Training in Reproductive Health Research 2008

WHO *27-02-2008*, Geneva

Dynamic Angiothermography

A new technology for breast cancer screening and diagnosis

Prof. Gian Carlo Montruccoli

Prof. Daniele Montruccoli

BARD1: Dr. Irmgard Irminger

Geneva Foundation
for Medical Education and Research

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

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),

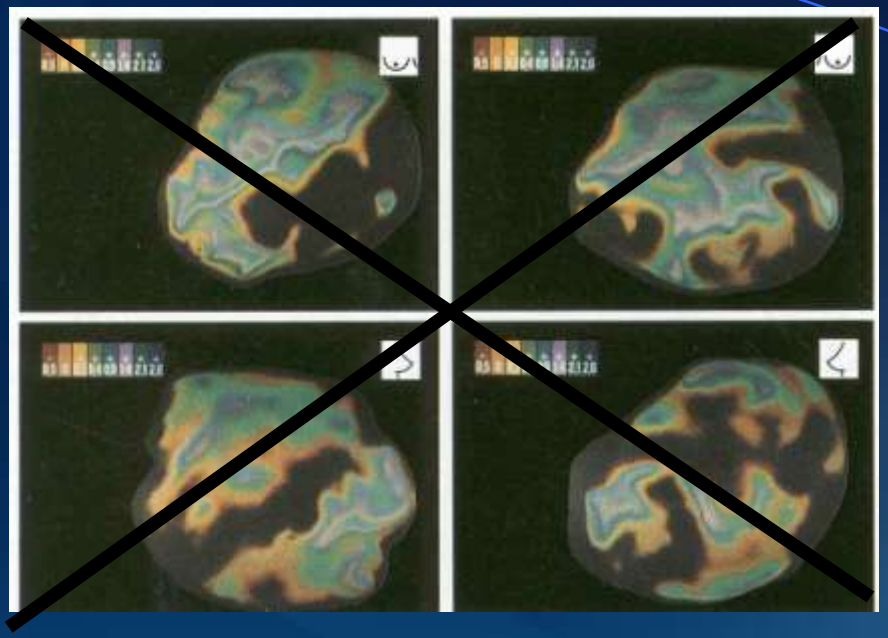
thermography.

http://women.cancer.gov/planning/whr0001/breast.shtml 21-2-08

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



Old Contact Thermography

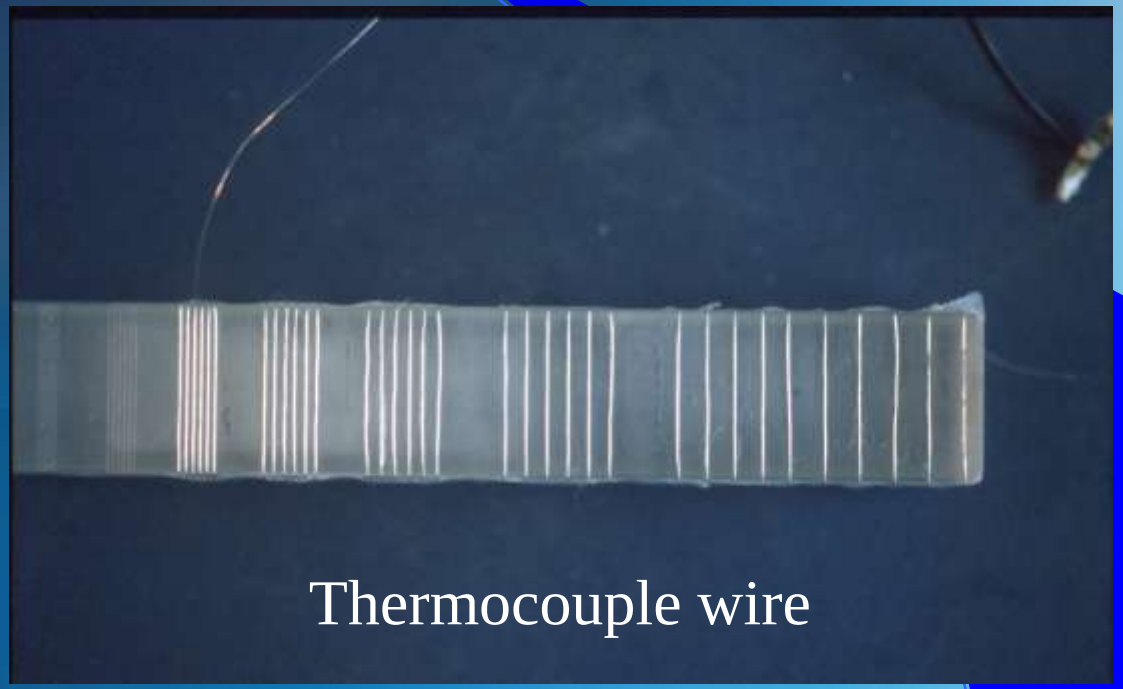
- Quantitative method
- Based on the measurement of thermal gradients (ΔT), evaluated by image coloration

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.

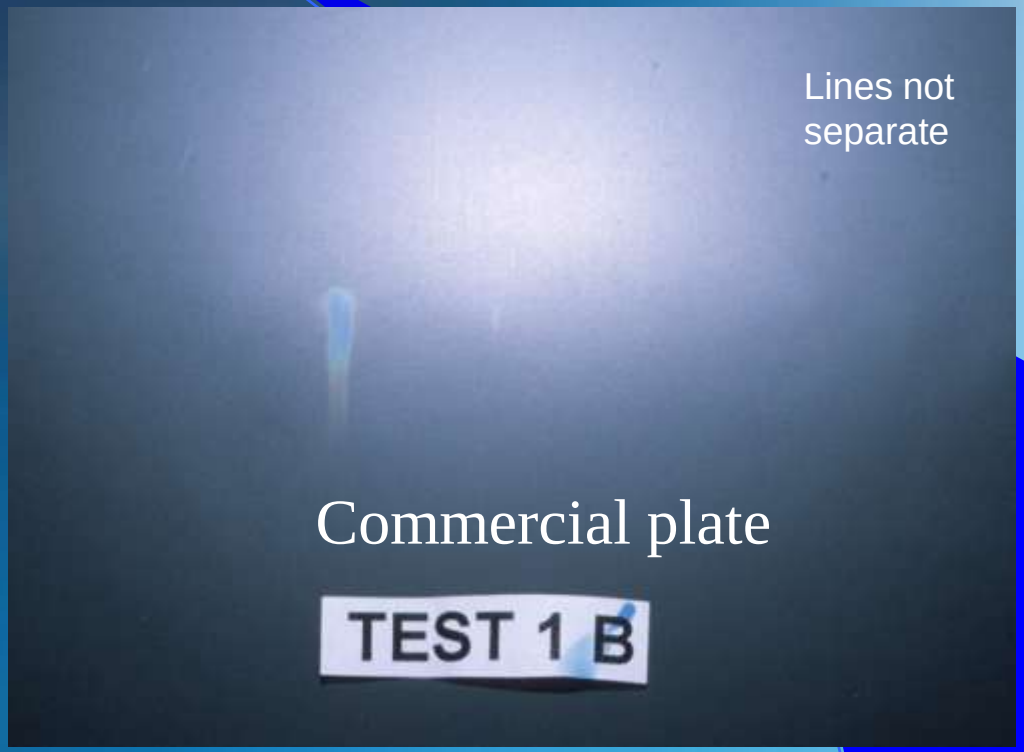


From: "A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms"-

Physica Medica (*Vol. XX , N. 1Januay-March 2004 pp.27-31)*

TEST 1

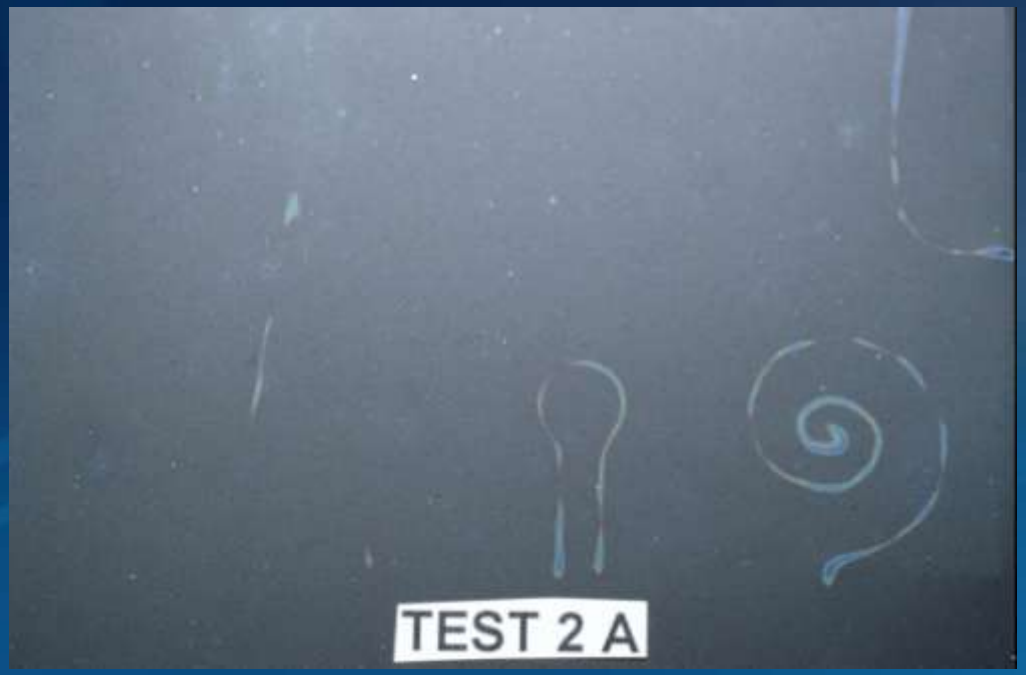
spatial resolution (as high as a tenth of a millimeter)

