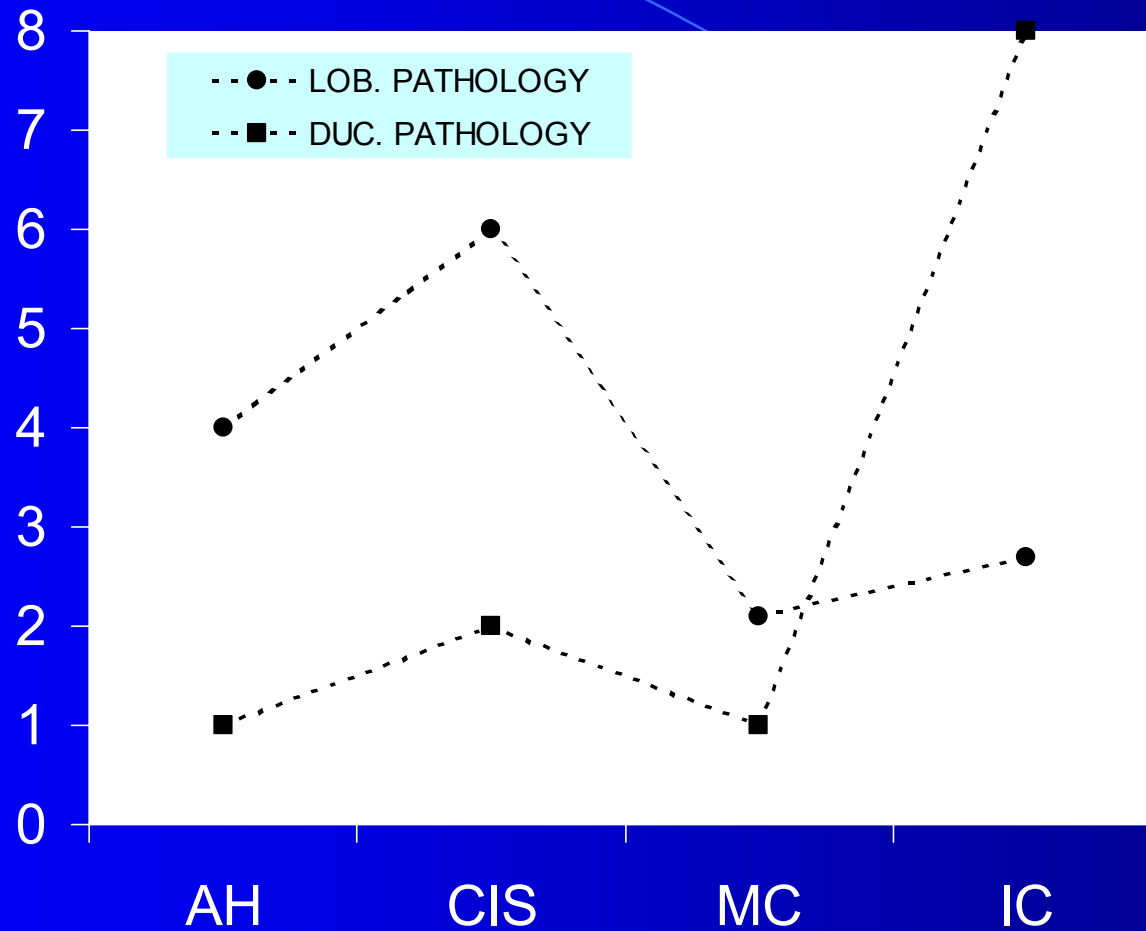
■ Note first that the rate of epithelial lesions runs as high 70% if simple hyperplasia is considered. (Molecular tests showed a loss of heterozygosity in 90% of hyperplasia cases)

■ 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	30.71
Mastitis and/or ectasia	184	17.28	
Simple ductal hyperplasia	182	17.09	39.91
Florid ductal hyperplasia	243	22.82	
Papillomatosis	48	4.51	4.51
Atypical duct hyperplasia	8	0.75	4.13
Atypical lobular hyperplasia	23	2.16	
Mixed atypical hyperplasia	13	1.22	
Ductal carcinoma in situ	16	1.50	5.54
Lobular carcinoma in situ	28	2.63	
Mixed carcinoma in situ	15	1.41	
Ductal microinvasive carcinoma	2	0.19	0.85
Lobular microinvasive carcinoma	5	0.47	
Mixed invasive carcinoma	2	0.19	
Ductal invasive carcinoma	130	12.21	14.09
Lobular invasive carcinoma	16	1.50	
Mixed invasive carcinoma	4	0.38	
Malignant phyllodes	3	0.28	0.28
TOTAL	1.065	100%	100%

DATG-detected Lobular and Ductal Pathology

Number of cases



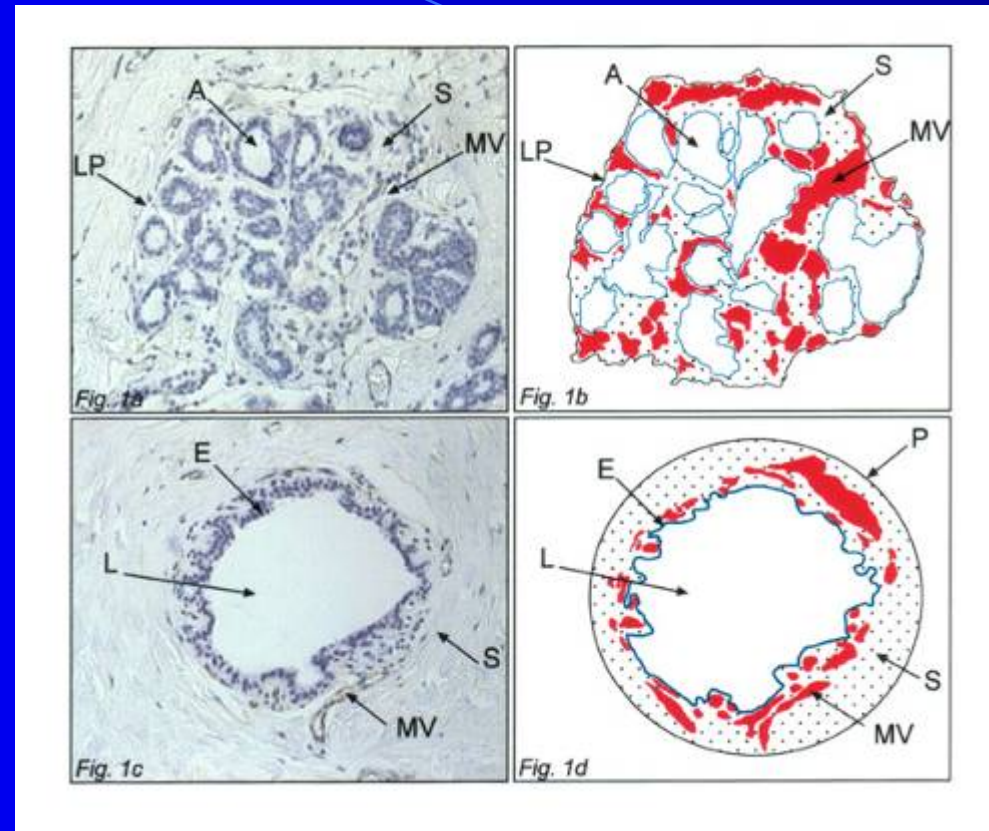
AH: ATYPICAL HYPERPLASIA; CIS: CANCER IN SITU;
MC: MICROINVASIVE CANCER; IC: INVASIVE CANCER

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.

