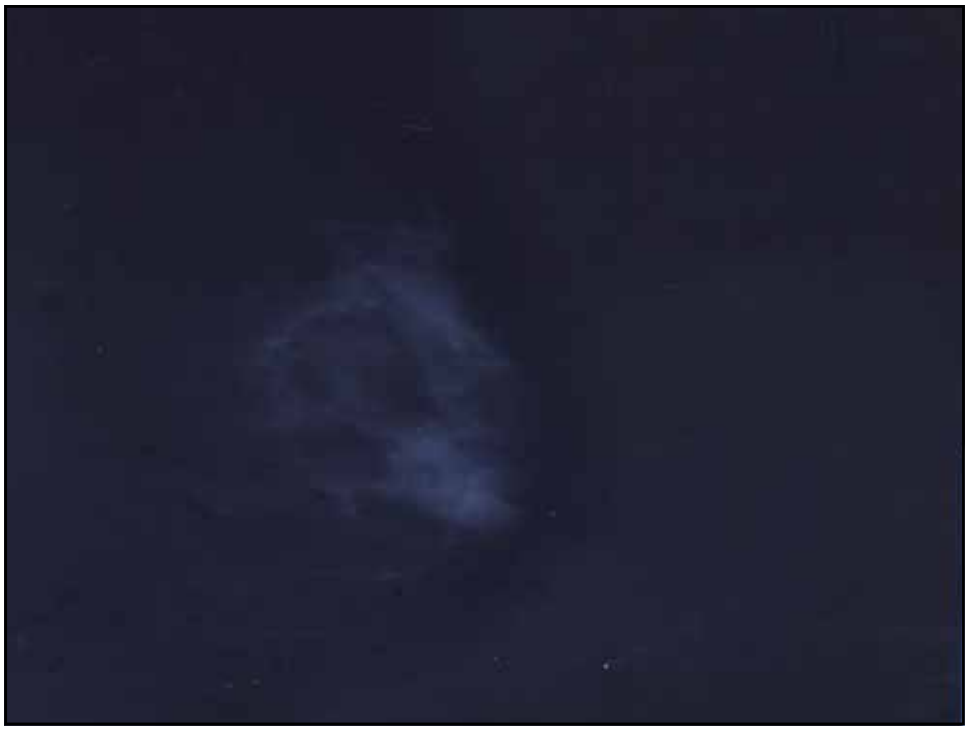
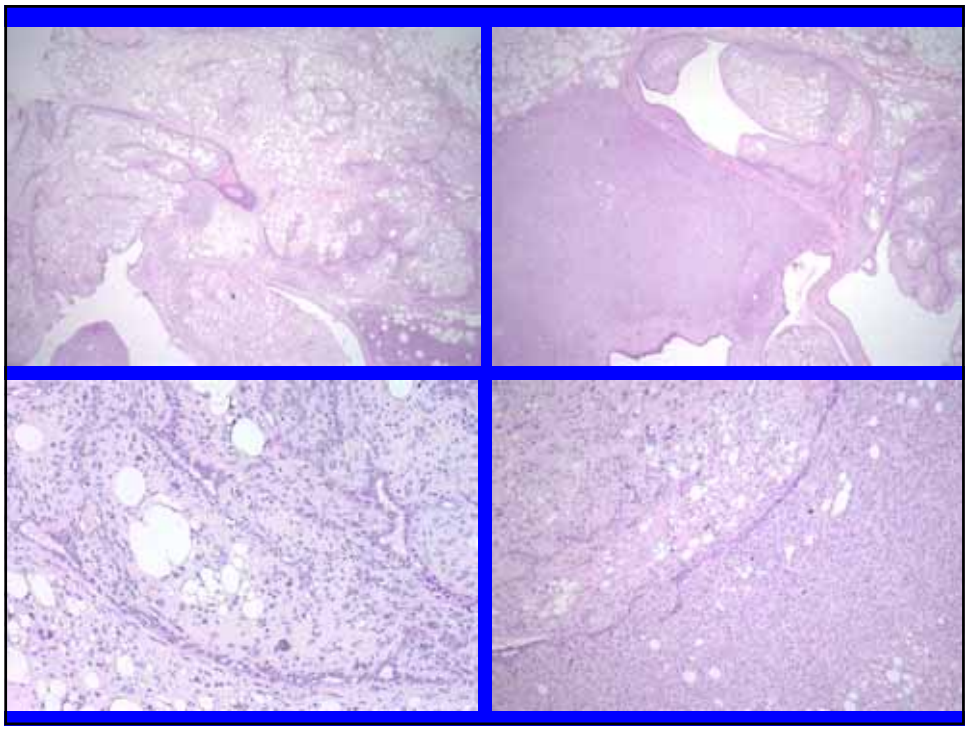
Case 1