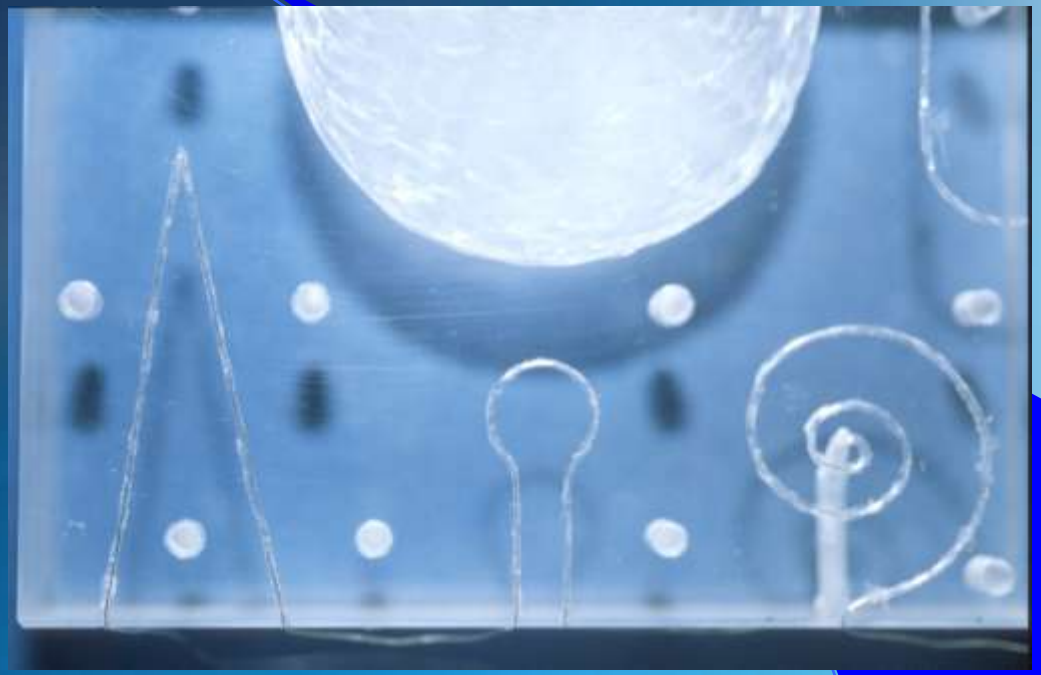


From: "A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms"-

Physica Medica (*Vol. XX , N. 1Januay-March 2004 pp.27-31)*

TEST 2A after 3’’ response time





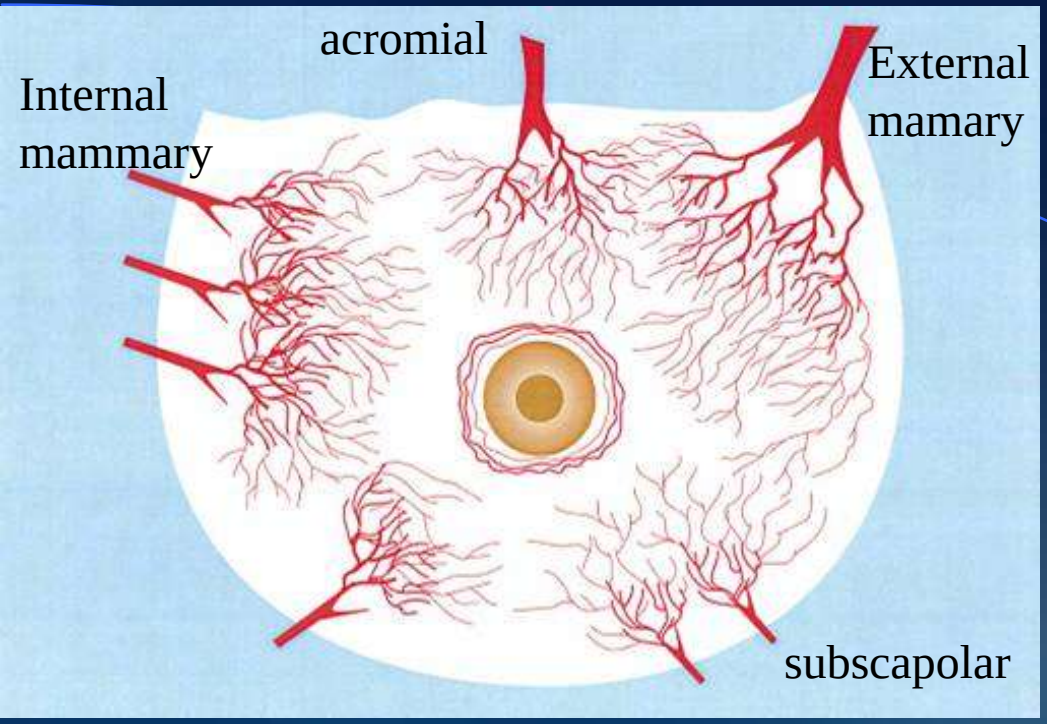
University of Bologna’s Department of Physics

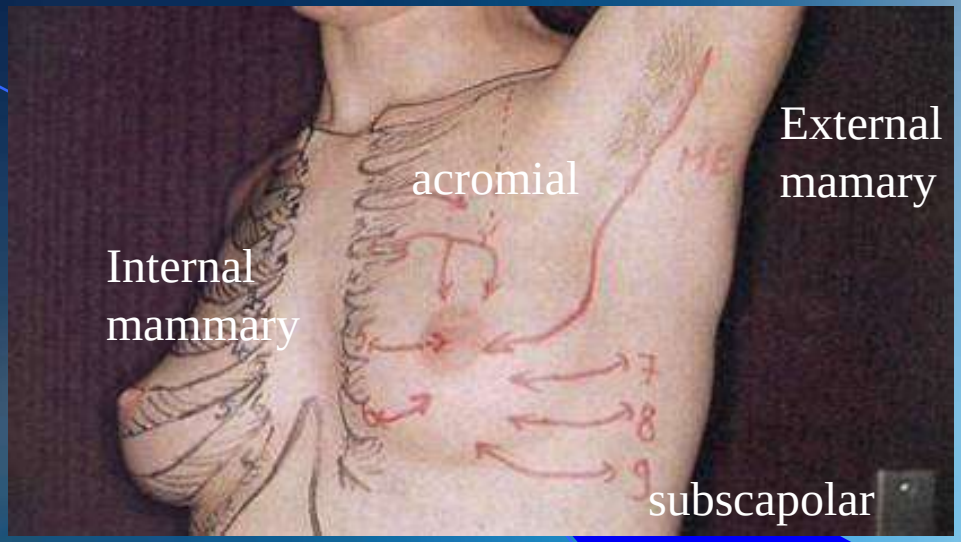
From: “A new type of breast contact thermography plate: a preliminary and qualitative investigation of its potentiality on phantoms”-

Physica Medica (*Vol. XX , N. 1January-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**

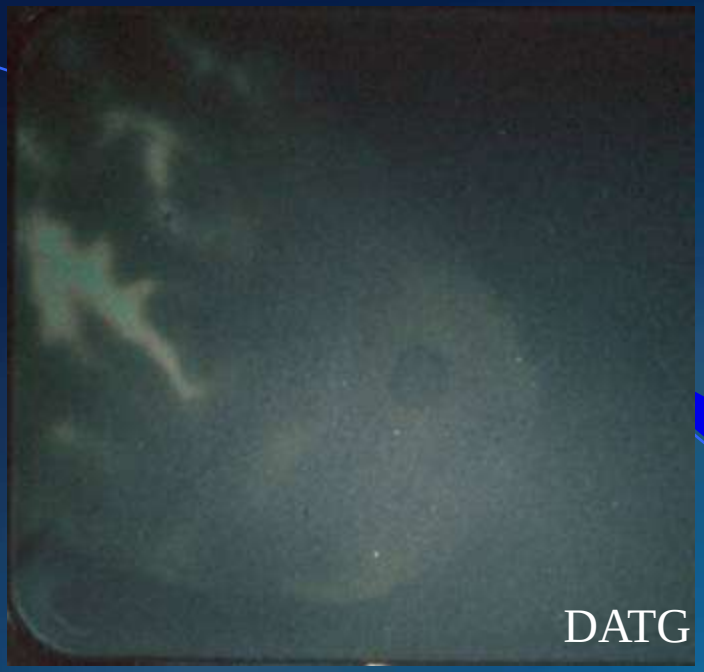
➢**Cutaneous projection of the breast's main arteries.**

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



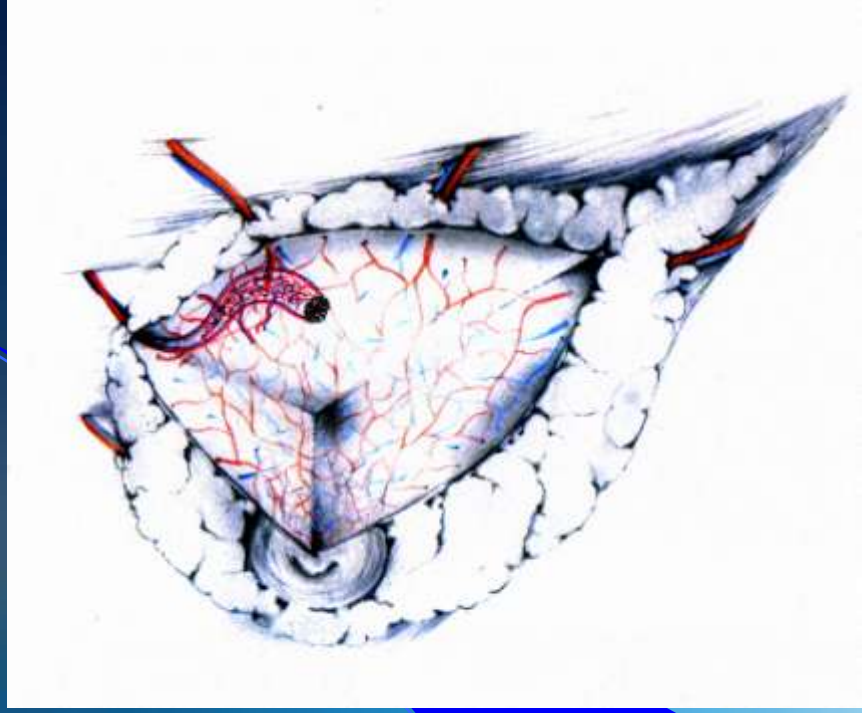
Normal flowlines

Normal angiothermographics flowlines reproduce the anatomy of the circulation of the breast

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).

- 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.



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.

Bologna, 10.3. 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.

Ax)
Bx4
Cx)
Dx)

I) prelievi random

Diagnosi:

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

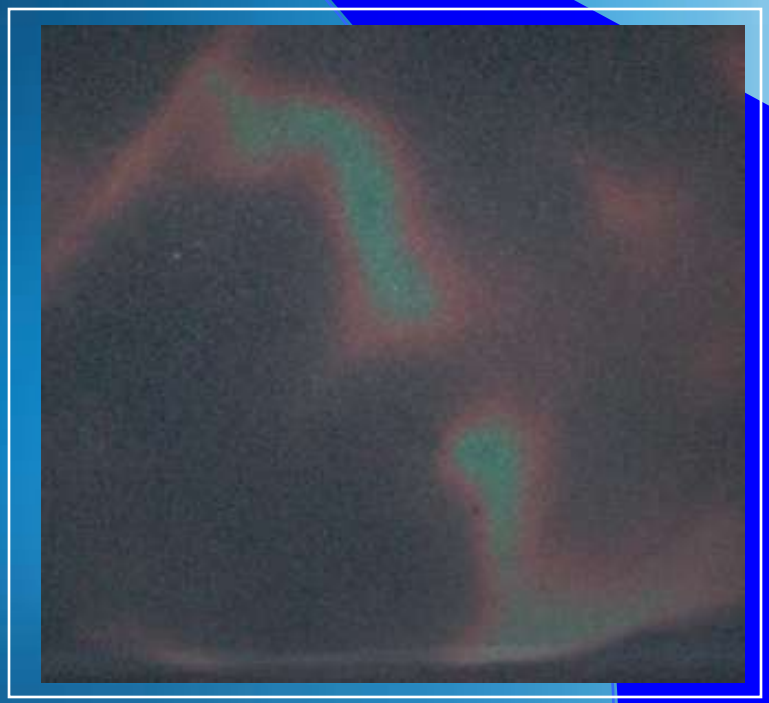
Histological report

Il Responsabile del Laboratorio

PER CONFORMITÀ
PROF. W.F. GRIGIONI

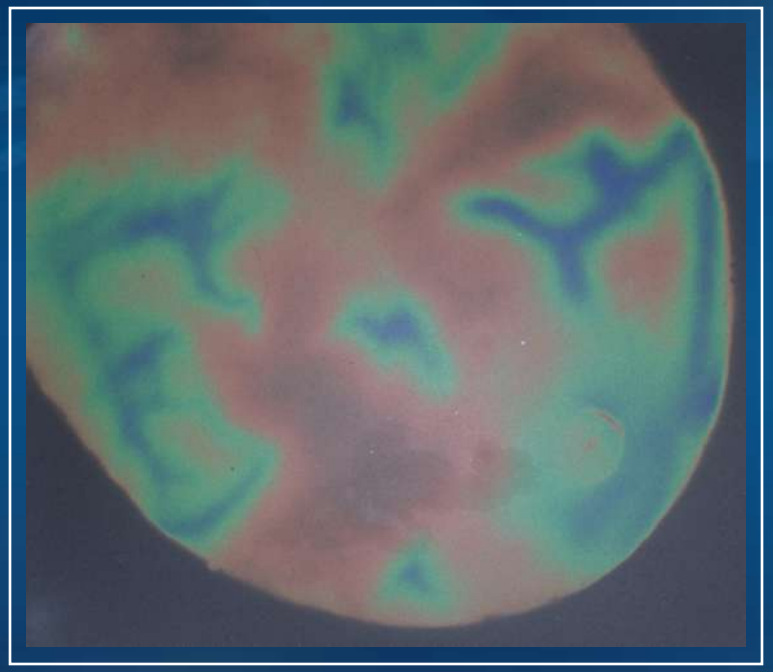
SUSPICIOUS FLOWLINES

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



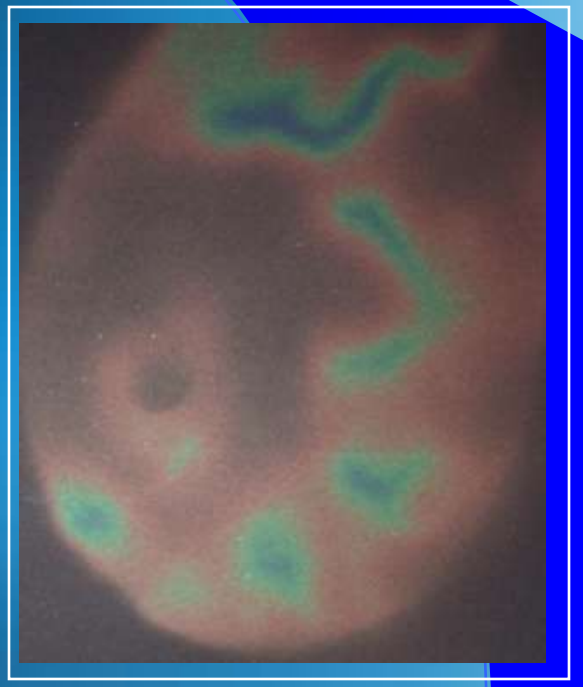
MALIGNANT FLOWLINES

- 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.