Abstract Submission Form

Details of the submitting speaker:

Surname:

Schmitt

First Name: Fernando

Title: Prof

IMMUNOHISTOCHEMICAL EXPRESSION OF VEGF-A AND ITS LIGANDS IN NON NEOPLASTIC LESIONS OF THE BREAST: CORRELATION WITH DYNAMIC ANGIOOTHERMOGRAPHY RESULTS

Longatto Filho A¹, Baltazar F¹, Costa SM¹, Milanezi F^{1,2}, D.Montruccoli³, G.C.Montruccoli⁴⁺, Schmitt FC^{2,5}

¹Life 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, ⁵Medical 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.

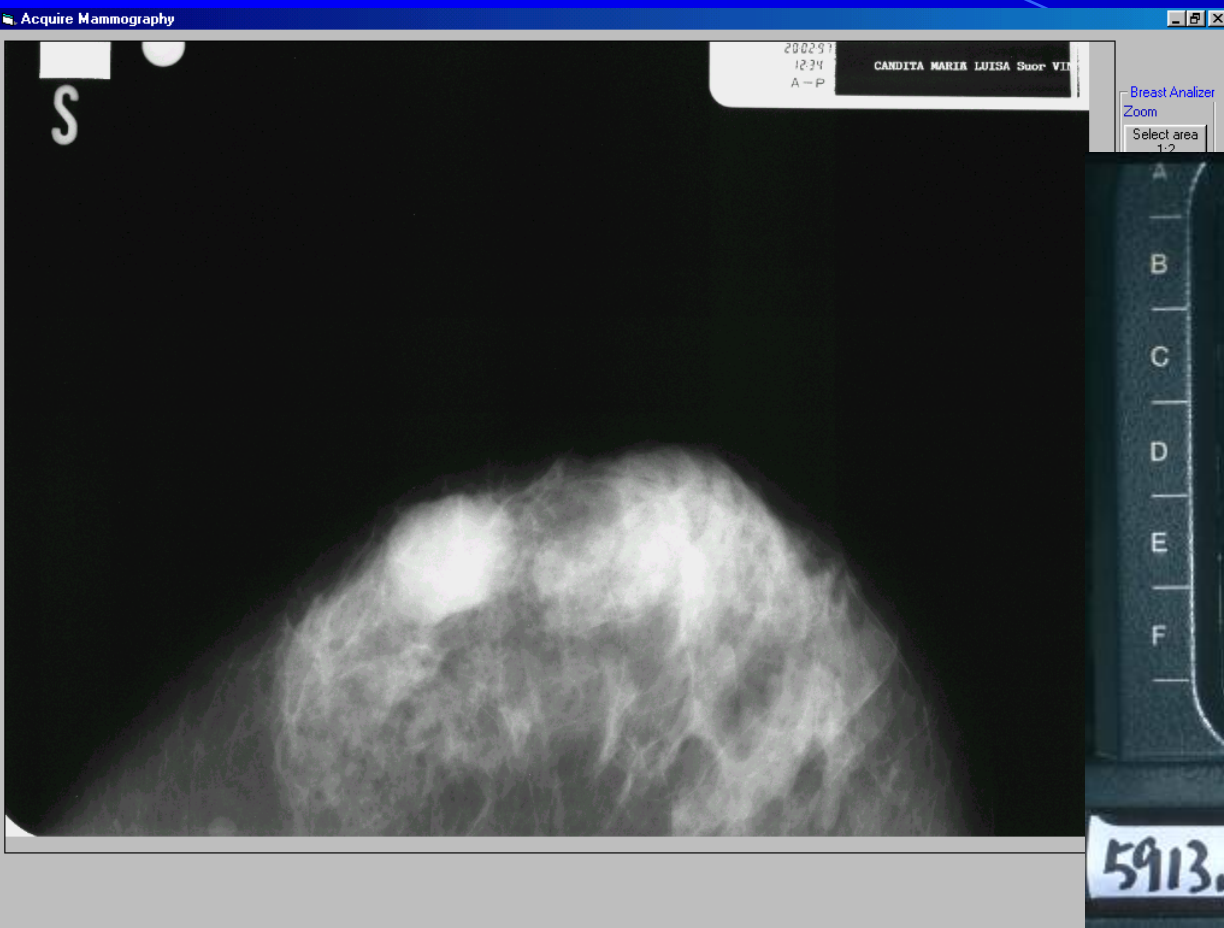
Acknowledgements. This study was partially supported by grants from FIGO.

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

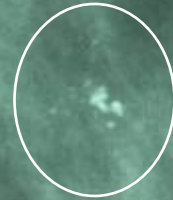


● 5913 Mammography 20-2-97

● 5913 left lateral 31-12-96

Pt 6128

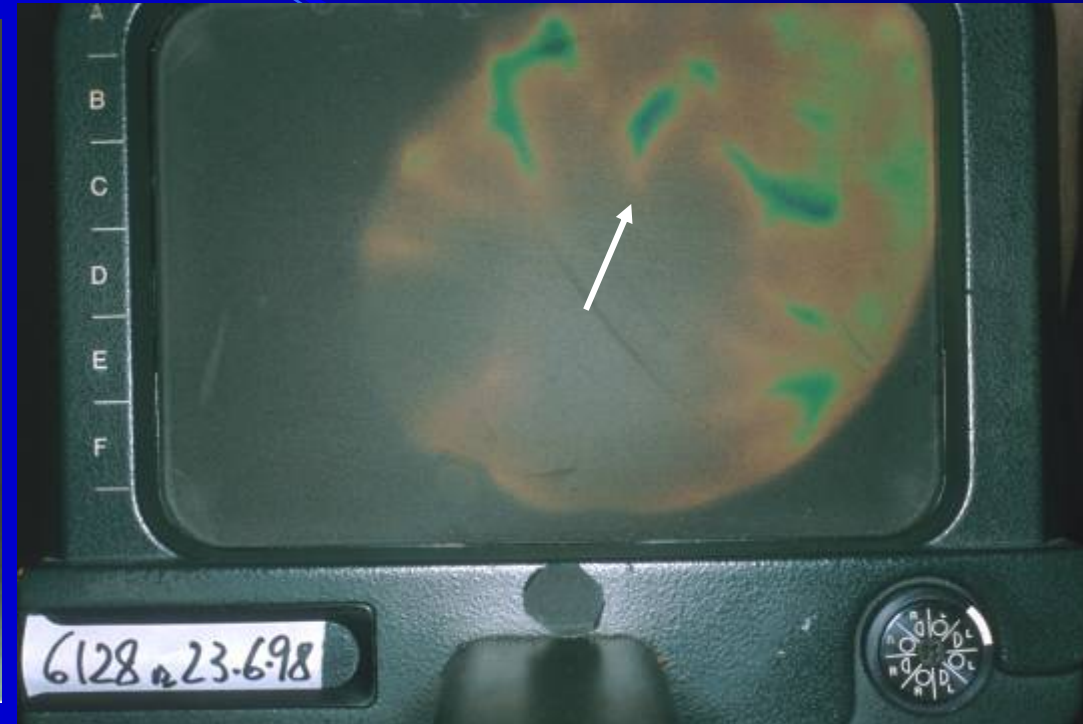
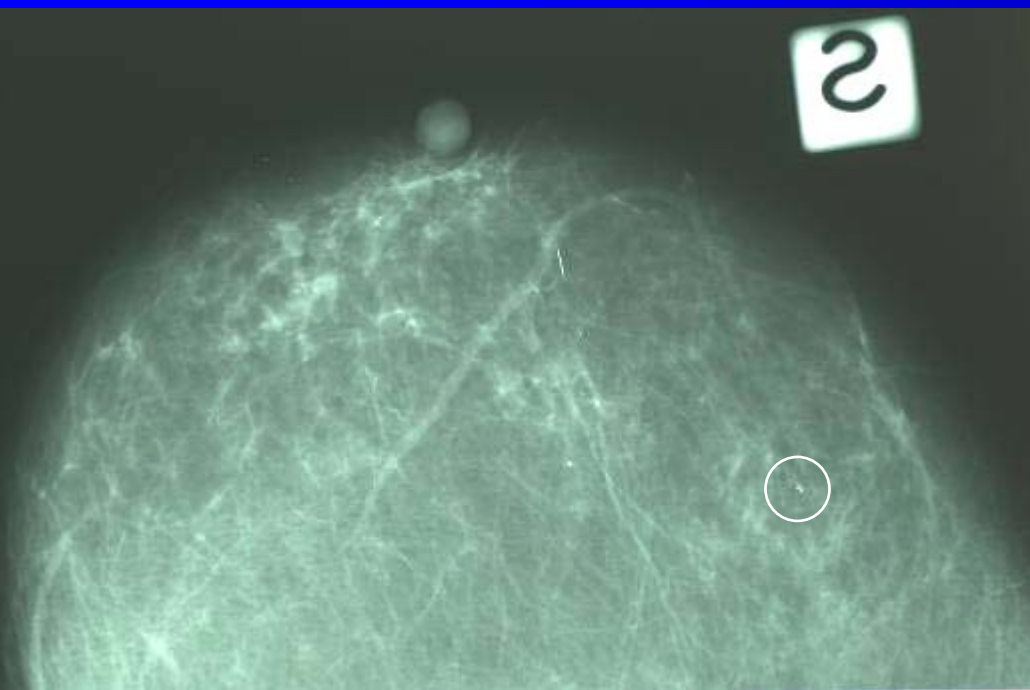
Appearance of microcalcifications :LCIS 3 mm.