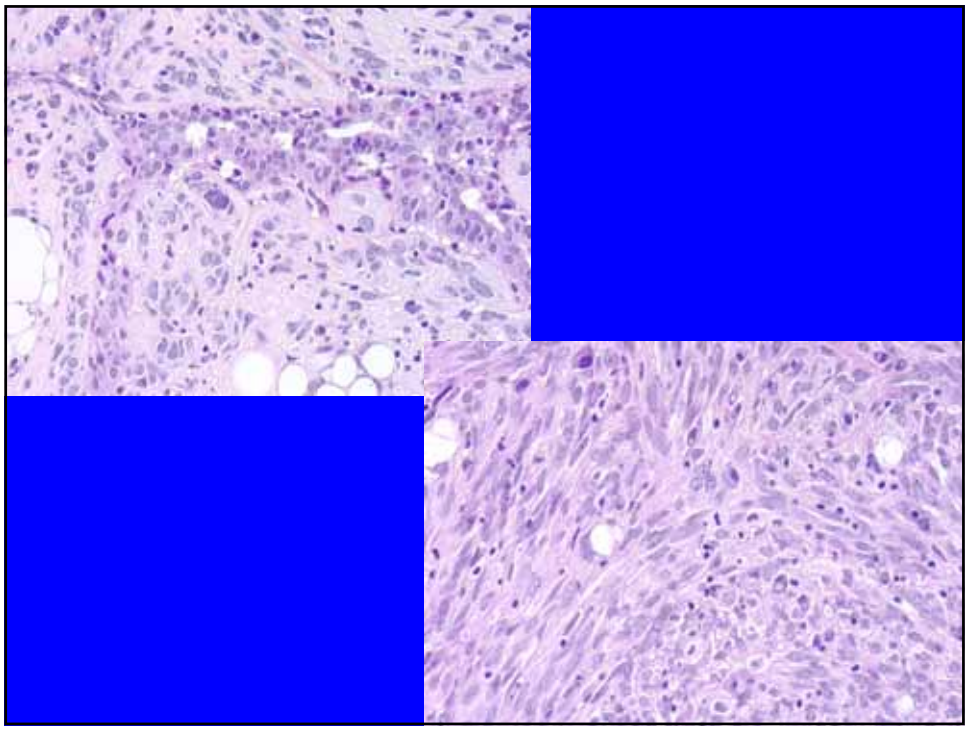
Antonio Llombart-Bosch

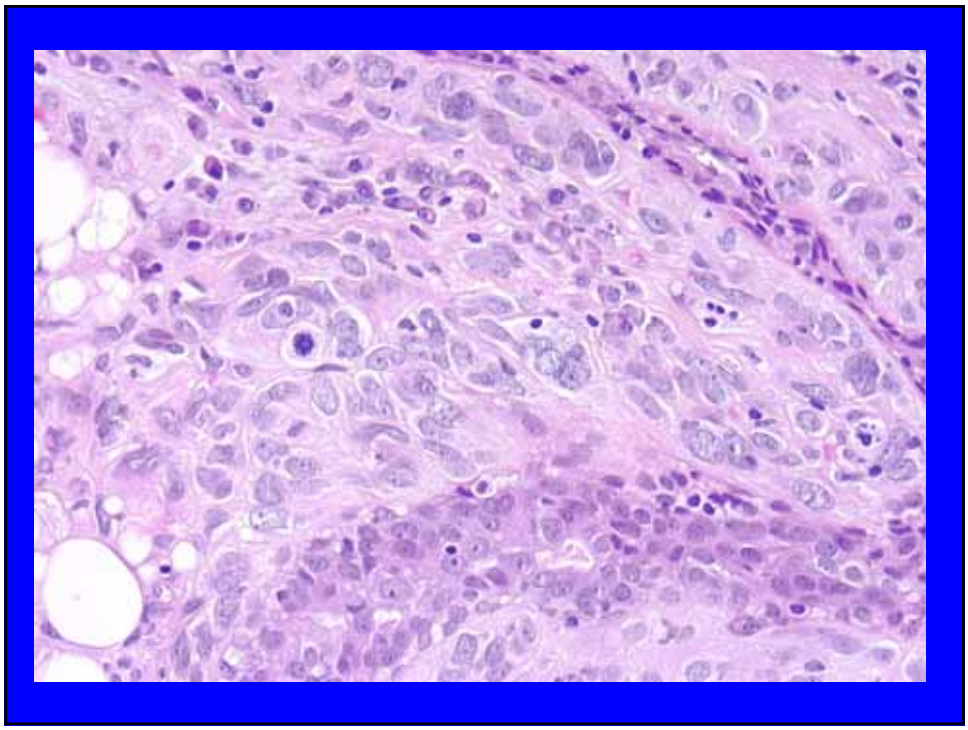
Clinical Data

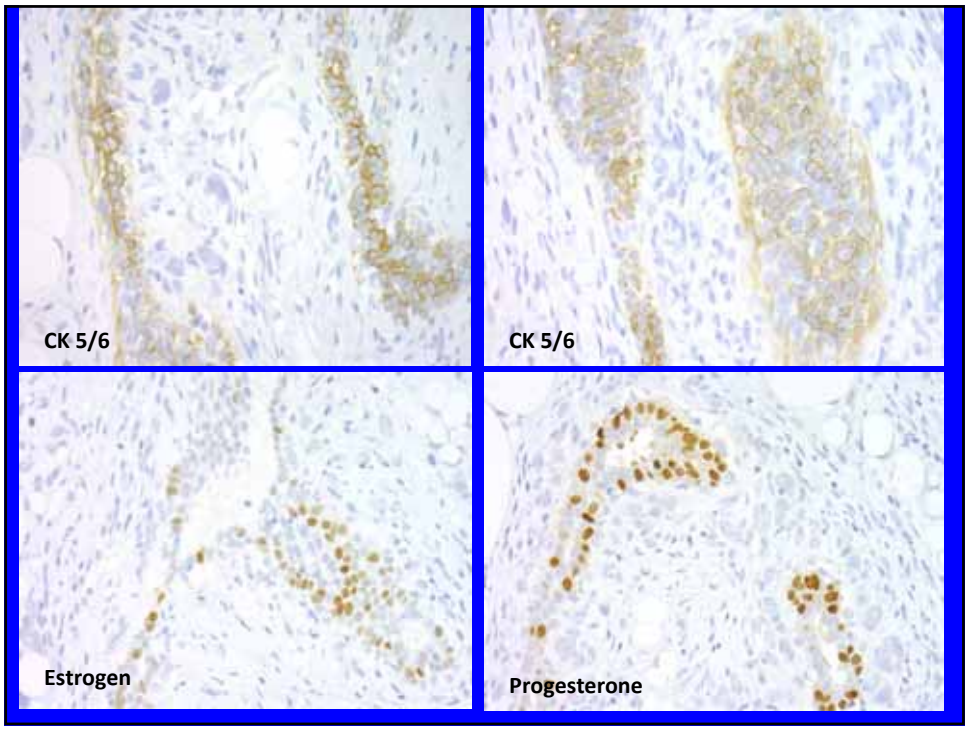
- ✓43-year-old woman with a nodule in the right breast.
- ✓No previous pathological breast lesion.
- ✓The tumor measured 6 cm.
- ✓Frozen biopsy and tumor exeresis.
- ✓10 months later, a new local recurrence was detected (5cms). Radical mastectomy.
- ✓4 years later, free of disease.