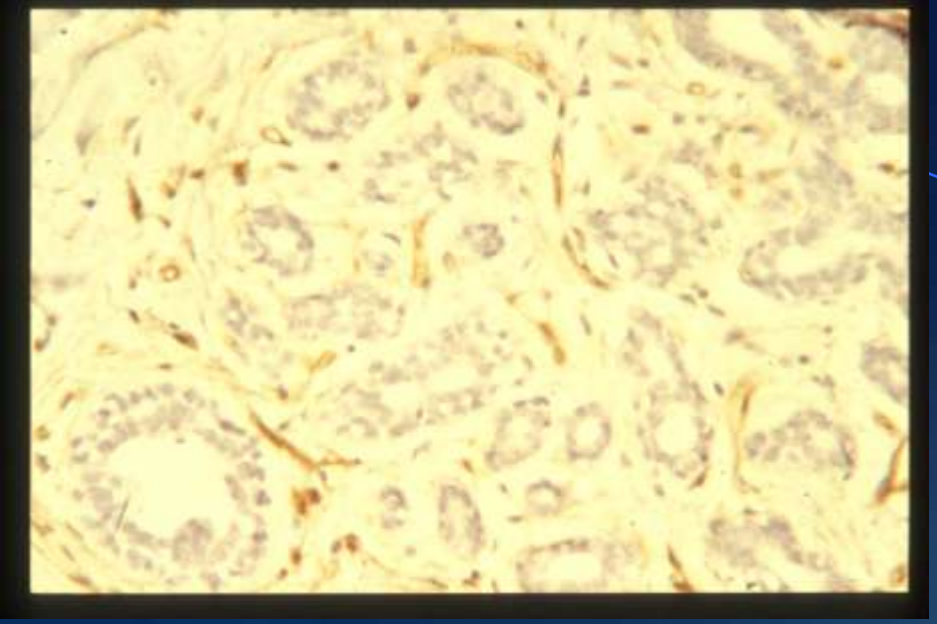
LCIS in pregnancy (8 weeks)

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.



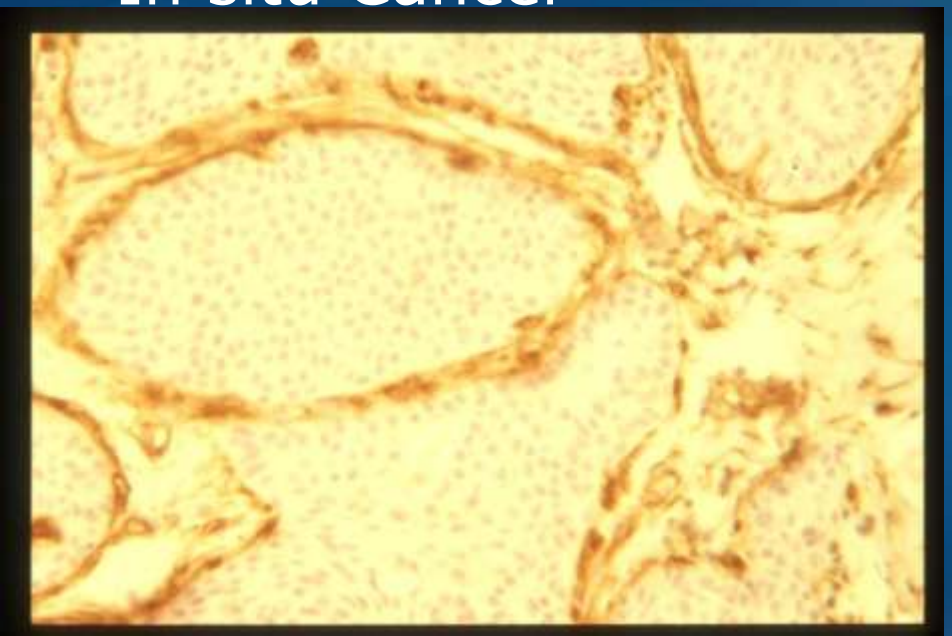
Normal

DATG

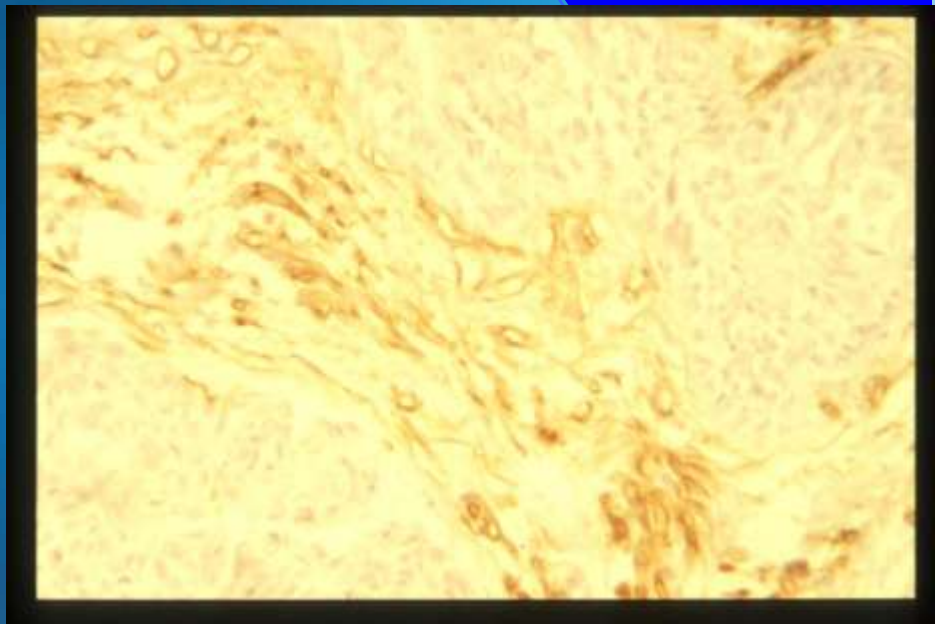
Hyperplasia

Progression of angiogenesis

In situ Cancer

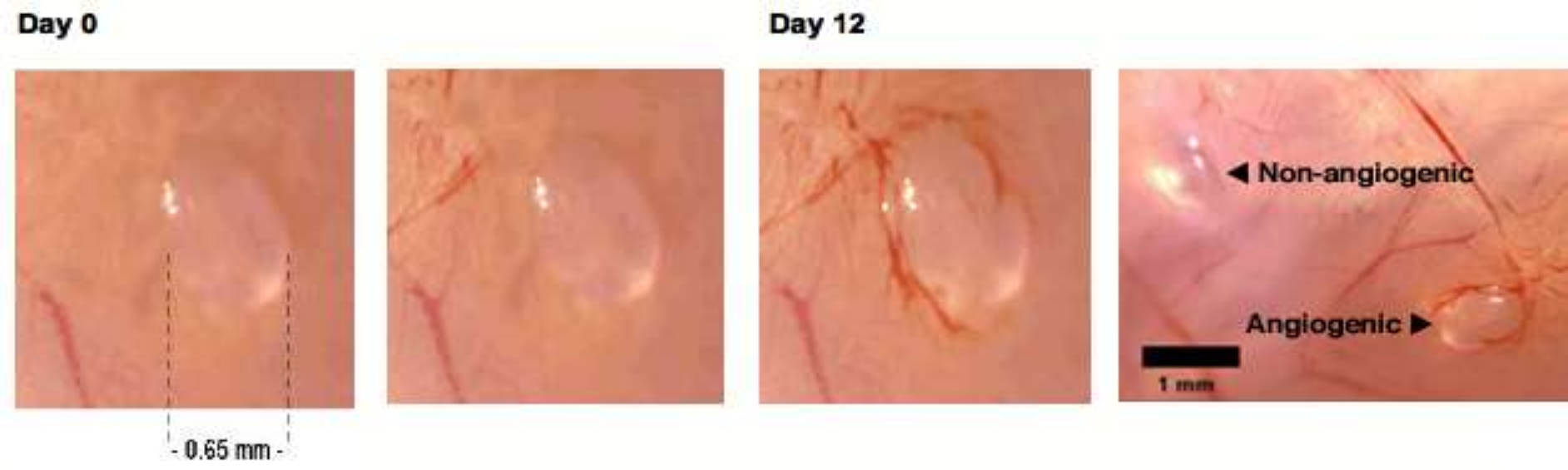


Invasive cancer



Visualizing the angiogenic switch

Neovascularization in a rat tumor model



Images reproduced with permission from Dr Judah Folkman.

ONCOLOGY REPORTS 18: 1201-1206, 2007

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

ADHEMAR LONGATTO FILHO[1], SANDRA M. COSTA[1], FERNANDA MILANEZI[1,2], DANIELE MONTRUCCOLI[3], GIAN CARLO MONTRUCCOLI[4], FáTIMA BALTAZAR[1] and FERNANDO C. SCHMITT[2,5]

[1]Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Campus of Gualtar, Braga; [2]Institute of Molecular Pathology and Immunology of University of Porto (IPATIMUP), Porto, Portugal; [3]Department of Surgery Pietro Valdoni, University of Rome La Sapienza, Rome; [4]Department of Obstetrics and Gynecology, Toniolo Private Clinic, Bologna, Italy; [5]Medical Faculty of University of Porto, Porto, Portugal

Received May 8, 2007; Accepted June 27, 2007

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?

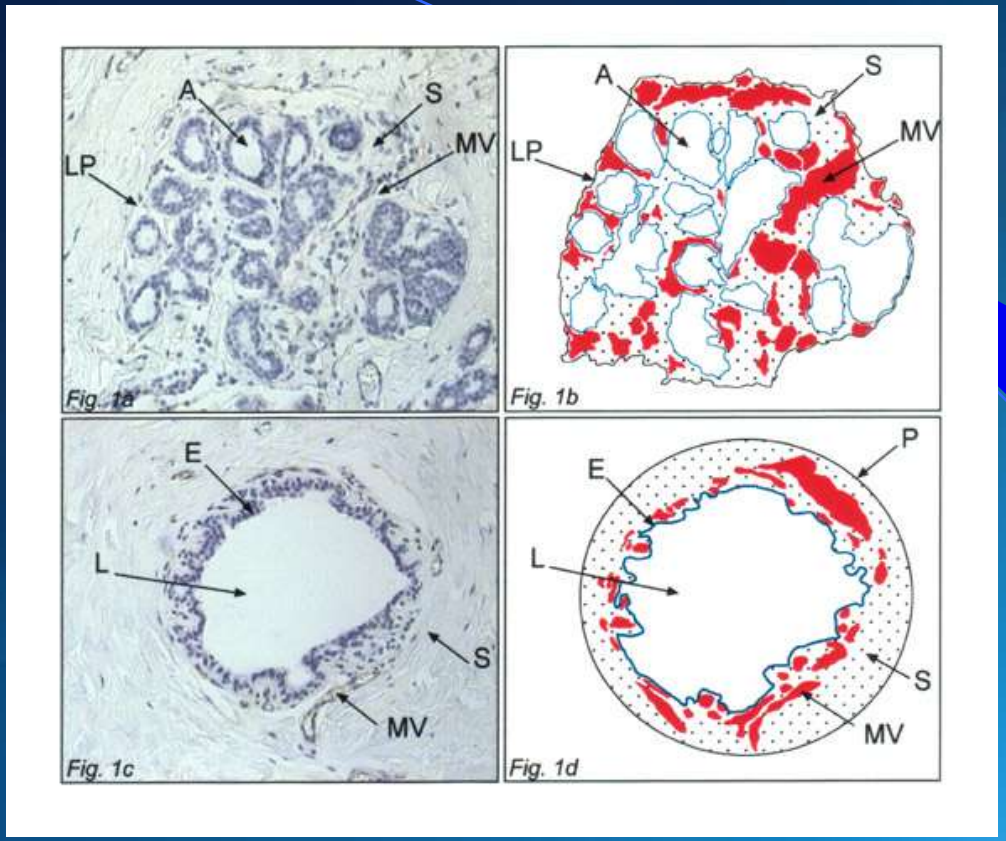
Diagnosis	No.	%	% Group
Benign	143	13.43	*30.71*
Mastitis and/or ectasia	184	17.28	
Simple ductal hyperplasia	182	17.09	39.91
Florid ductal hyperplasia	243	22.82	
Papillomatosis	48	4.51	4.51
Atypical duct hyperplasia	8	0.75	4.13
Atypical lobular hyperplasia	23	2.16	
Mixed atypical hyperplasia	13	1.22	
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%

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.