MAMMOGRAPHY LEFT 2-6-1998 MICROCALCIFICATIONS

Pt 6128

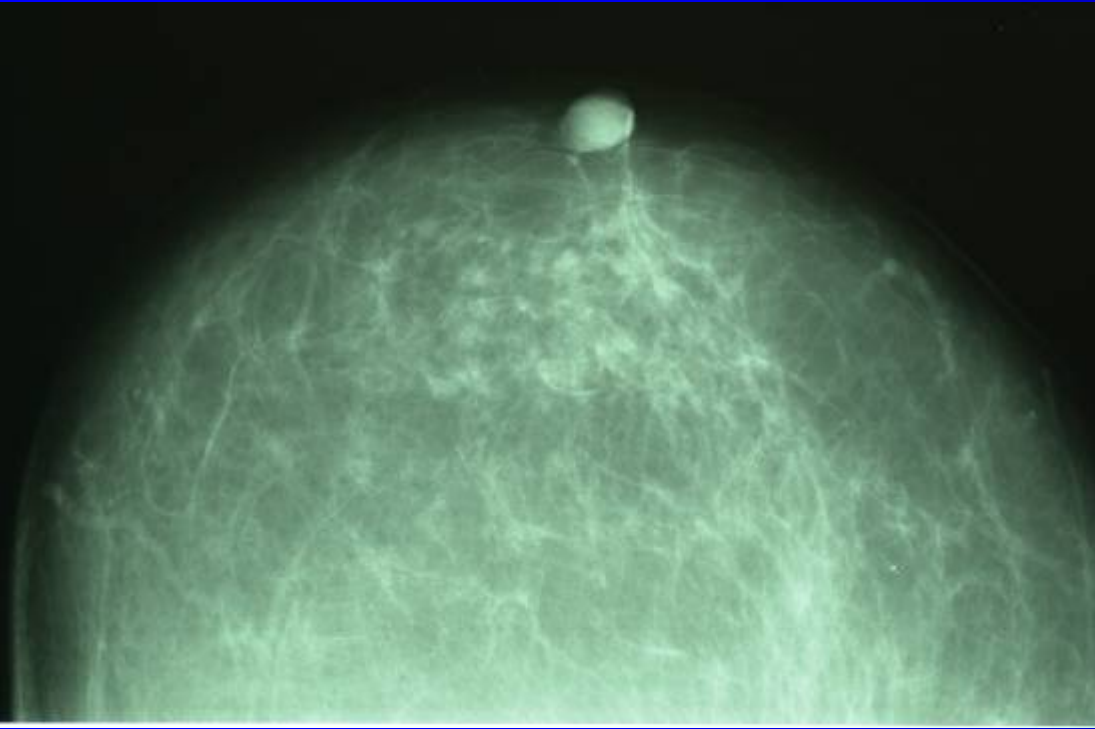
Appearance of microcalcifications :LCIS 3 mm.