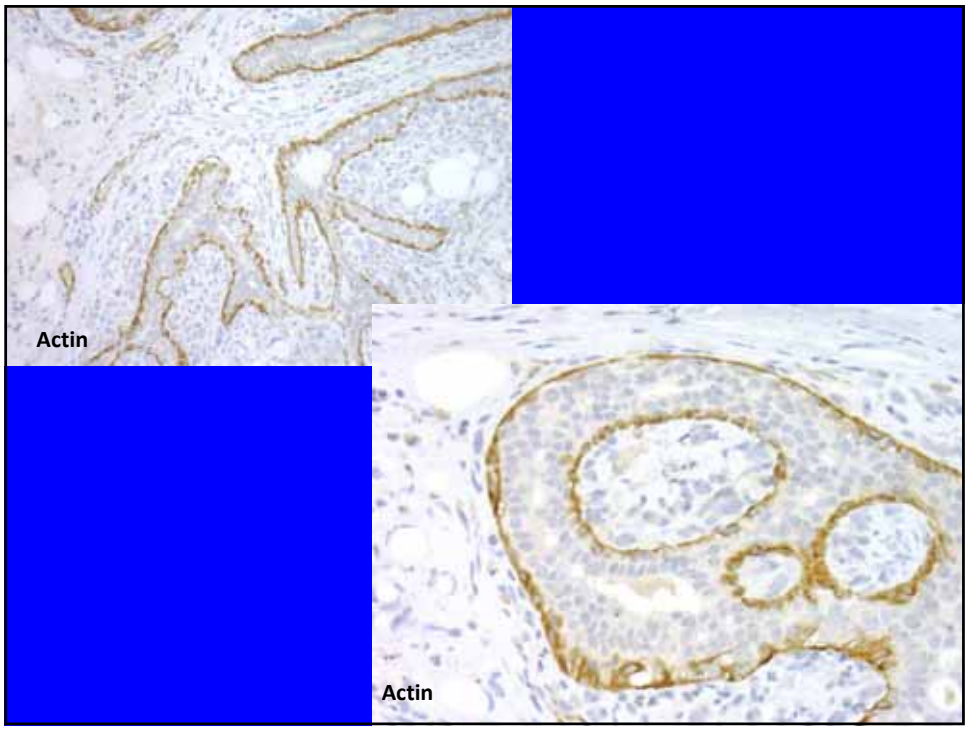


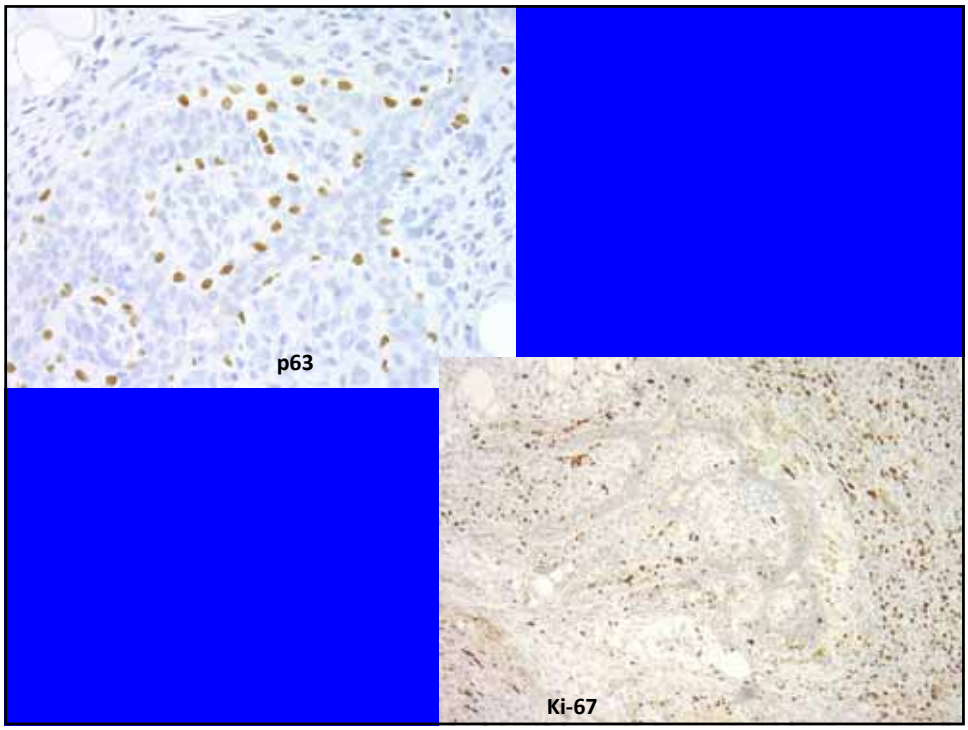


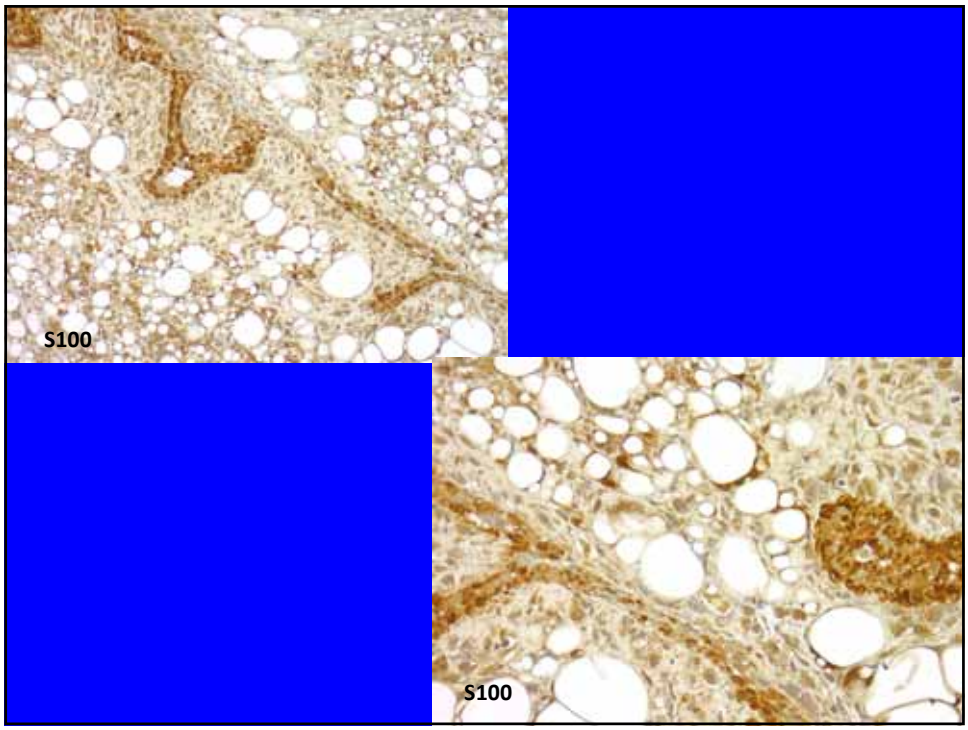





CK 5/6
CK 5/6
Estrogen
Progesterone


Actin
Actin

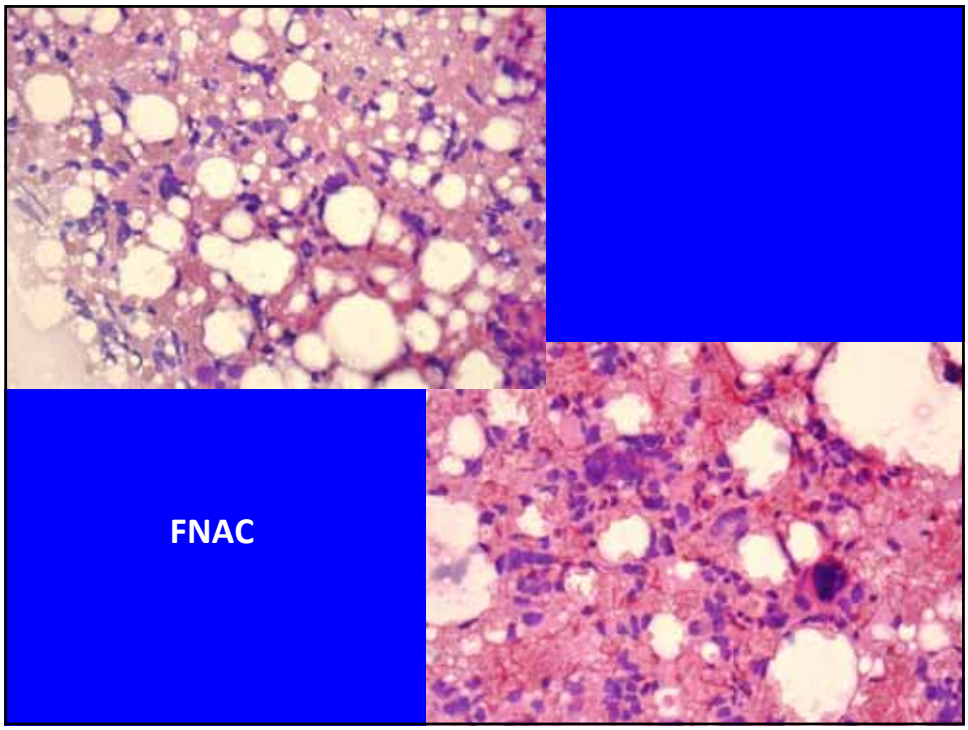

p63
Ki-67

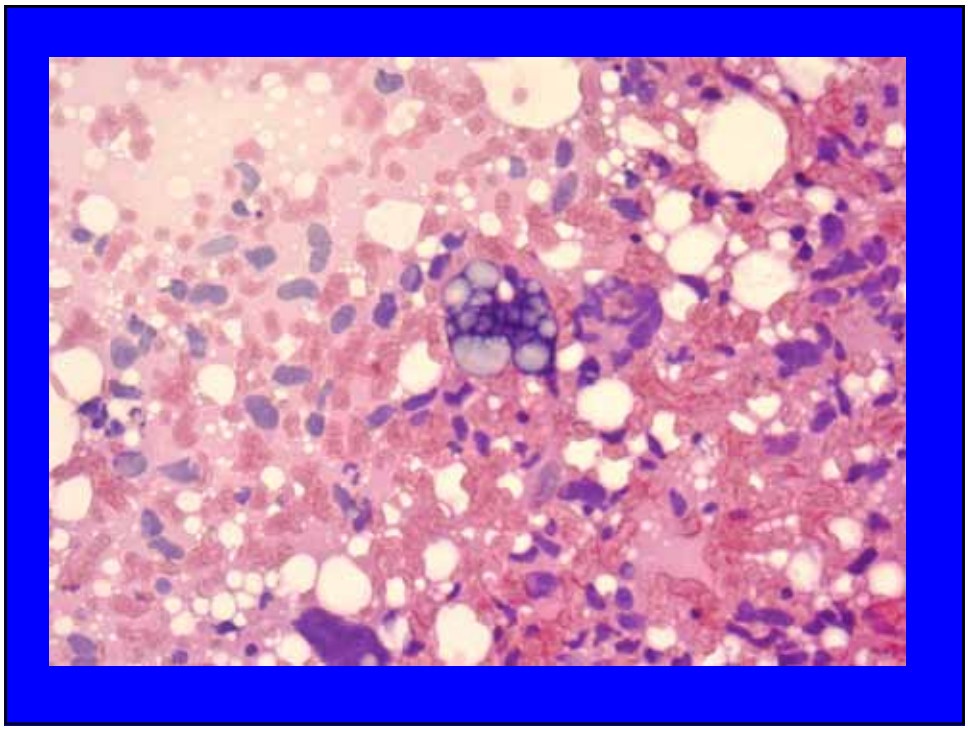

S100
S100