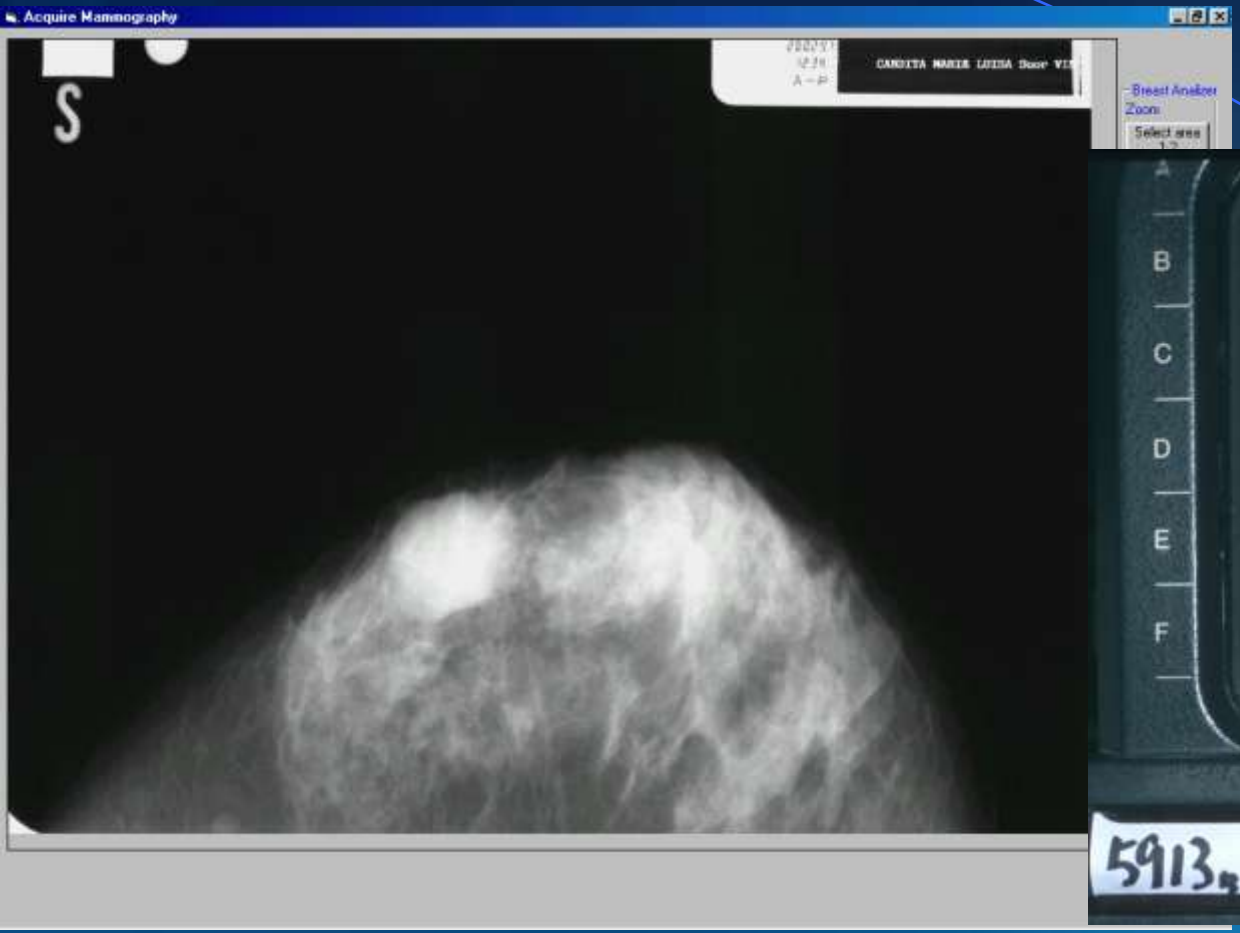
Journal of Anatomy vol. 203, pp. 599-603, 2003"



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.

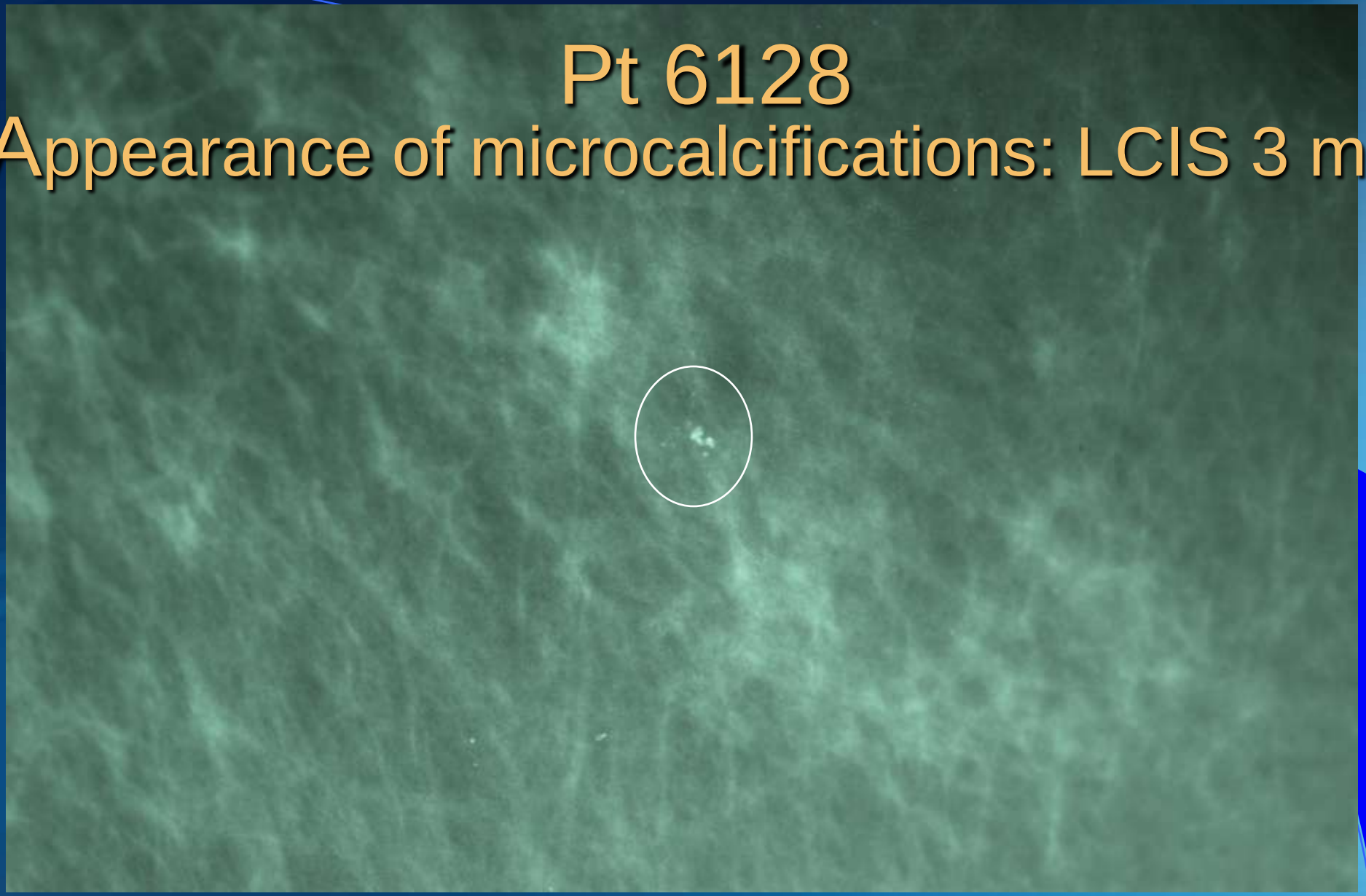
Comparison of Diagnostic Techniques

5913



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

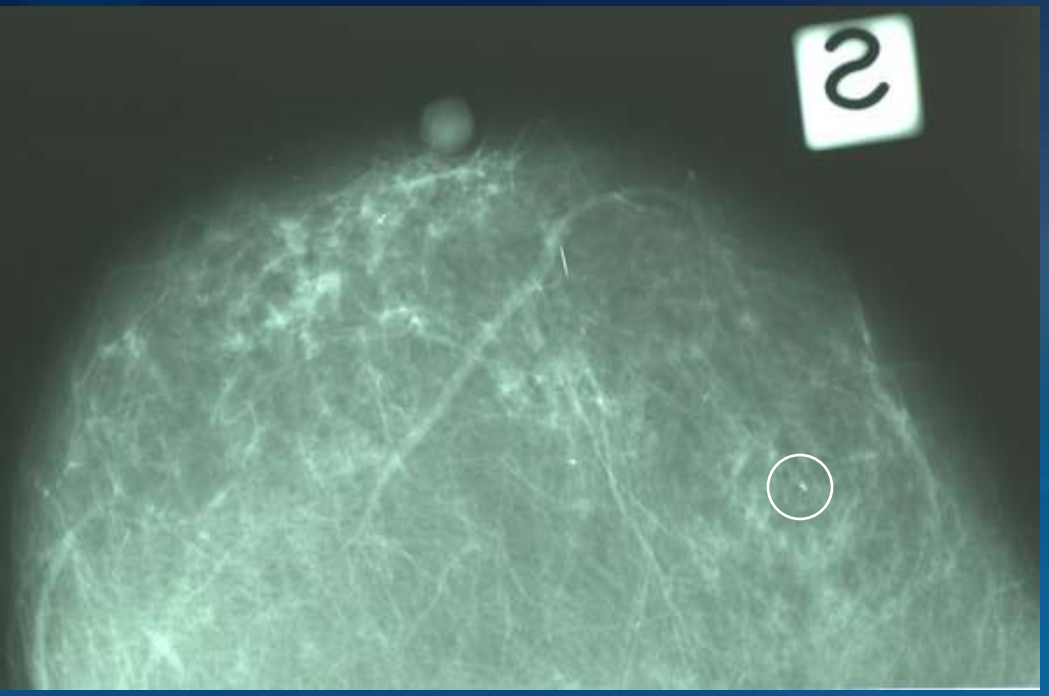
Pt 6128
Appearance of microcalcifications: LCIS 3 mm