● MAMMOGRAPHY LEFT 2-6-1998

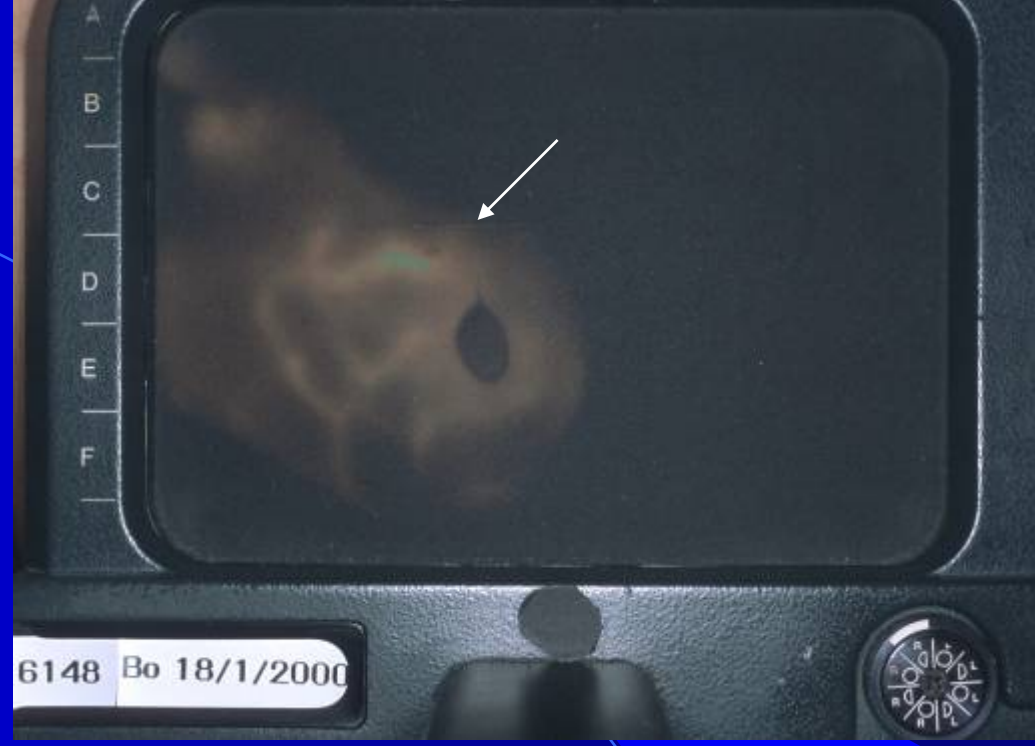
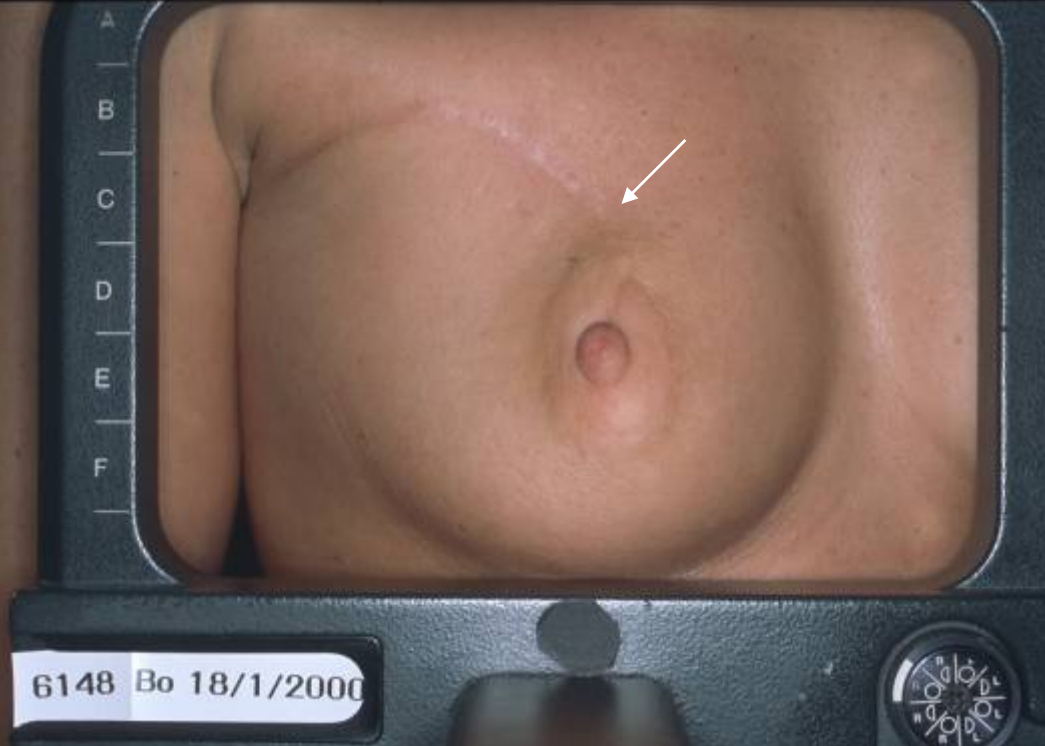
● Pz. 6128 Left Lateral Pre-op

Pt.6128 after surgery : Normal



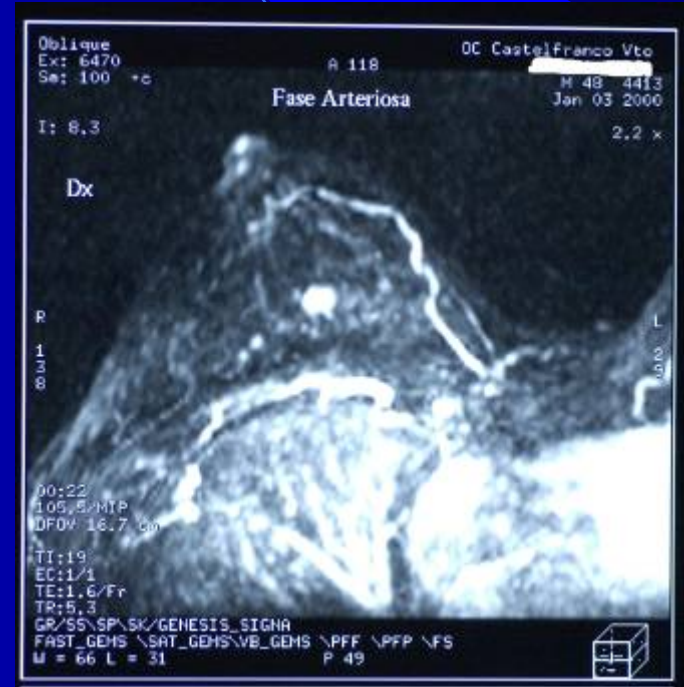
● Pz.6128 Mammography 25-10-1999

● Pz.6128 lateral left 18-10-2000



6148 correspondence between MRI and DATG

- A 40-year-old woman operated elsewhere for Ductal Infiltrating Carcinoma with radiotherapy. MRI shows a local relapse that is supported by DATG.





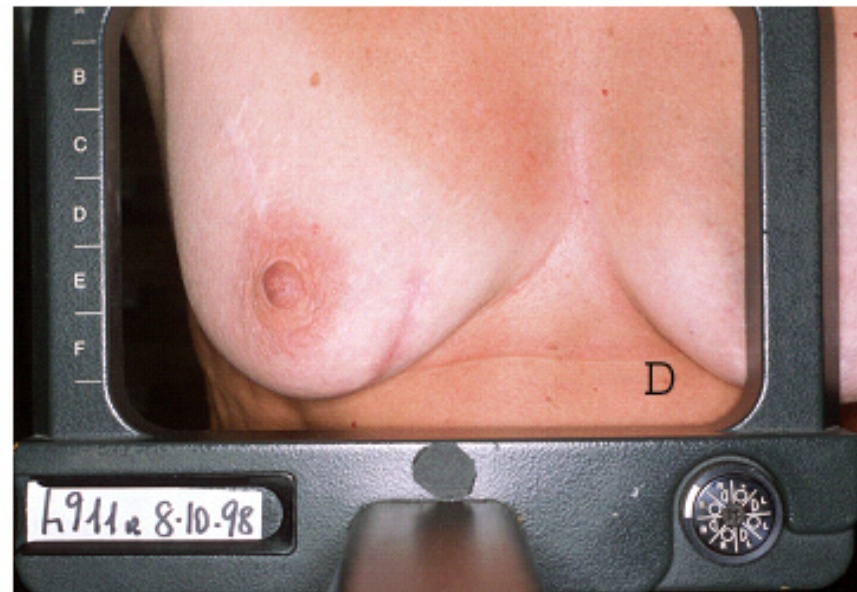
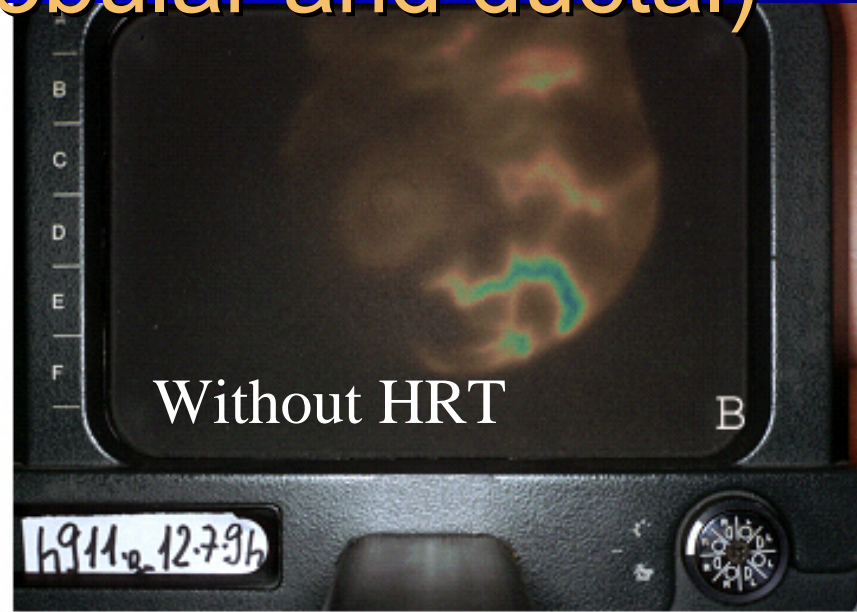
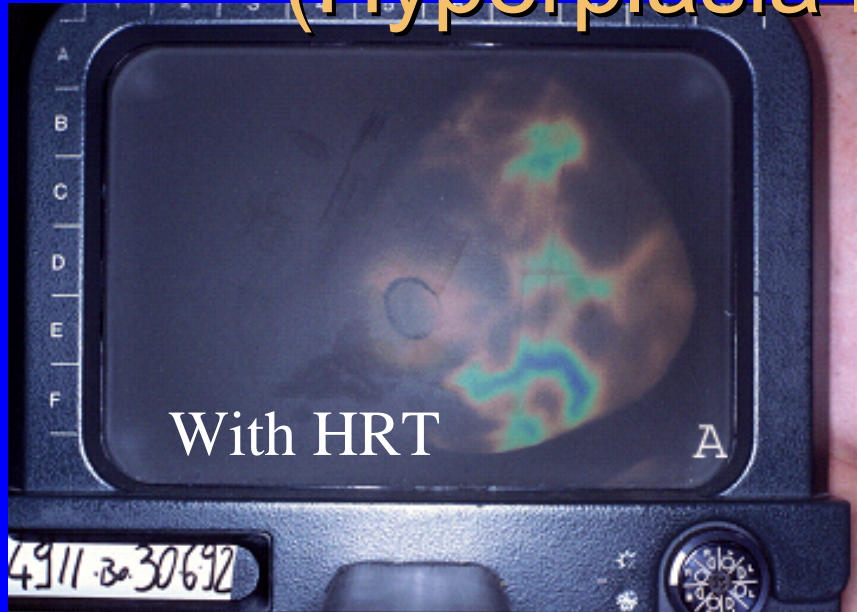
DATG Applications