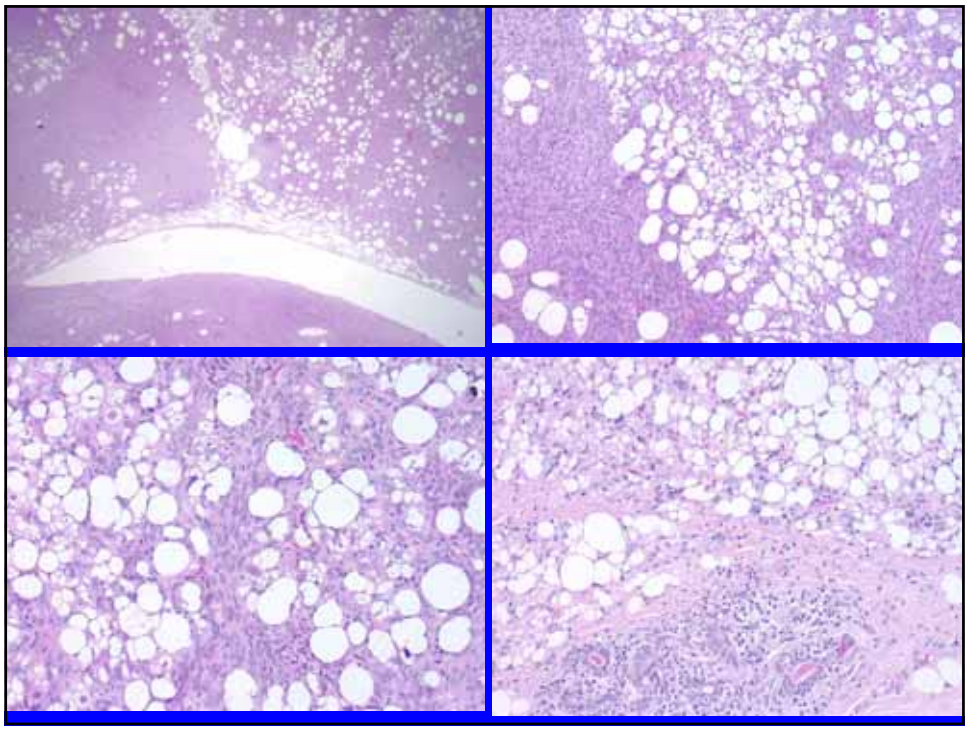
Phyllodes tumor Grade III

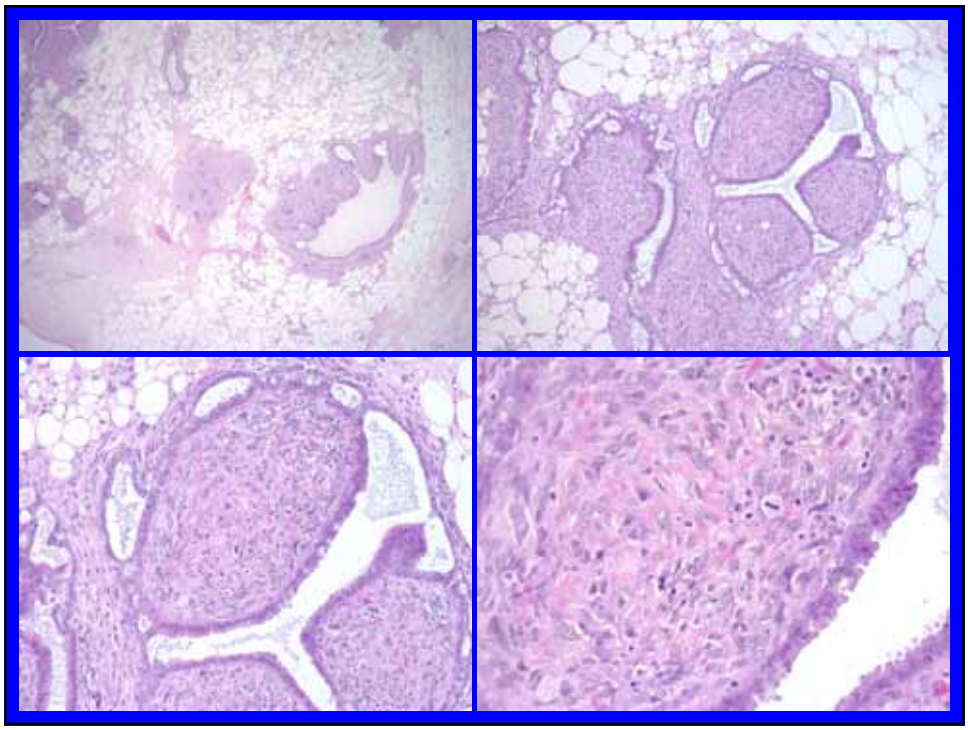
Recurrence/Relapse

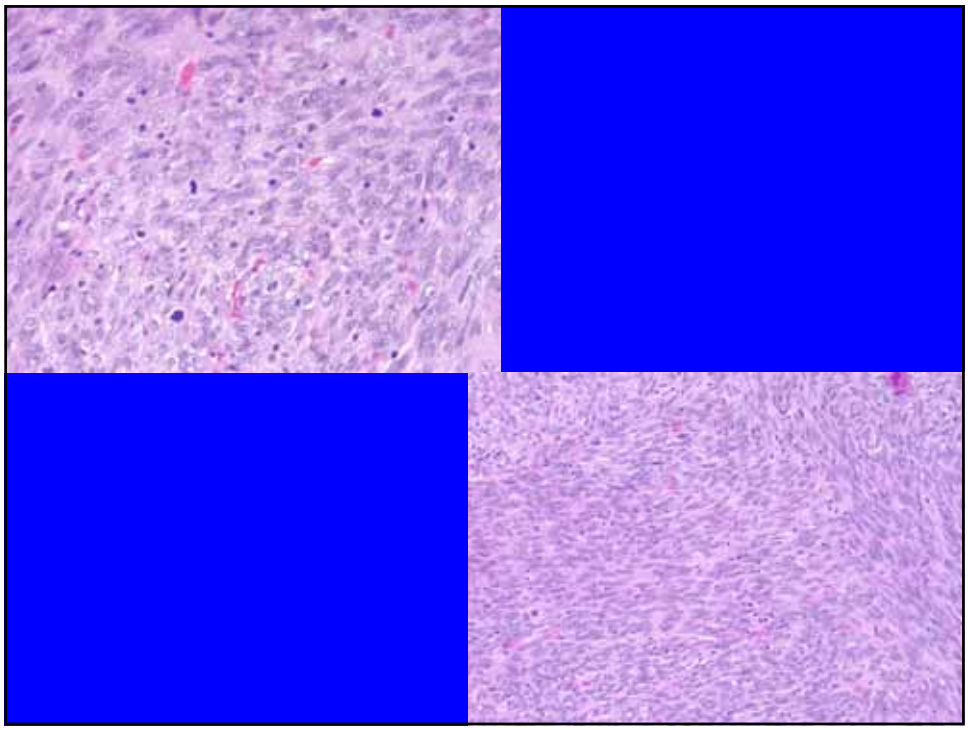
Local recurrence (10 months later). Nodule (4cms). Cytology and frozen biopsy. Radical mastectomy and lymph node exeresis.