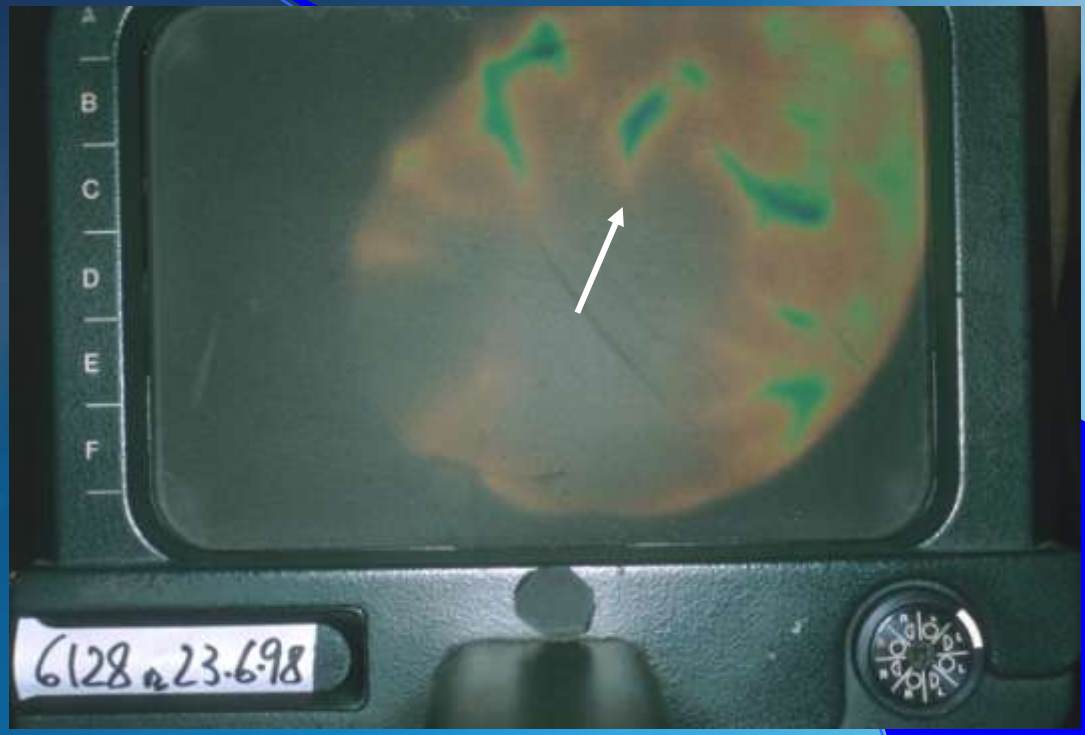


MAMMOGRAPHY LEFT 2-6-1998 MICROCALCIFICATIONS

Pt 6128

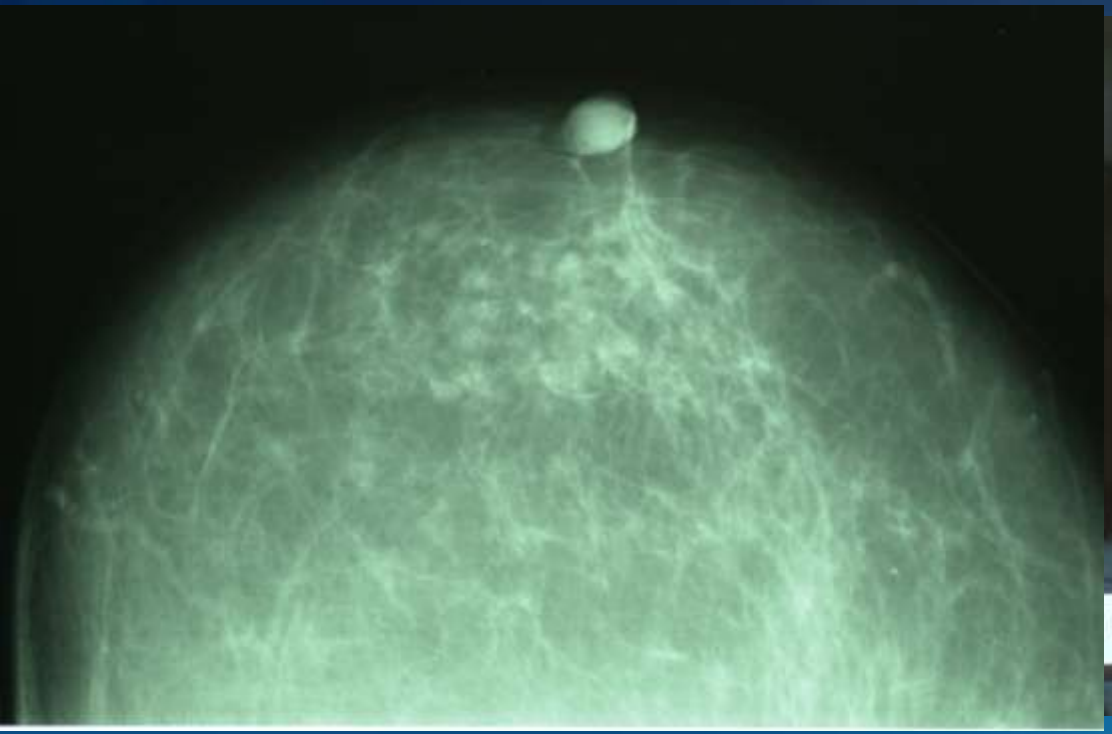
Appearance of microcalcifications: LCIS 3 mm



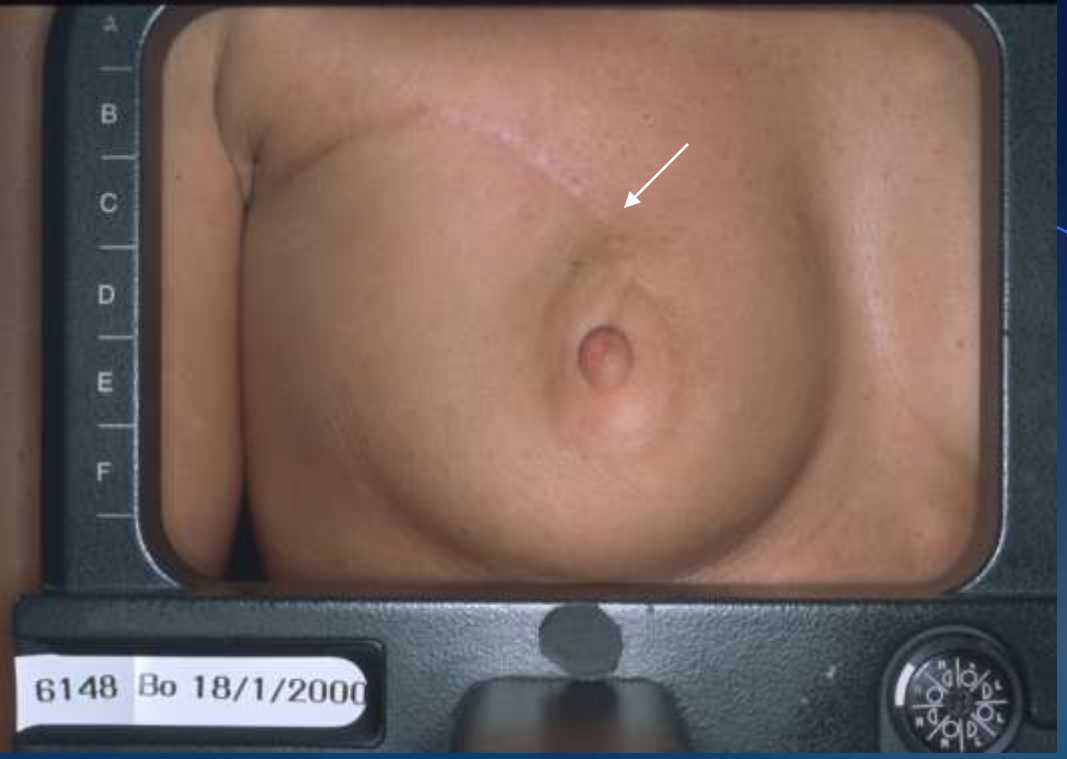


- MAMMOGRAPHY LEFT 2-6-1998
- Pz. 6128 Left Lateral Pre-op

Pt.6128 after surgery : Normal

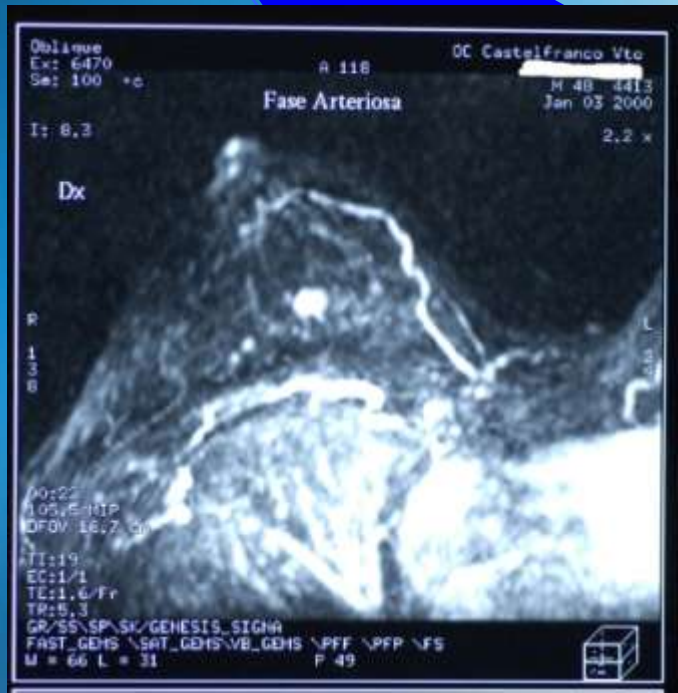


- Pz.6128 Mammography 25-10-1999
- Pz.6128 lateral left 18-10-2000

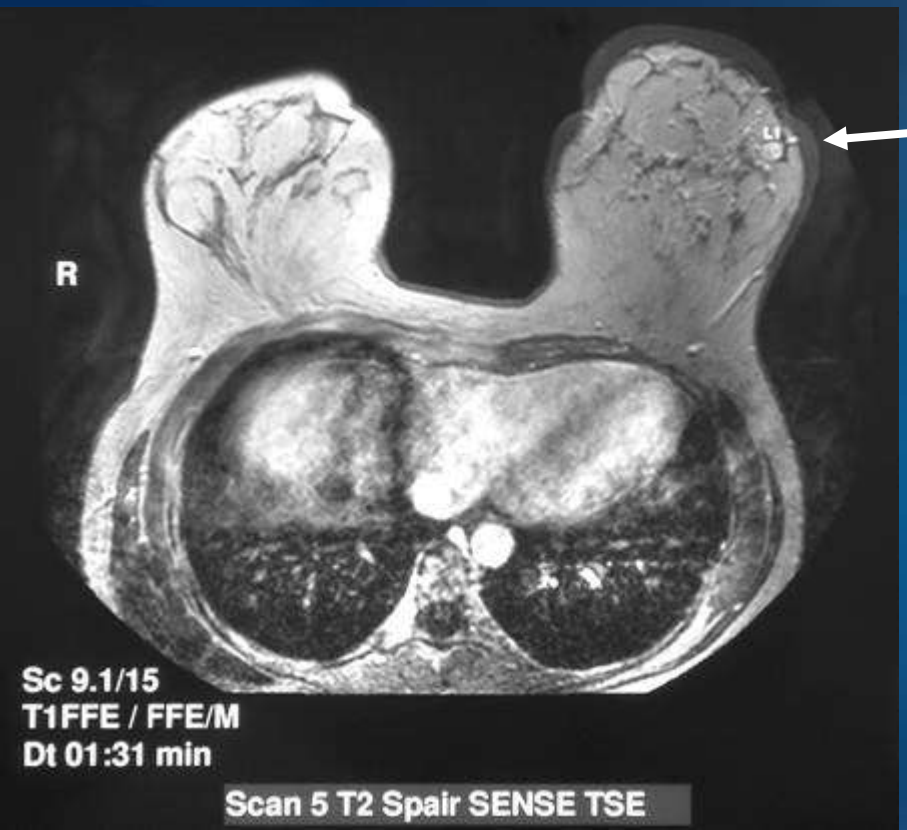


6148
correspondence between MRI and DATG

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



2°localization ?