Hormone Replacement Therapy

604 Long follow-up with HRT



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



Genetics



4779

BRCA1



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”

-post. op-

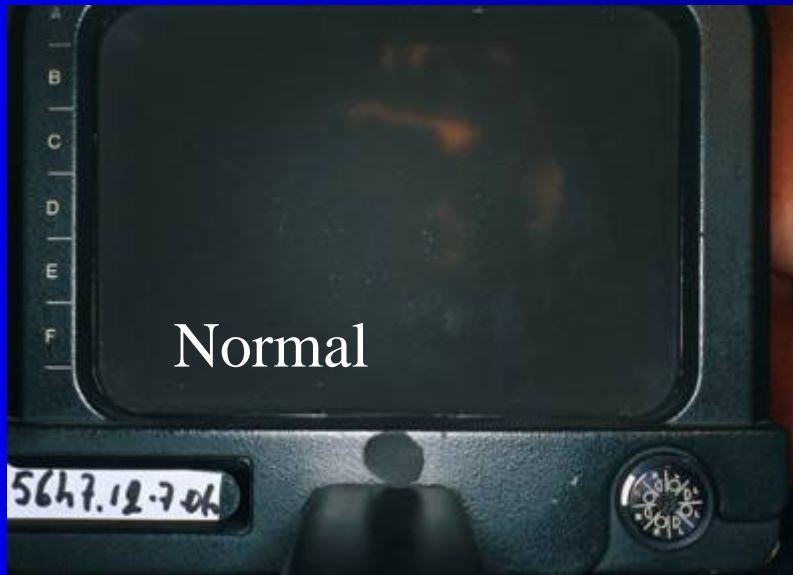
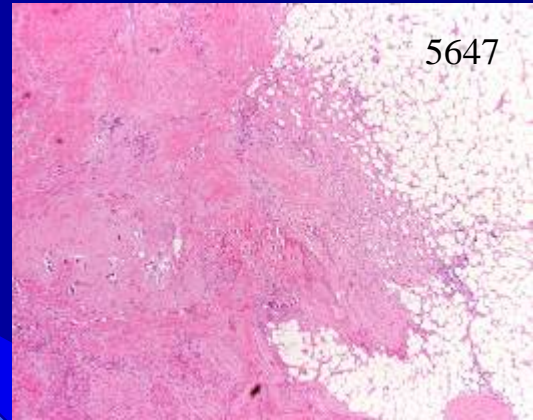
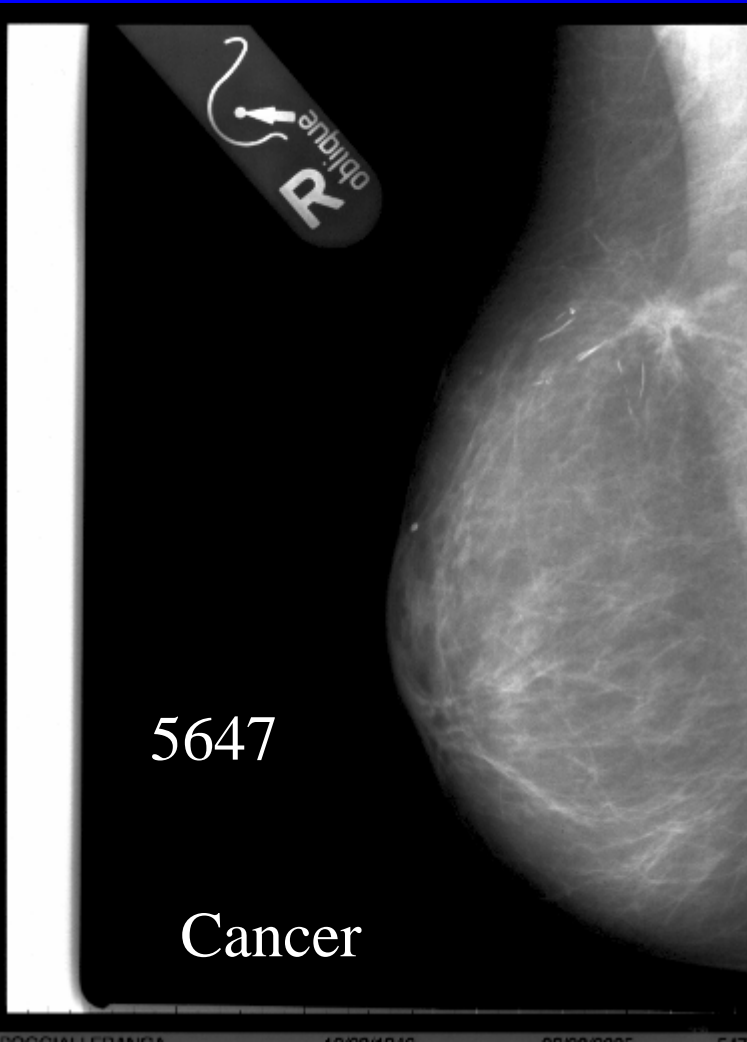


3634-front left 23-6-87
Pre-op.