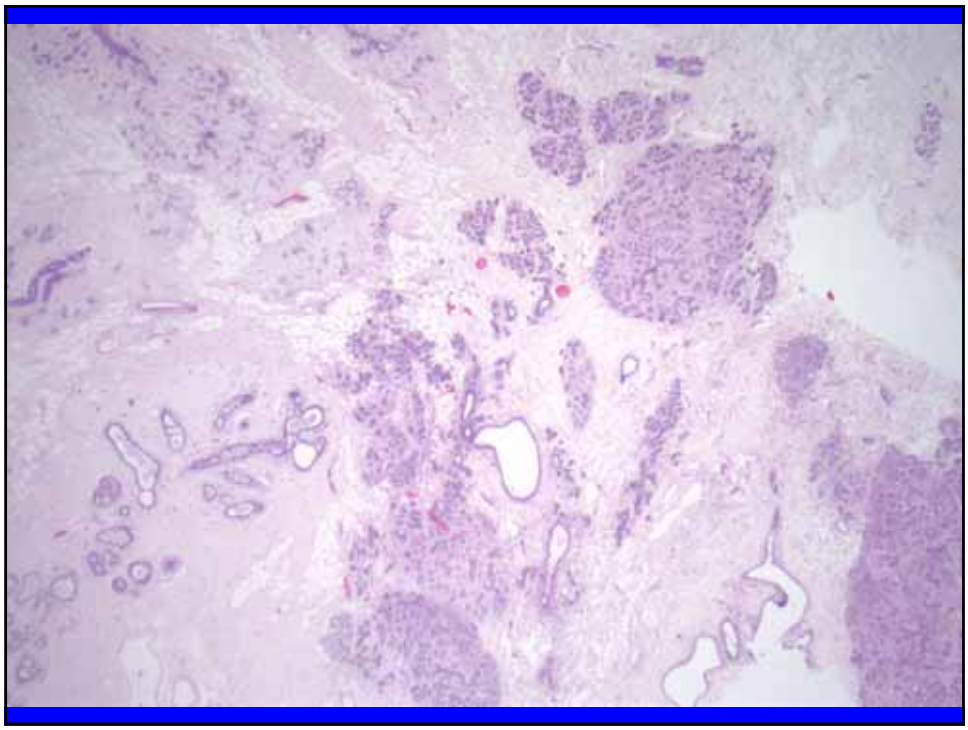

FNAC

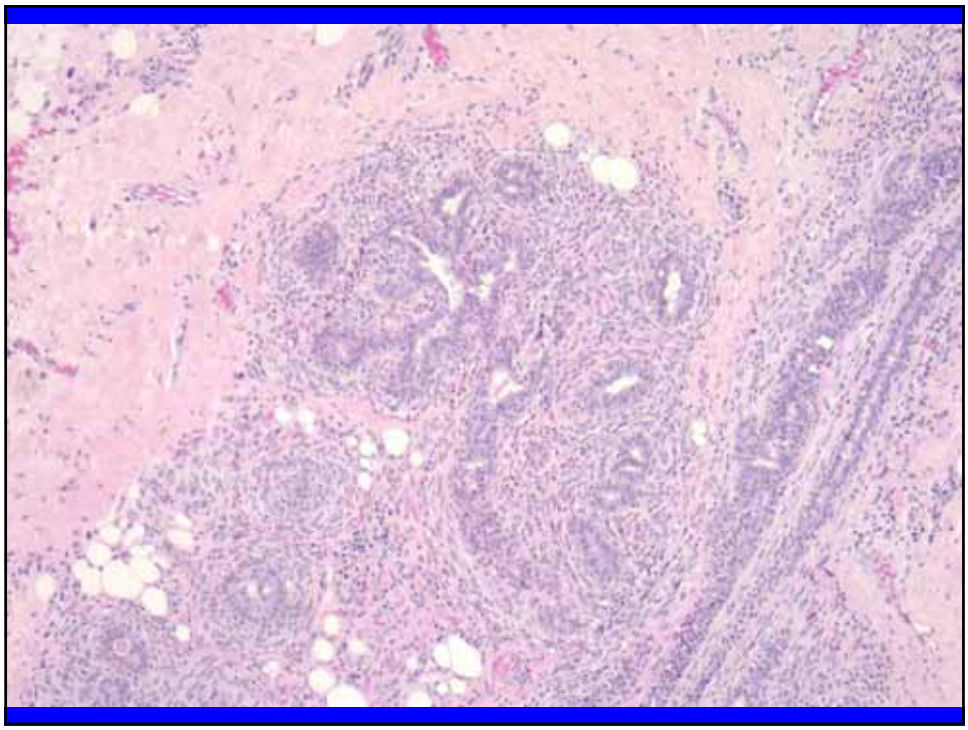


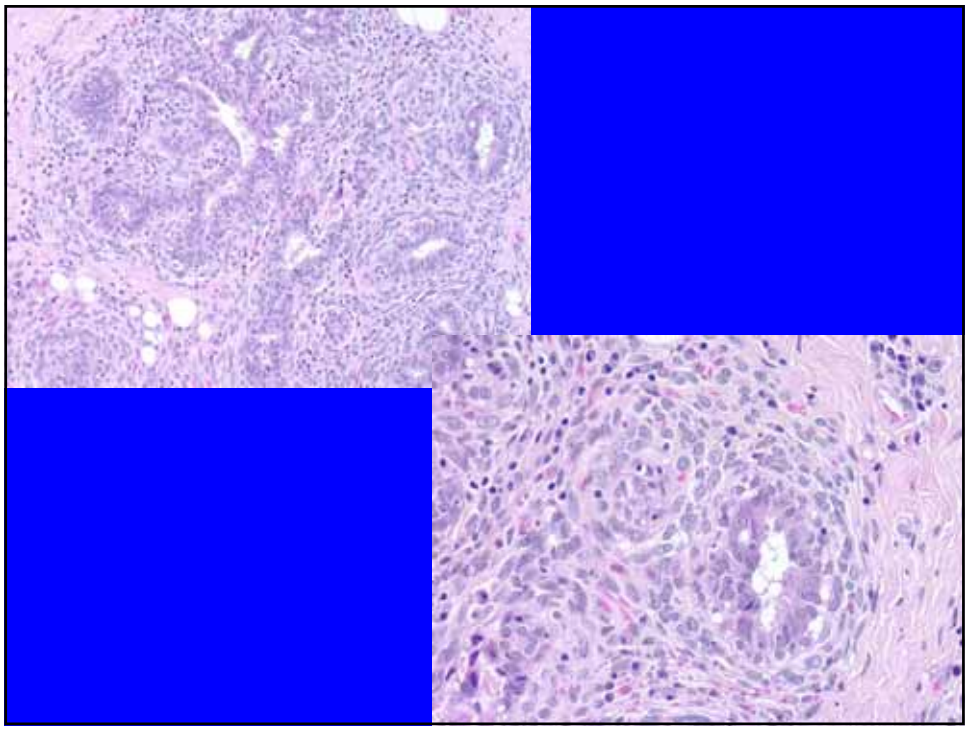


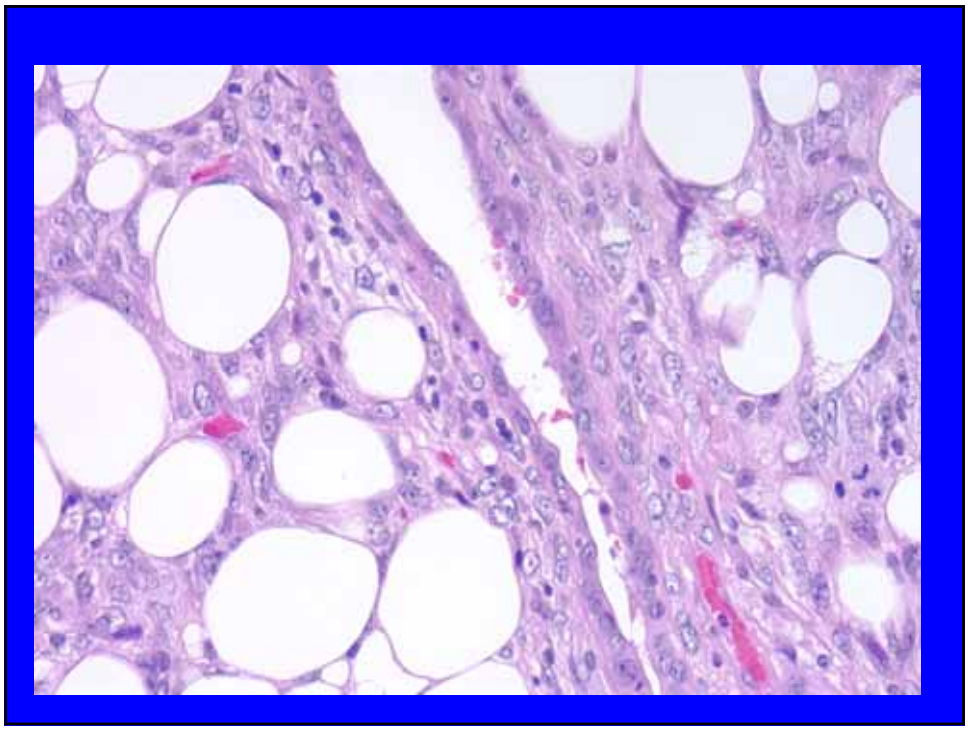


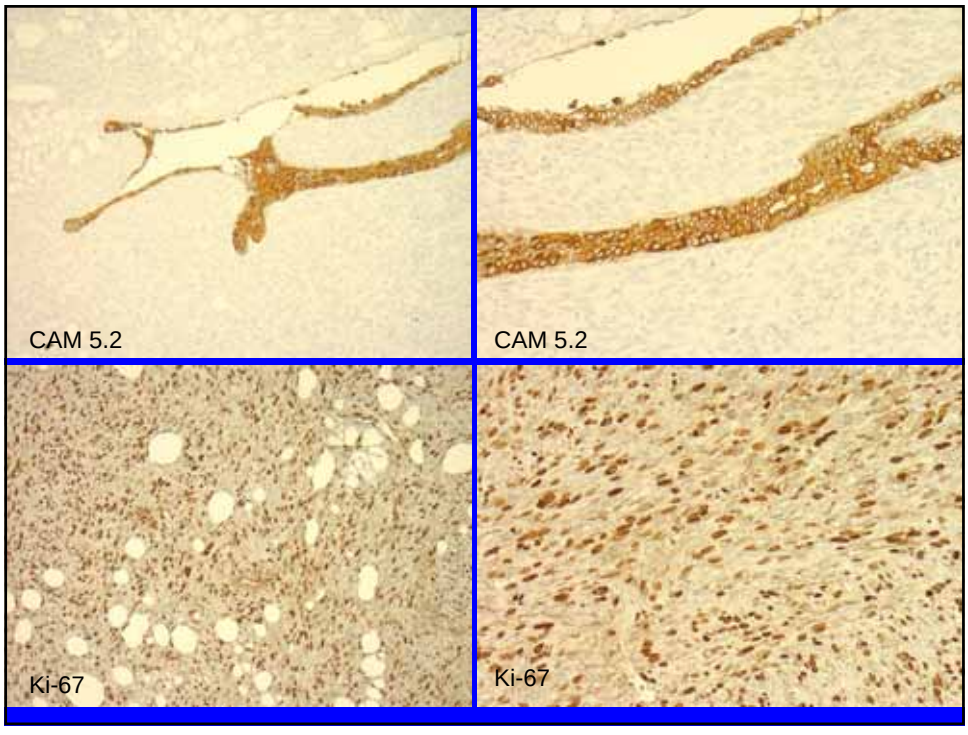