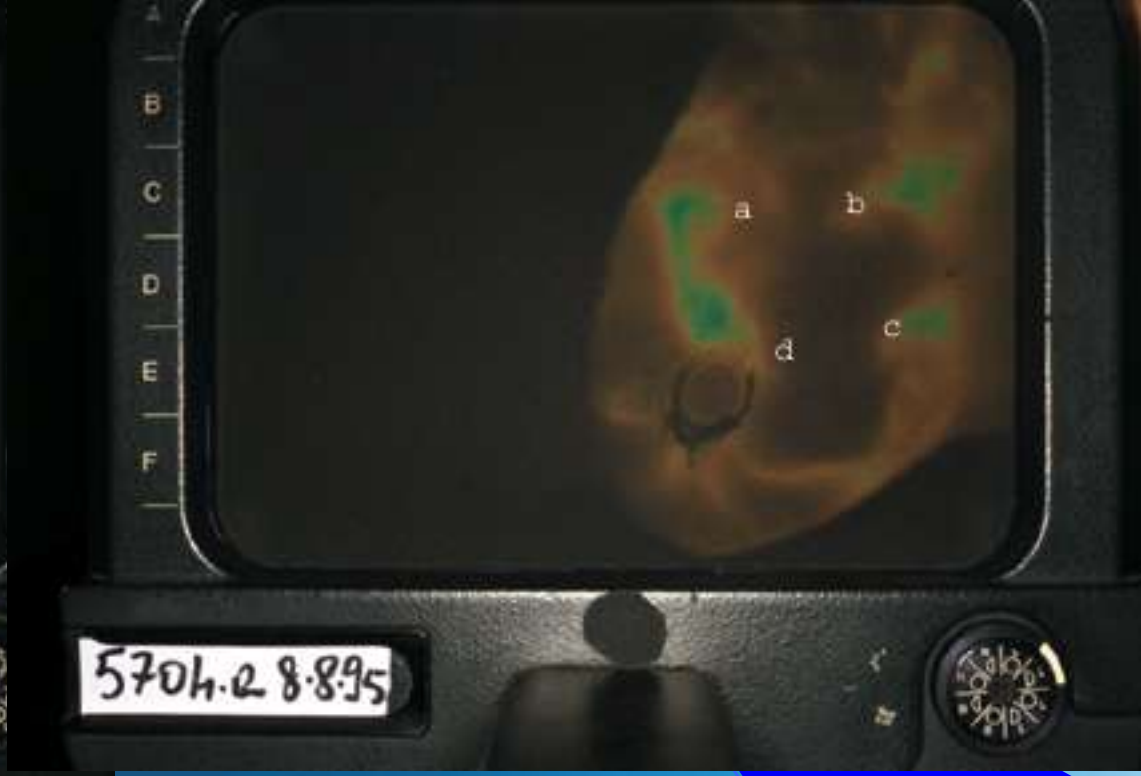
DATG vs RMN

ID	Age	RMN	DATG	X-MAMOGRAPHY	US	FAMILIARITY	HISTOLOGY	note
BN	40	+	+	-	+	no	Infiltrating ductal carcinoma-relapse	
SC	42	-	-	-	-	yes	no	Nipple discharge
BB	30	+	+	-	+	no	Infiltrating Ductal Carcinoma	Pre-op chemotherapy
DS	42	+/-	+	-	-	yes	Infiltrating Ductal Carcinoma 4 mm.	Mammary implants
DPS	44	+	+	-	-	yes	Infiltrating lobular carcinoma-multicentric	Mammary implants
UP	55	-	+	-	-	no	Relapse following quarth	
BL	45	+	+	+	-	yes	2 cancer: -Infiltrating ductal (RMN and DATG) -ductal in situ only DATG	
SM	60	+	+	-	-	no	Pre-invasive lesion	
MC	49	-	+	-	-	no	Ductal in situ o,4 e 0,6 only with DATG	
CS	39	-	+	-	-	yes	Ductal in situ controlateral	

DATG Applications

Detection of Breast Cancer

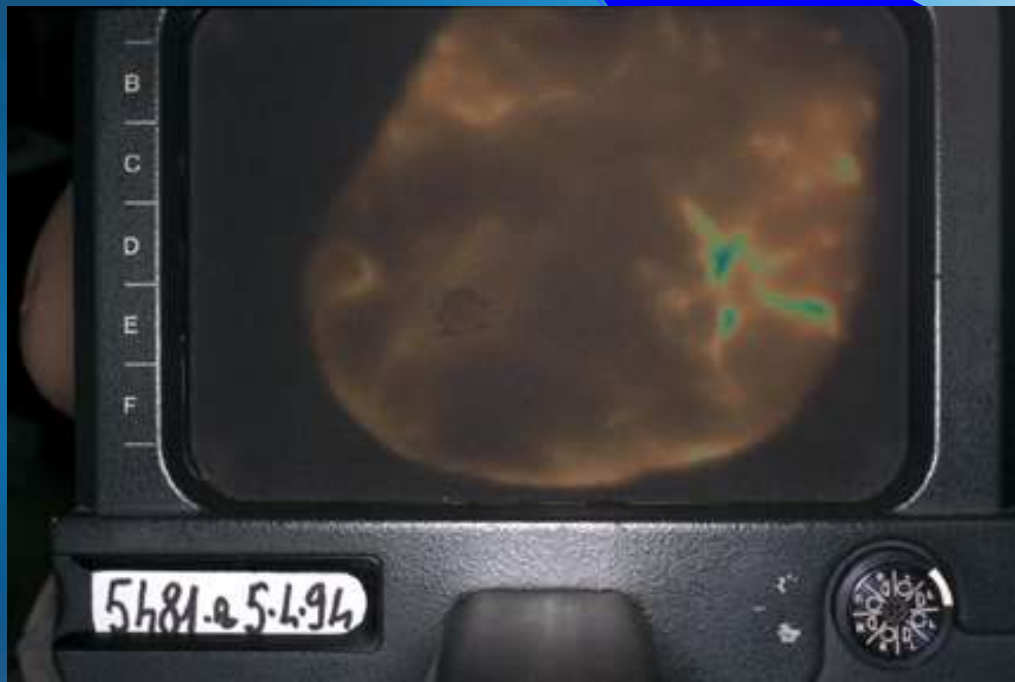

A
B
C
D
E
F
570h.e 8·8·95


A
B
C
D
E
F
a
b
c
d
570h.e 8·8·95


B
C
D
E
F

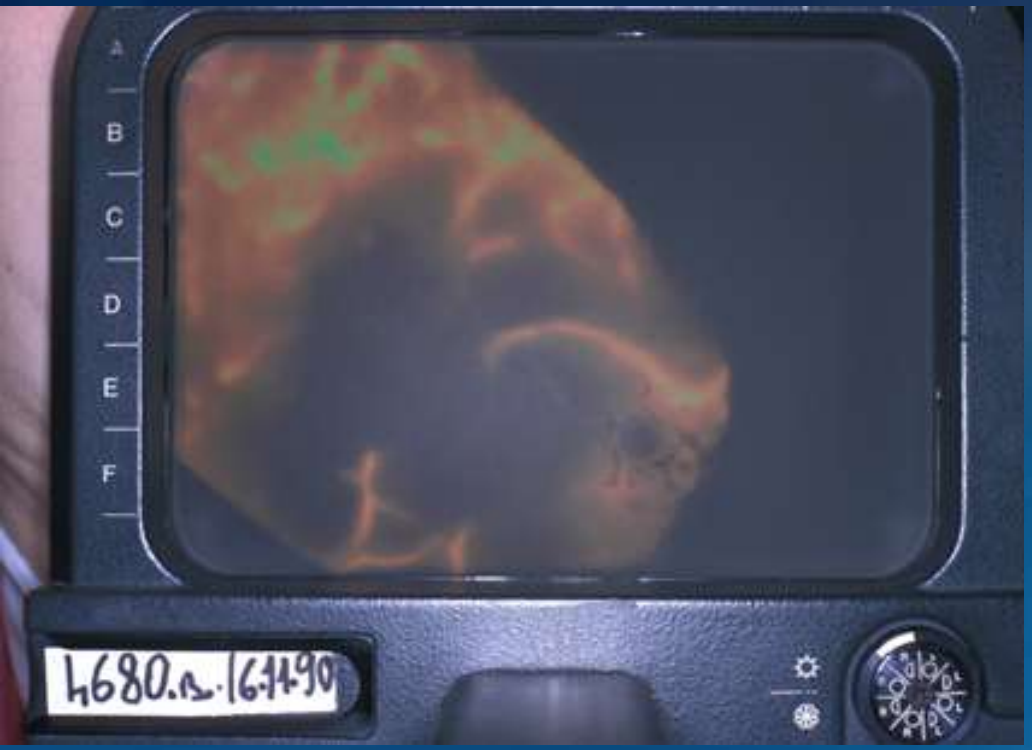

B
C
D
E
F


B
C
D
E
F


B
C
D
E
F


5256
15·12·03


5256
15·12·03


A
B
C
D
E
F
4680.n.16.1.90


A
B
C
D
E
F
4680.n.16.1.90

Tumore della mammella durante la gravidanza

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

- 6389 right lateral
  2-8-2000
- after biopsy


A
B
C
D
E
F
4398 Bo 14.11.89

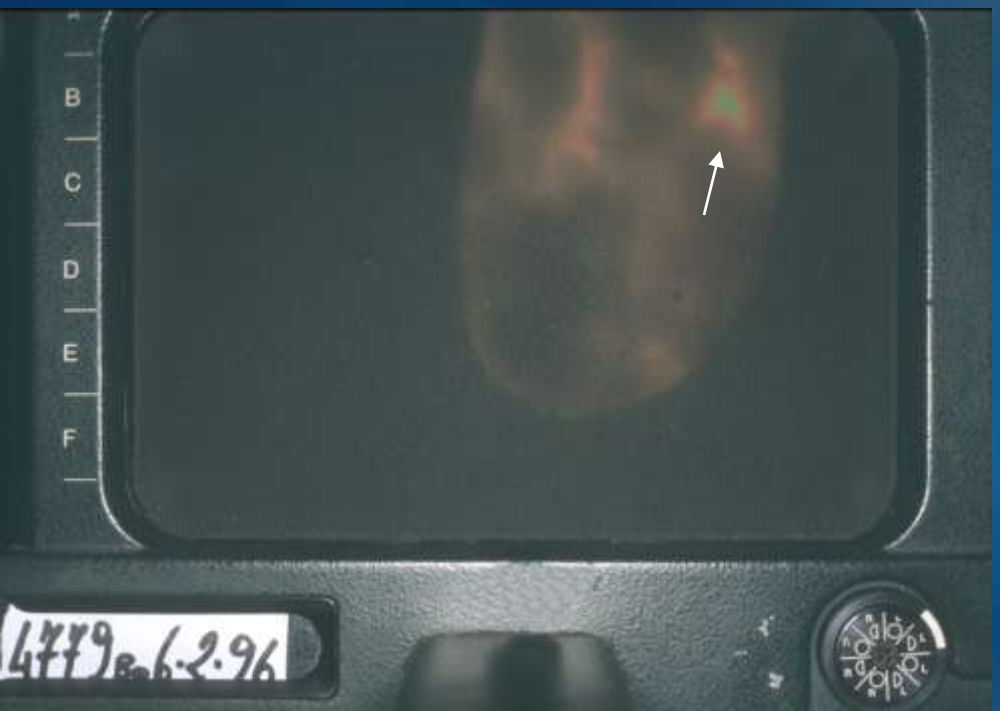

A
B
C
D
E
F
4398 Bo 14.11.89


A
B
C
D
E
F
4398 Bo 14.11.89

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.

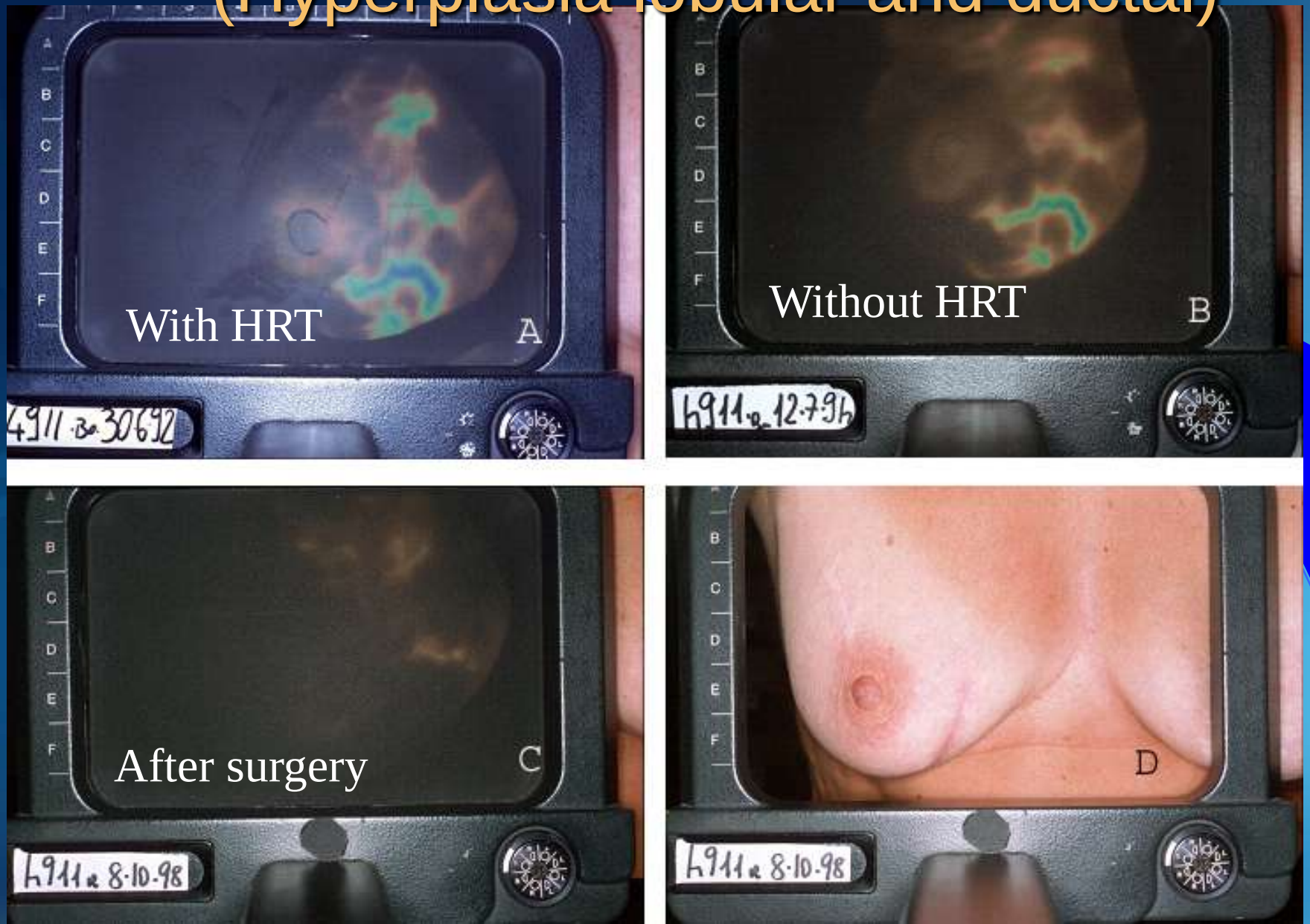
3634-front left 2-12-02
Post-op.