3634-front left 2-12-02
Post-op.

Integrated Diagnosis



34 year old patient
Hormonal stimulation for infertility



3N+/15

A: Ductal Infiltrating
Carcinoma
G3

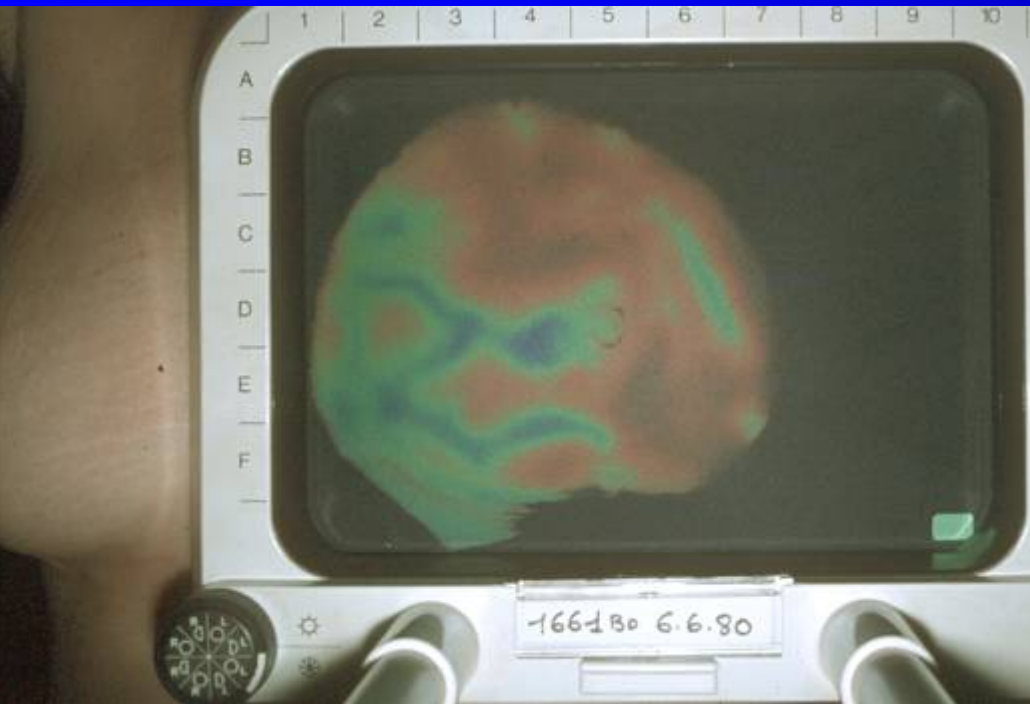
Controlateral is normal

B: Ductal Infiltrating
Carcinoma
with intraductal
G2

Patient with fine needle aspiration (elsewhere)
positive for infiltrating ductal carcinoma. **A**
The DATG shows a second neoplastic localization
B

Pre-operative Chemotherapy

1661

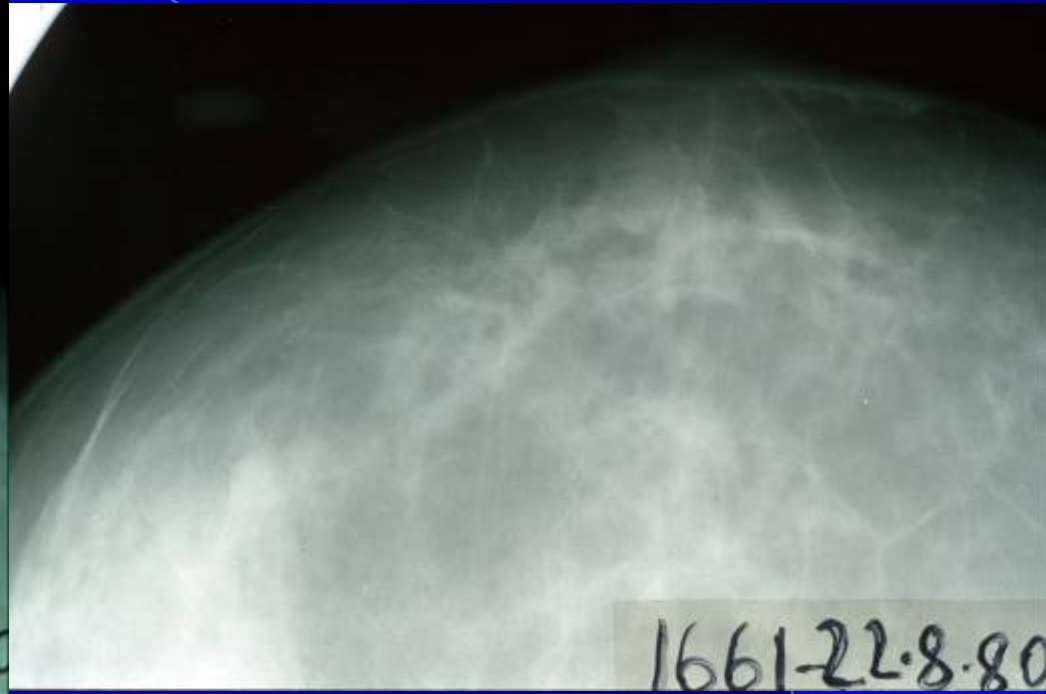
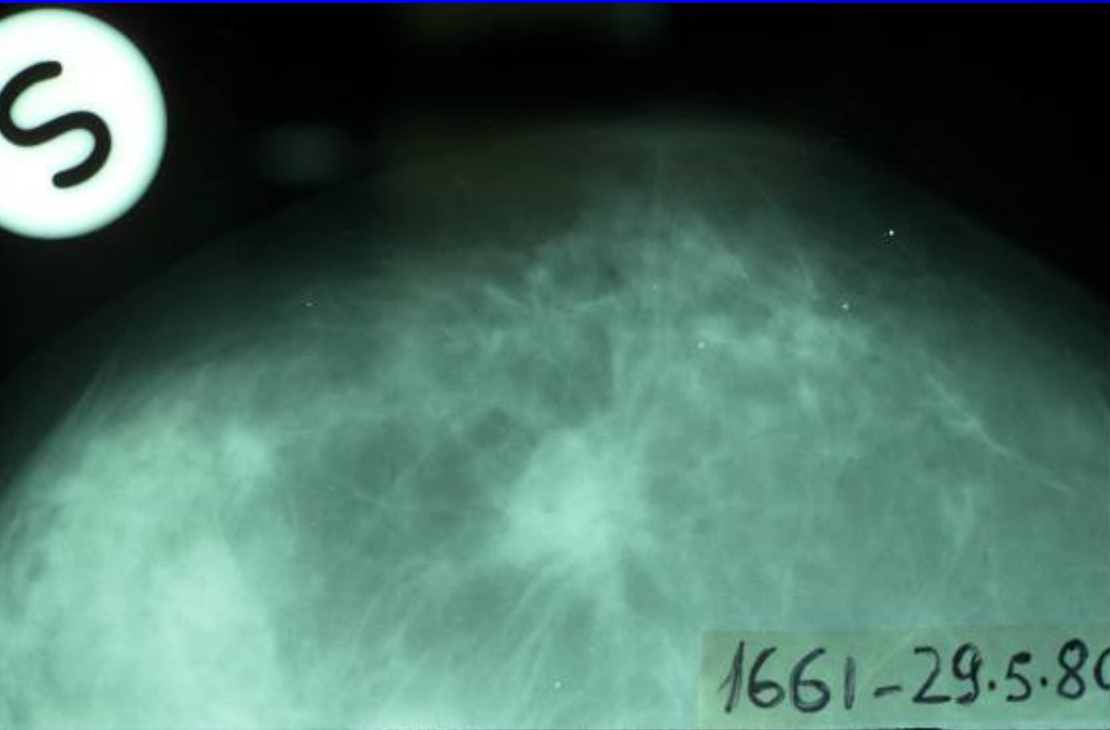