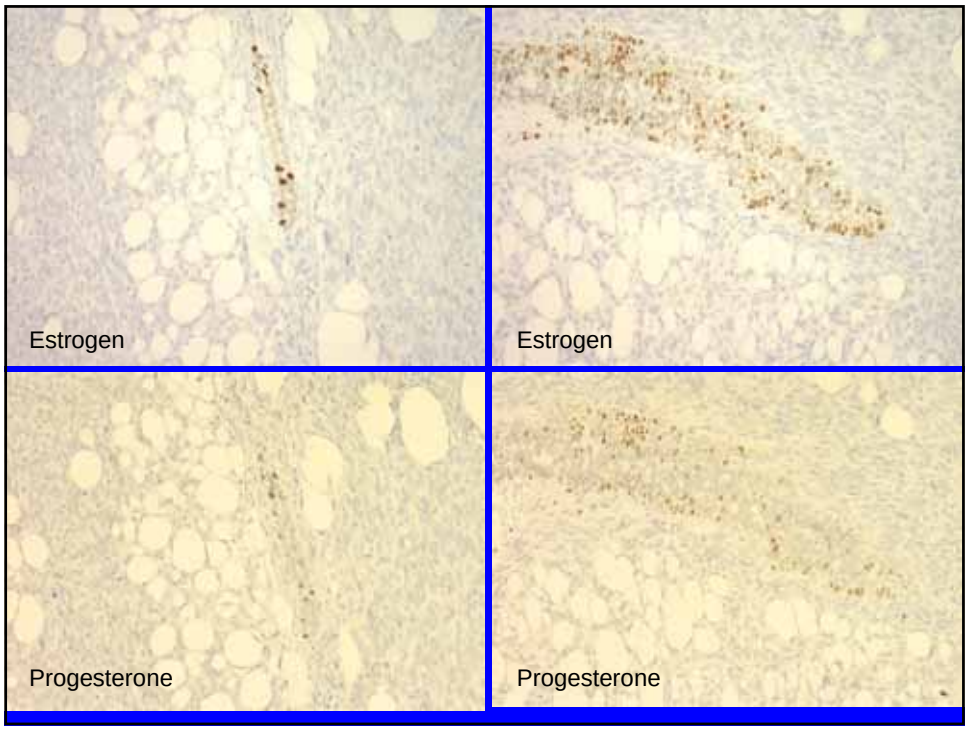


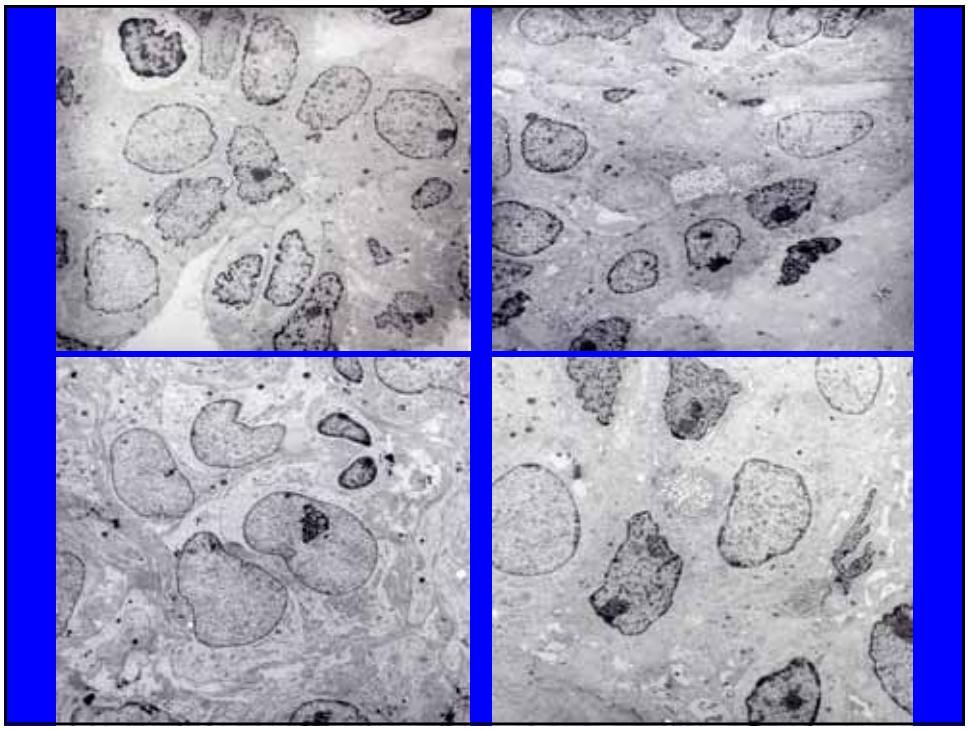







CAM 5.2
CAM 5.2
Ki-67
Ki-67


Estrogen
Estrogen
Progesterone
Progesterone



FINAL DIAGNOSIS

- PHYLLODES TUMOR GRADE III
- PHYLLODES SARCOMA / PLEOMORPHIC LIPOSARCOMA.