Monitoring the Therapy

Hormone Replacement Therapy

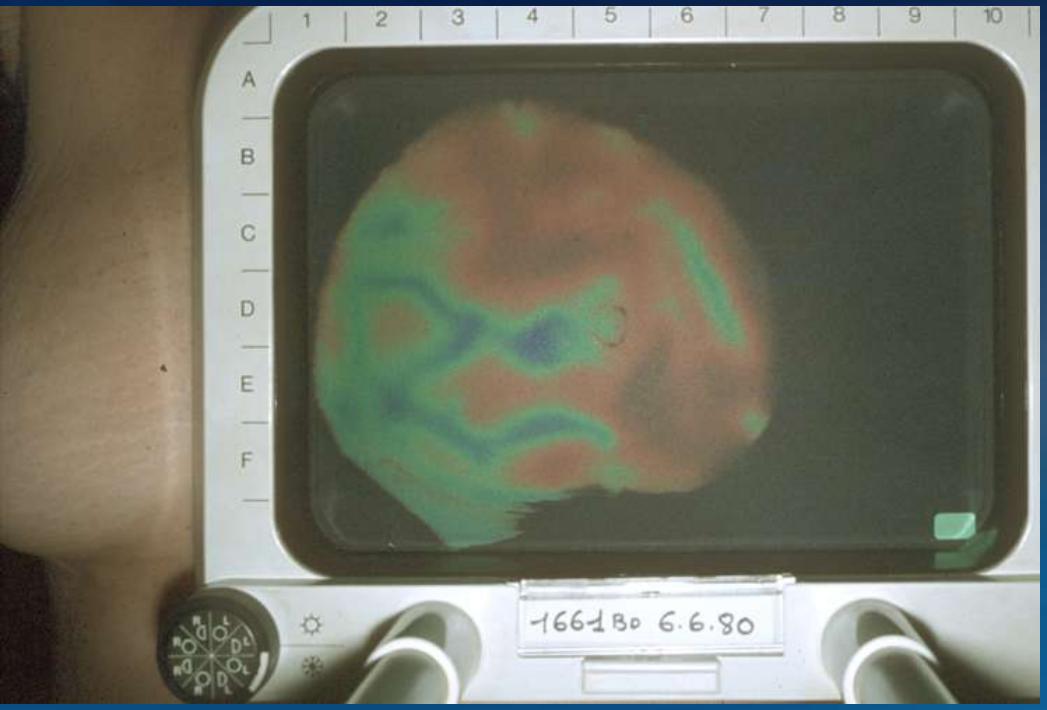
604 Long follow-up with HRT

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



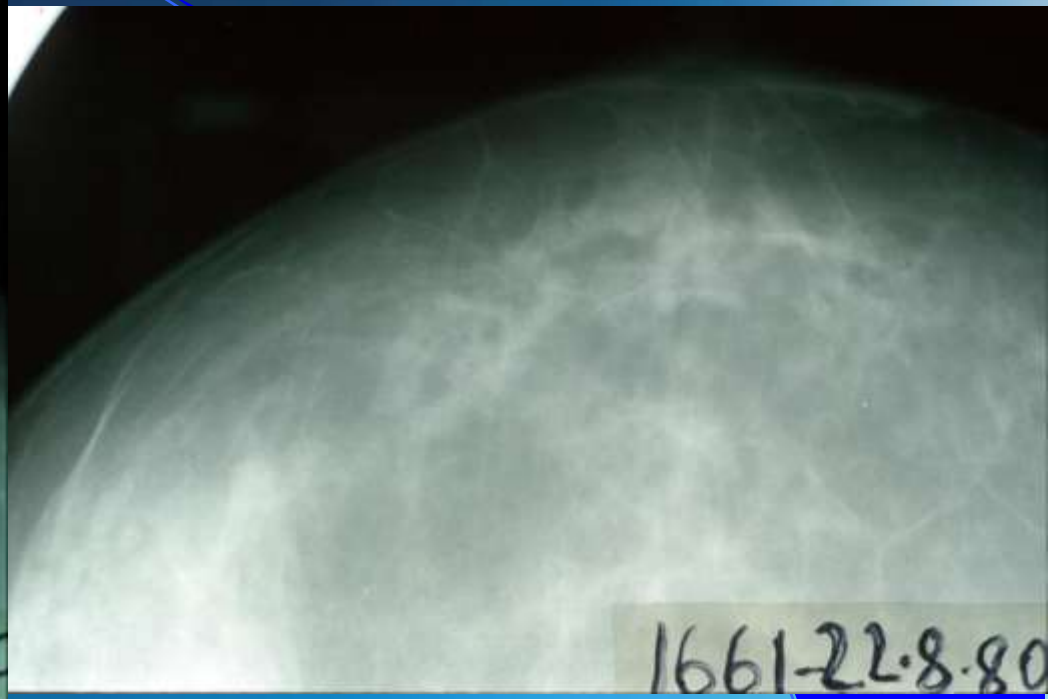
Antiblastic Therapy

1661 After antiblastic therapy



- 1661 Left frontal 6-6-80
- 1661 Left frontal 19-6-80

1661 Monitoring antiblastic therapy



- 1661 Left XRM 29-5-80
  At diagnosis
- 1661 Left XRM 22-8-80
  After antiblastic therapy

2423 At diagnosis

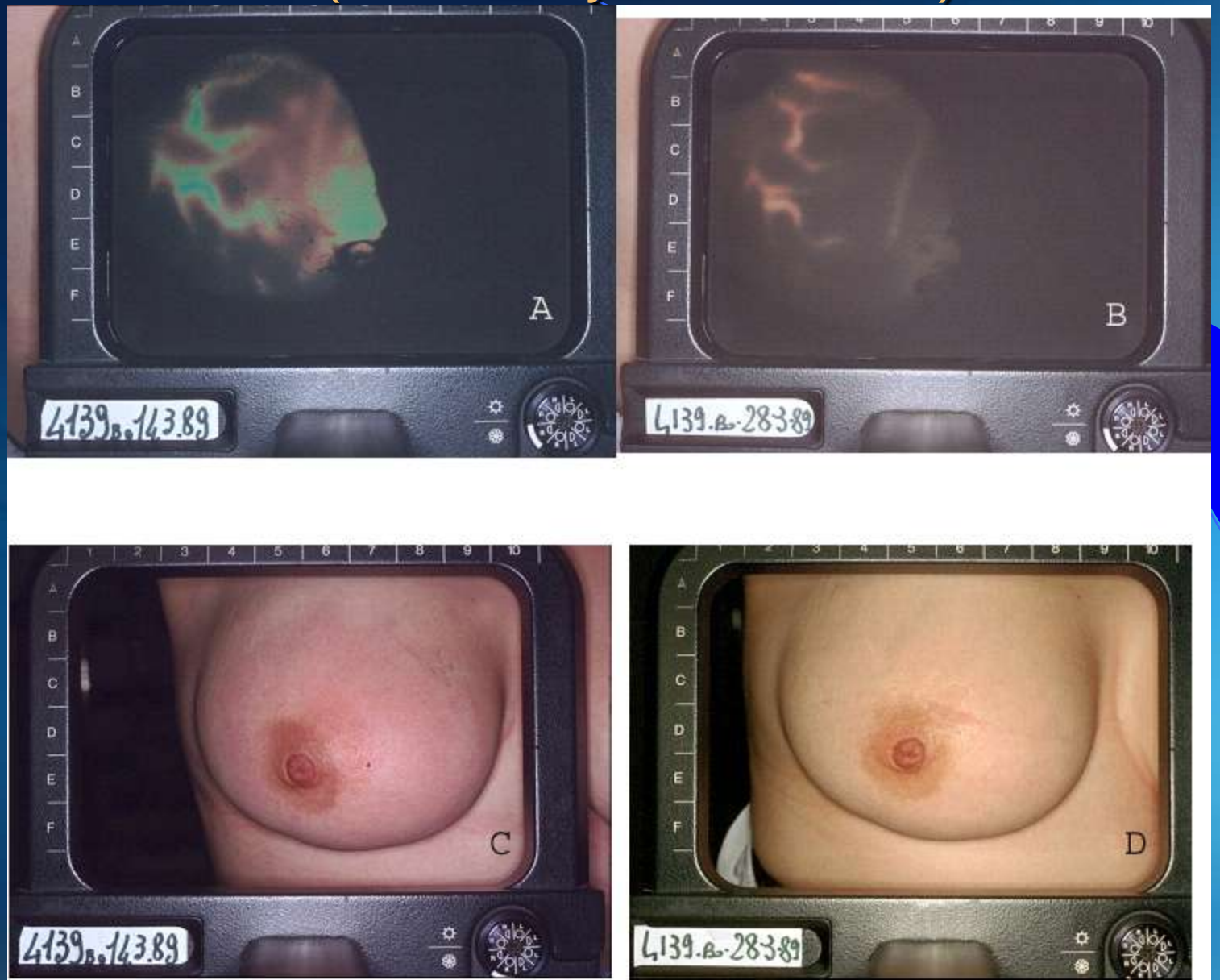
- 2423 Left frontal 1-10-82
- 2423 Left lateral 1-10-82

2423 After 2 months of Tamoxifen

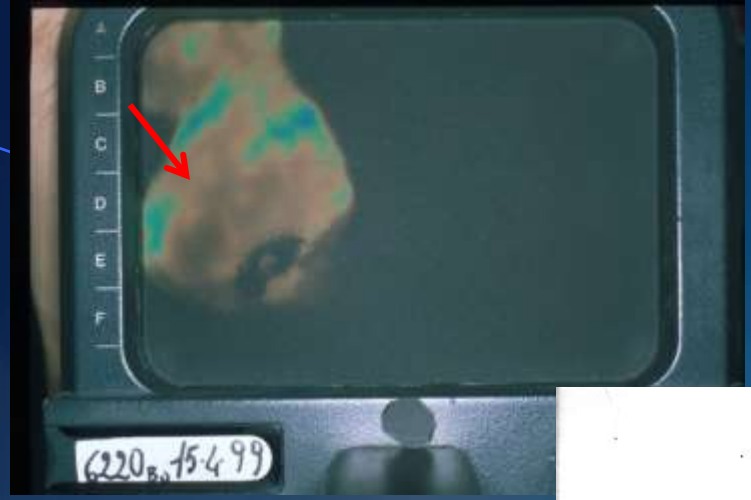
- 2423 Left frontal 2-12-82
- 2423 Left lateral 2-12-82

Benign: mastitis

(after 14 days of antibiotics)



Follow Up



CASA DI CURA PRIVATA
«MADRE FORTUNATA TONIOL

Data: 22/04/99

Nome e Cognome:

D. nascita: 28/04/39

Via: VIA MURGIA, 33 VILLACIDRO

Tel: 070 932250

Camera: 205 A

Progressivo: 9232

(segue da pag. 1)

MAMMELLA DESTRA: CARCINOMA DUTTALE INFILTRANTE GR2 A MARGINI INFILTRATIVI (F) CON ESTENSIONE METASTATICA AD 1 LINFONODO INTRAMAMMARIO.
ANAPLASIA NUCLEARE: MODERATA.
TESSUTO MAMMARIO CON MARCATA STEATONECROSI E REAZIONE GIGANTOCELLULARE COME DA PRECEDENTE INTERVENTO.
METASTASI IN 2 LINFONODI DEL CAVO ASCELLARE SU 14 ESAMINATI.