- 1661 front. Sin 6-6-80



- 1661 front. Sin 19-6-80

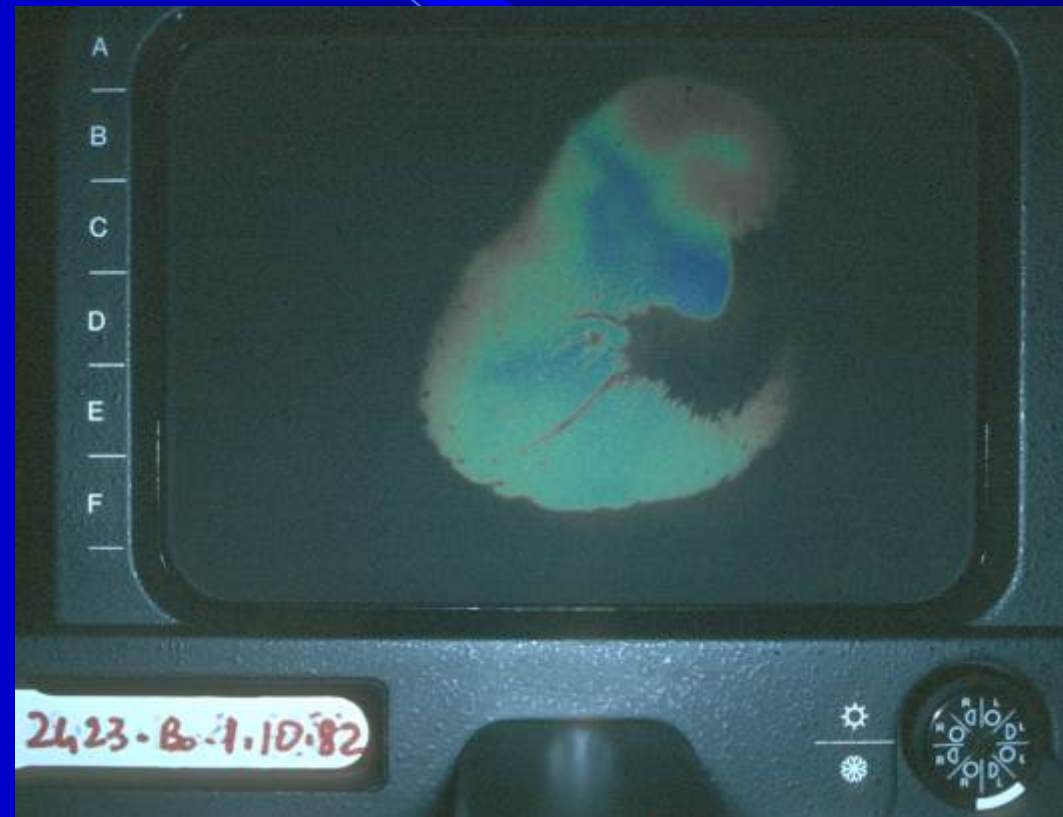
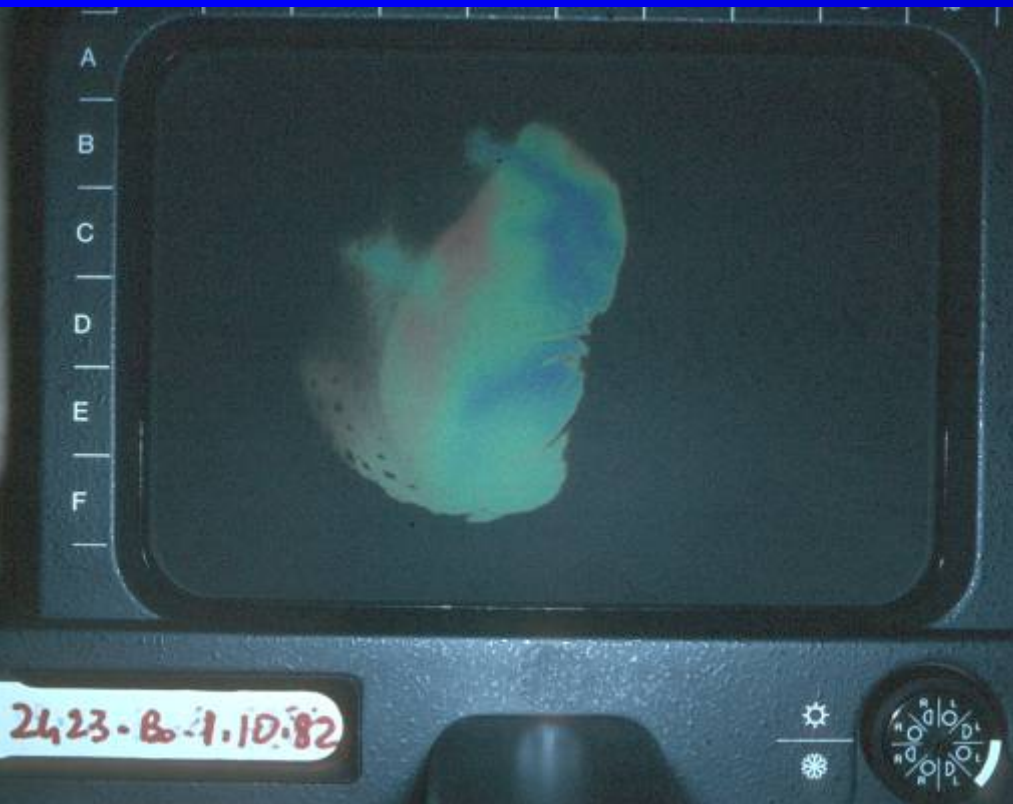
1661



- 1661 mammografia
- 29-5-80

- 1661 mammografia
- 22-8-80

2423
B.C.



2423

After two course
of pre-op chemotherapy



The image features a solid blue background. A thin white curved line starts from the top left and arcs across the upper portion of the frame. In the lower right area, there is a bright yellow triangle pointing towards the center. The word "Screening" is written in a bold, yellow, sans-serif font, centered horizontally and positioned between the white line and the yellow triangle.