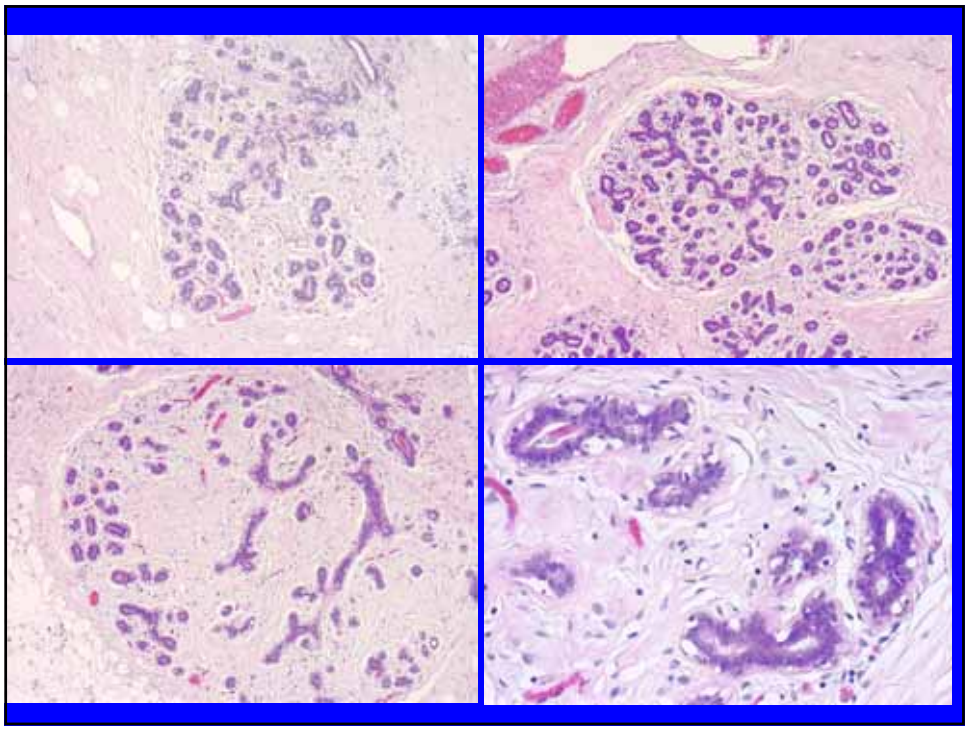
Journal of Clinical Pathology, 1978, **31**, 897-903

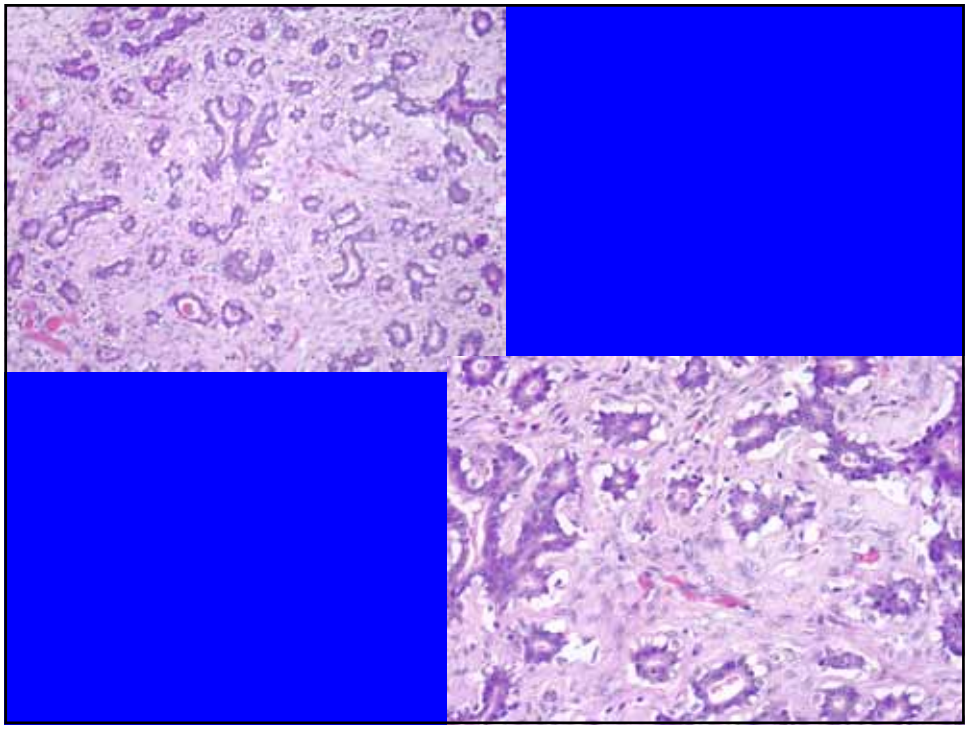
Multifocal histogenesis of a cystosarcoma phyllodes

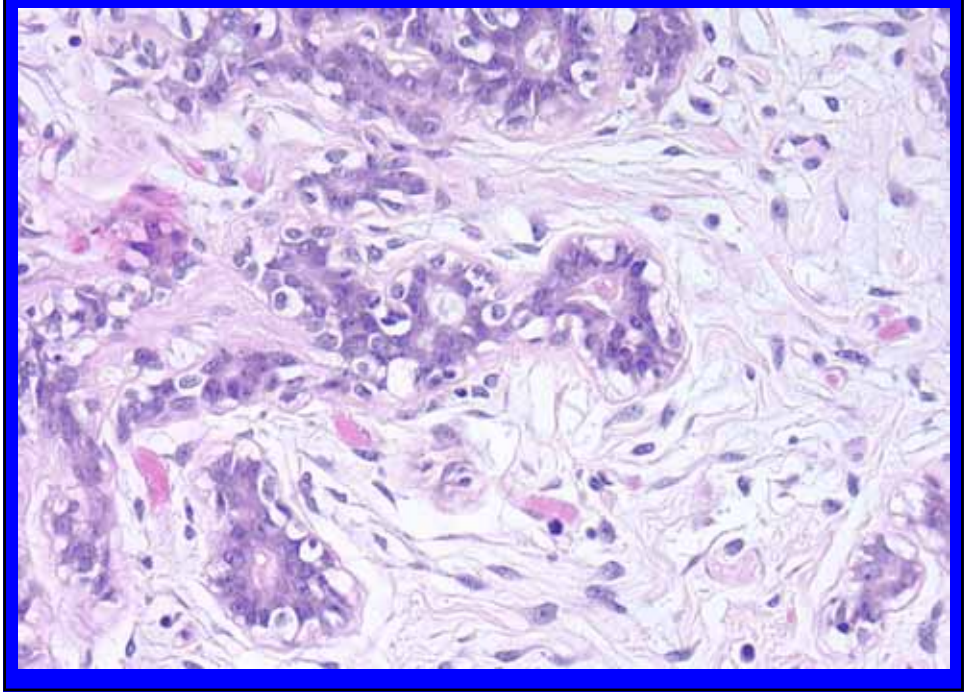
R. SALM

From the Department of Histopathology, Royal Postgraduate Medical School, Hammersmith Hospital, London W12 0HS, UK

SUMMARY An unusual multifocal cystosarcoma phyllodes is reported. It presented as a small, circumscribed tumour mass, which was associated with two diffuse neoplastic lesions which arose sequentially in two geographically separate parts of the mammary disc. Microscopically the tumour appeared to have been enlarging by the formation of isolated satellite tumour nodules within the adjacent normal breast tissue, which represents a third, though rarer way in which a cystosarcoma phyllodes may enlarge.







Phyllodes Tumors of the Breast

The Role of Pathologic Parameters

Puay-Hoon Tan, MD,[1] Thiyagarajan Jayabaskar, MBBS,[2] Khoon-Leong Chuah, FRCPA,[1] Hwei-Yee Lee, MBBS,[1] Yen Tan, MSc,[3] Maryam Hilmy, MSc,[1] Huynh Hung, PhD,[3] Sathiyamoorthy Selvarajan, MBBS, MSc,[1] and Boon-Huat Bay, PhD[4]

Key Words: Grade; Surgical margins; Recurrence; Pseudoangiomatous stromal hyperplasia

DOI: 10.1309/USDVBFM81MLJC1FN

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Anatomic Pathology / Phyllodes Tumors of the Breast