MAMMELLA SINISTRA: TESSUTO MAMMARIO CON ASPETTI DI INVOLUZIONE DEI LOBULI E DI FIBROSI STROMALE.

recettori estrogenici.80.(0-30 bassa espressione; 30-60 moderata espressione; > 60 alta espressione).

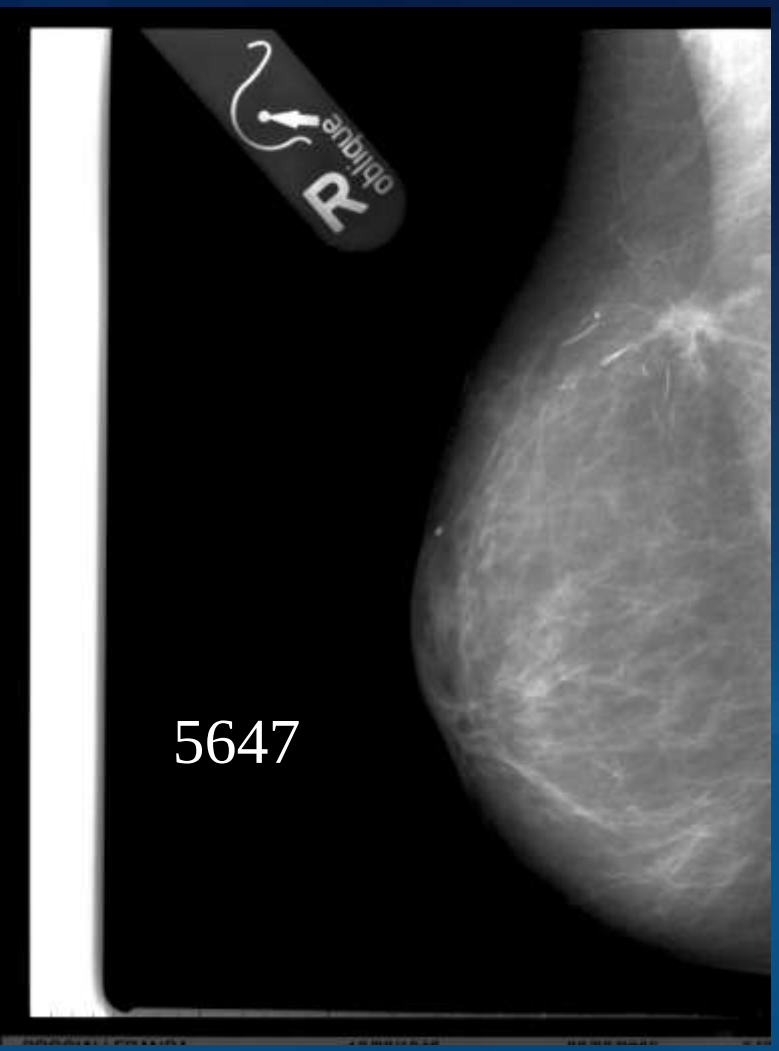
recettori progestinici.
80.(0-30 bassa espressione; 30-60 moderata espressione; > 60 alta espressione).

indice di proliferazione con anticorpo Ki 67.5.(<5 bassa proliferazione; 5-10 moderata proliferazione; > 10 alta proliferazione).

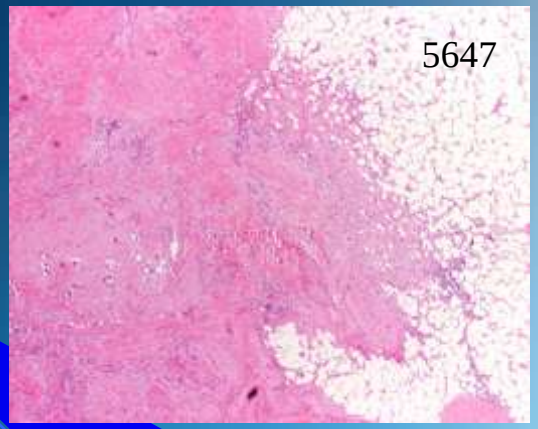
E-ERB-B2: NEGATIVO.

GRIGIONI PROF.WALTER FRANCO

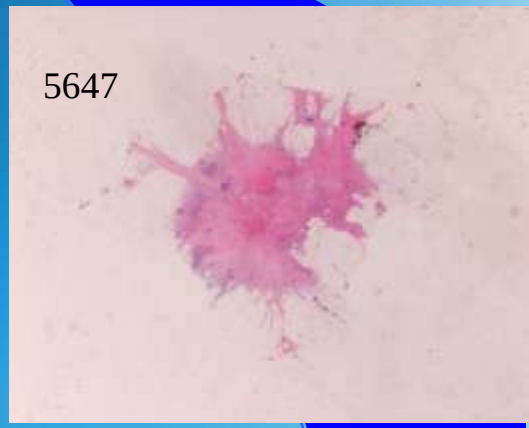
Integrated Diagnosis


oblique
R
5647


A
B
C
D
E
F
5647.12.7 oh


5647


A
B
C
D
E
F
5647.12.7 oh


5647

34 year old patient
Hormonal stimulation for infertility

3N+/15

A: Ductal Infiltrating Carcinoma G3

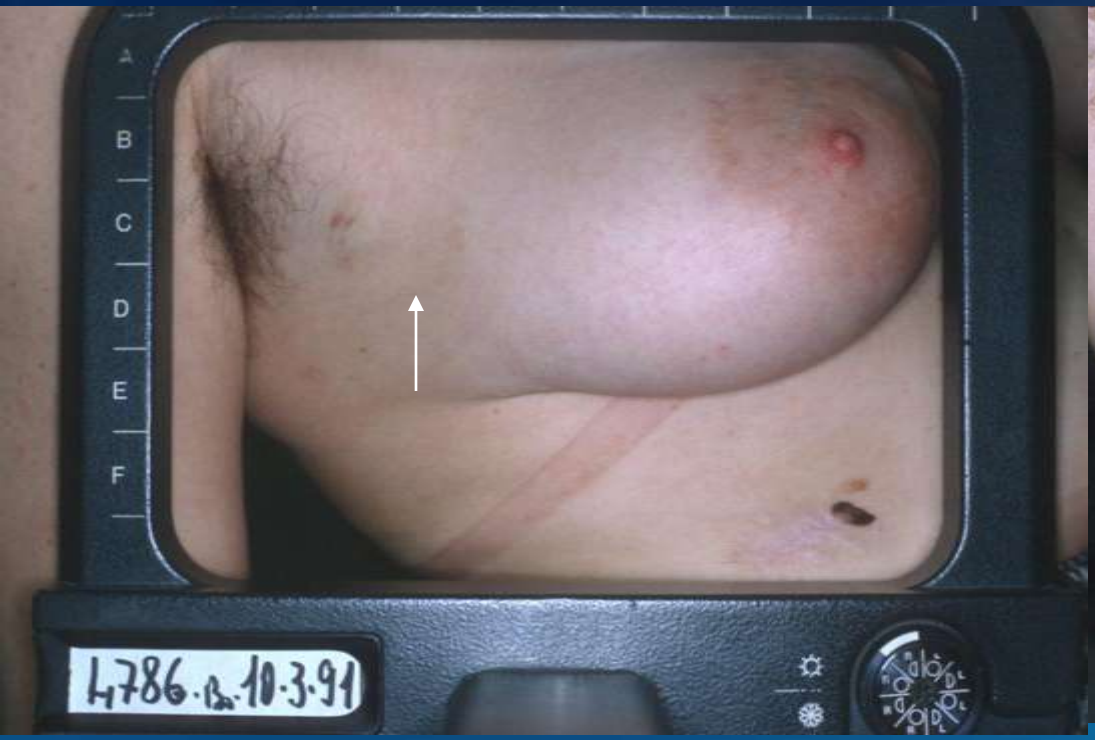
Controlateral is normal

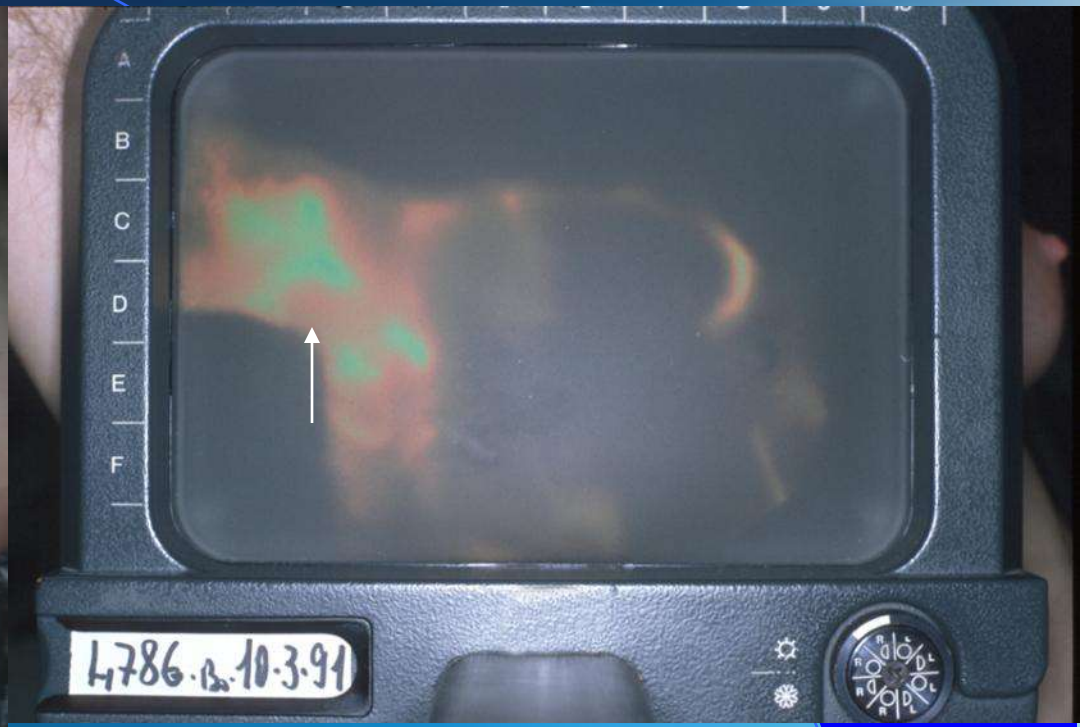
B: Ductal Infiltrating Carcinoma with intraductal G2

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

Other Applications

4786 melanoma





- 4786 clinica 10-3-91
- 4786 laterale destra10-3-91

4786
melanoma

- 4786 laterale destra10-3-91
- 4786 laterale sinistra 10-3-91

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

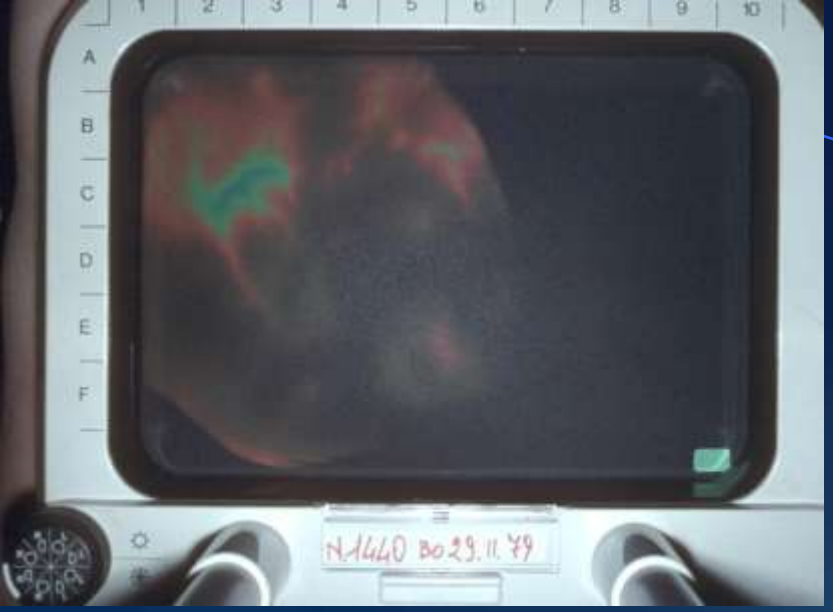
DATG is useful for screening

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

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

Prof.Gian Carlo Montruccoli

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

Thank You