Screening

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

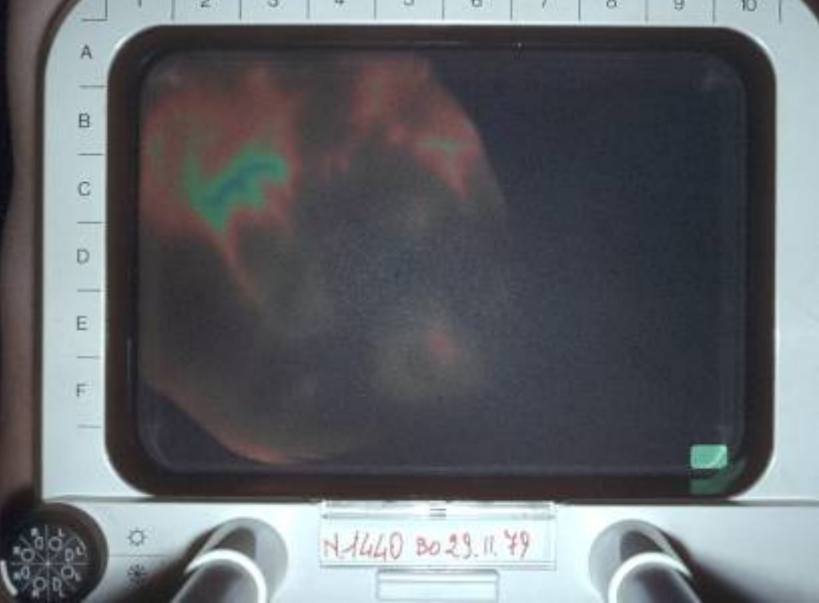
1° Visit : normal



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

Latest references

2003-6

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Bio-morphological events in the development of the human female mammary gland
from fetal age to puberty.
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G.C. Montrucoli, D. Montrucoli Salmi, F. Casali
A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms.
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*Daniele Montrucoli , Franco Casali , Stefano Brusori, Paolo Barillari,
Corrado Scipioni et Gian Carlo Montrucoli*
“L’angiothermographie dynamique : un avenir ?”
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G.C. Montrucoli, D. Montrucoli, D. Barnabe’, V. Altomare
Thermography fiction or reality?
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Vol. 83 Supplement N.3 pag.18 November 2-7 2003

*G. C. Montrucoli, D. Montrucoli, 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.
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AACR ANNUAL MEETING 27-31 MARCH 2004

*Viacava P., Naccarato A.G., Bocci G., Fanelli G., Aretini P., Lonobile A.,
Montrucoli 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*
Université 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





<p align="center"><u>PROT.1</u> <u>Time:6 month to 1year</u></p>	<p align="center"><u>PROT. 2</u> <u>Time:6 month to 1year</u></p>	<p align="center"><u>PROT.3</u> <u>Time:6 month to 1year</u></p>
<ul style="list-style-type: none"> • MAMMOGRAPHY BIRADS 1-2-3-4-5 • DATG • BIOPSY <p>N.Patients included: to discuss with the statisticians</p>	<ul style="list-style-type: none"> • MRI SUSPIOUS OR POSITIVE IN BRCA1-2 POSITIVE PATIENTS • DATG • BIOPSY <p>N.Patients included: to discuss with the statisticians</p>	<ul style="list-style-type: none"> • CLINICAL, MAMMOGRAPHICAL AND HISTOLOGICAL PROUVED BREAST CANCER SELECT FOR NEO-ADJUVANT CHEMOTHERAPY • TUMOUR ASSESMENT BY MAMMOGRAPHY (SIZE), US (SIZE) ,DATG(VASCULAR PATTERN) • NEO-ADJUVANT CHEMOTHERAPY FOR 3-6 COURSE • TUMOR RESPONSE ASSESMENT BY MAMMOGRAPHY ,ULTRASOUND, DATG AND HISTOLOGY <p>N.Patients included: to discuss with the statisticians</p>
<p>ESPECTED RESULTS: <u>IN CANCER:</u> AT LEAST THE SAME SENSITIVITY AND SPECICICITY WITH MAMMOGRAPHY</p> <p><u>IN PRE-INVASIVE LESION:</u> DATG MORE ACCUTATE WITH MAMMOGRAPHY</p>	<p>ESPECTED RESULTS: DATG CAN HAVE AT LEAST THE SAME SENSITIVITY AND THE SPECIFICITY OF MRI WITH LOW COST</p>	<p>ESPECTED RESULTS: DATG CAN BE MORE ACCUTATE THEN MAMMOGRAPHY OR US IN ASSESS TO TUMOUR RESPONSE TO CHEMOTHERAPY</p>

Dynamic angiothermography

A new technology for breast cancer screening and diagnosis



Prof. Giancarlo Montruccoli

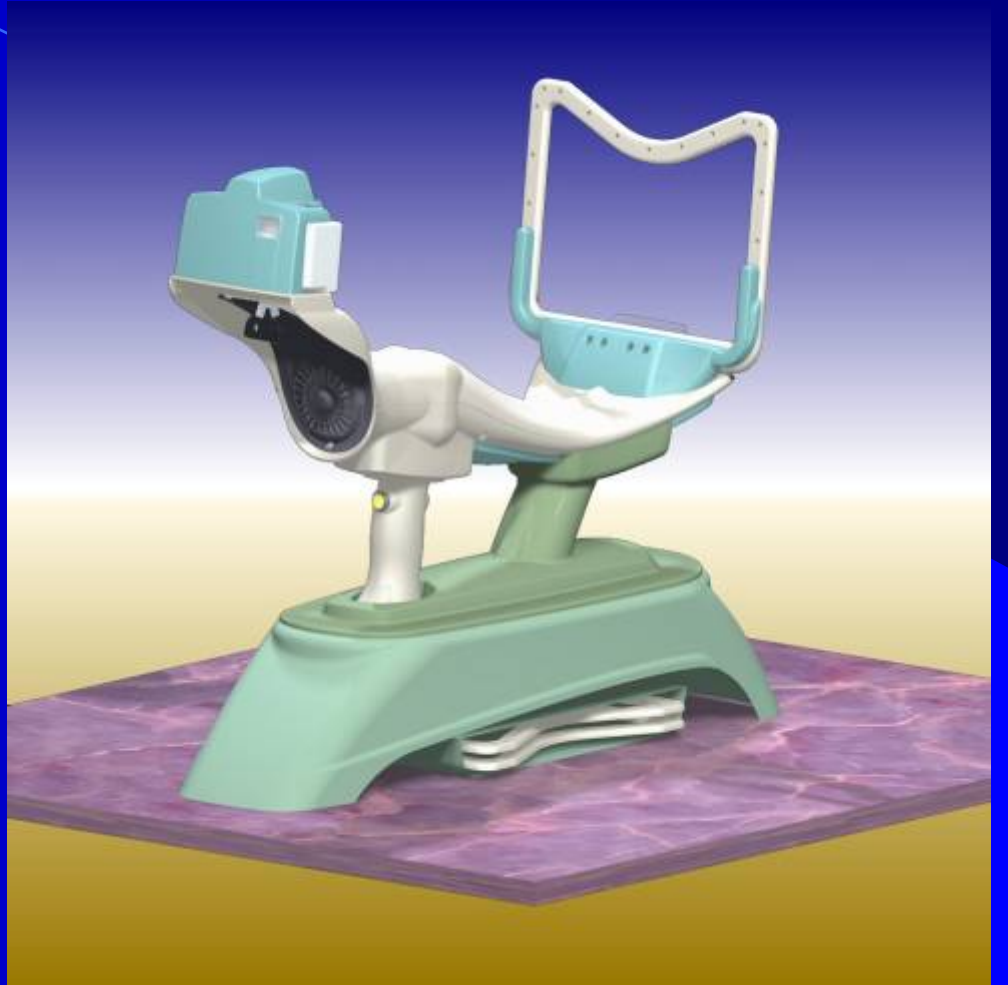
Gynaecologist, member of the Gynaecology and Oncology Committee
of the International Federation of Gynaecology and Obstetrics (FIGO)
Member of the International Society of Senology (S.I.S.) Committee of Experts

Prof. Daniele Montruccoli

Oncologist and Gynaecologist
Fellow in Oncology at the Institute Gustave - Roussy 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