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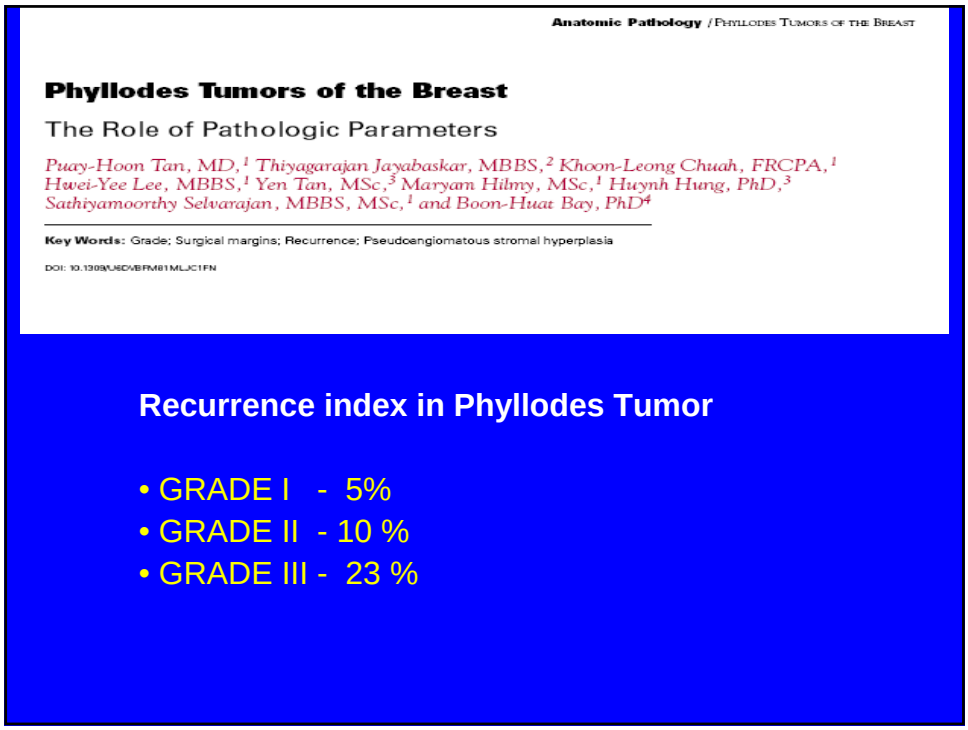
MALIGNANCY CRITERIA:

- Abundant cellularity
- Nuclear atypia
- Necrosis
- Mitosis >5 per 10HPF
- Peripheral tumor infiltration
- Capsule absence
- Pseudoangiomatous stromal hyperplasia absence



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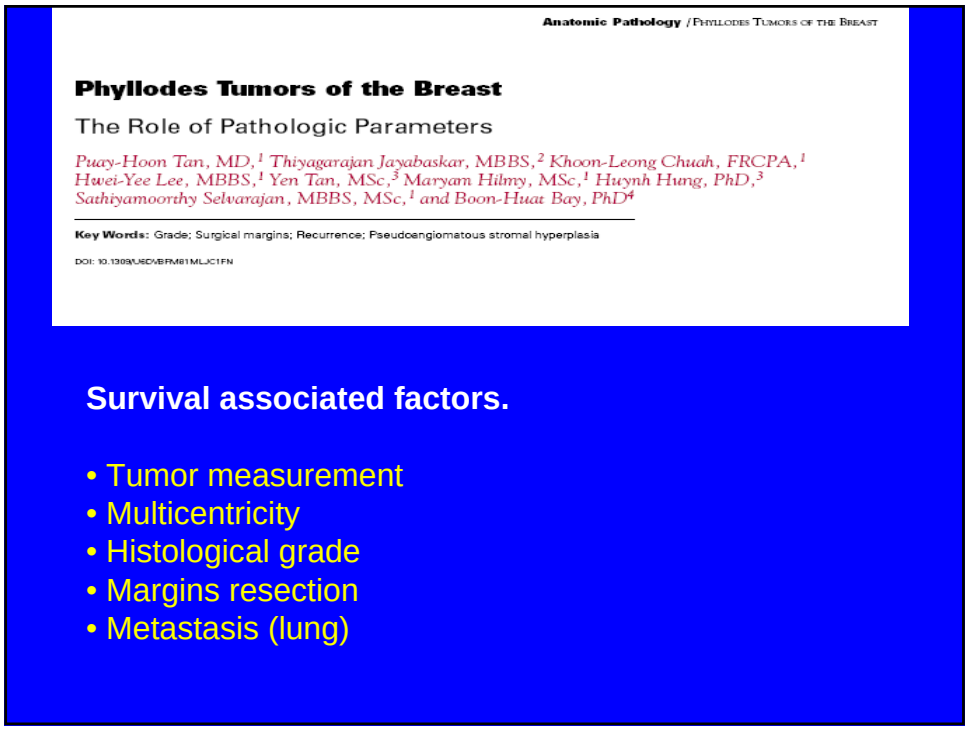
Recurrence index in Phyllodes Tumor

- GRADE I - 5%
- GRADE II - 10 %
- GRADE III - 23 %



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DOI: 10.1309/UECVBFM81MLJC1FN

Survival associated factors.

- Tumor measurement
- Multicentricity
- Histological grade
- Margins resection
- Metastasis (lung)

Modern Pathology (2007) 20, 435–444
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www.modernpathology.org

Phyllodes tumors of the breast segregate in two groups according to genetic criteria

Marick Laé[1], Anne Vincent-Salomon[1], Alexia Savignoni[2], Isabelle Huon[3], Paul Fréneaux[1], Brigitte Sigal-Zafrani[3,4], Alain Aurias[5], Xavier Sastre-Garau[1] and Jérôme Couturier[3]

[1]Département de Biologie des Tumeurs, Service de Pathologie, Institut Curie—Hôpital, Paris, France; [2]Département de Biostatistiques, Institut Curie—Hôpital, Paris, France; [3]Département de Biologie des Tumeurs, Service de Génétique Oncologique, Institut Curie—Hôpital, Paris, France; [4]Institut Curie Breast Cancer Study Group, Institut Curie—Hôpital, Paris, France and [5]Département de Biologie des Tumeurs, Inserm U509, Institut Curie—Hôpital, Paris, France

Phyllodes tumors are rare fibroepithelial tumors of the breast. The pathologic grading of phyllodes tumors based on the aspect of the stromal component, is divided into 2 or 3 grades according to the system used. To determine whether genetic markers could be of use for improving the classification of phyllodes tumors and to provide a better knowledge of the genetic alterations in these tumors, we analyzed chromosomal changes detected by comparative genomic hybridization (CGH) in comparison with histological data, in a series of 30 cases. Recurrent chromosome imbalances were observed in 55, 91 and 100% of benign, borderline and malignant phyllodes tumors, respectively. The mean number of chromosome changes was one in benign, six in borderline, and six in malignant phyllodes tumors. Most frequent genetic imbalances were +1q (12/30), −13q (7/30), −6q (9/30), +5 (9/30) and −10p (8/30). Gains of 1q, present in only one of nine benign tumors, were found in 11/21 (51%) borderline or malignant tumors. Losses of 13q have 13q14.2 as smallest region of overlap, suggesting that the *RB1* gene could be the target of deletions. Amplifications of 12q14, involving the *MDM2* locus, and of 8p24, involving the *MYC* gene, were observed in one case each. Borderline and malignant phyllodes tumors could not be differentiated on the basis of their genomic imbalances (presence and number of chromosomal changes, presence of 1q gain and/or 13q loss). Conversely, benign tumors could be significantly differentiated from the group composed of borderline and malignant tumors ($P<0.01$). This study reveals two distinct patterns of genomic imbalance in phyllodes tumors: benign, with none or a few chromosome changes and malignant, with numerous recurrent chromosomal changes, in particular 1q gain and 13q loss. Helpful additional pathological criteria for differentiating the two genetic groups of phyllodes tumors are the nuclear size and the mitotic rate.
Modern Pathology (2007) **20**, 435–444, doi:10.1038/modpathol.3800756; published online 2 March 2007

Keywords: phyllodes tumors; comparative genomic hybridization; FISH; *MDM2*; *MYC*; *RB1*

Breast Cancer Res Treat (2008) 109:199–207
DOI 10.1007/s10549-007-9652-2

REVIEW

Spindle cell lesions of the breast—the pathologic differential diagnosis

Gary M. K. Tse · Puay Hoon Tan · Philip C. W. Lui · Thomas C. Putti

Received: 4 June 2007 / Accepted: 7 June 2007 / Published online: 18 July 2007

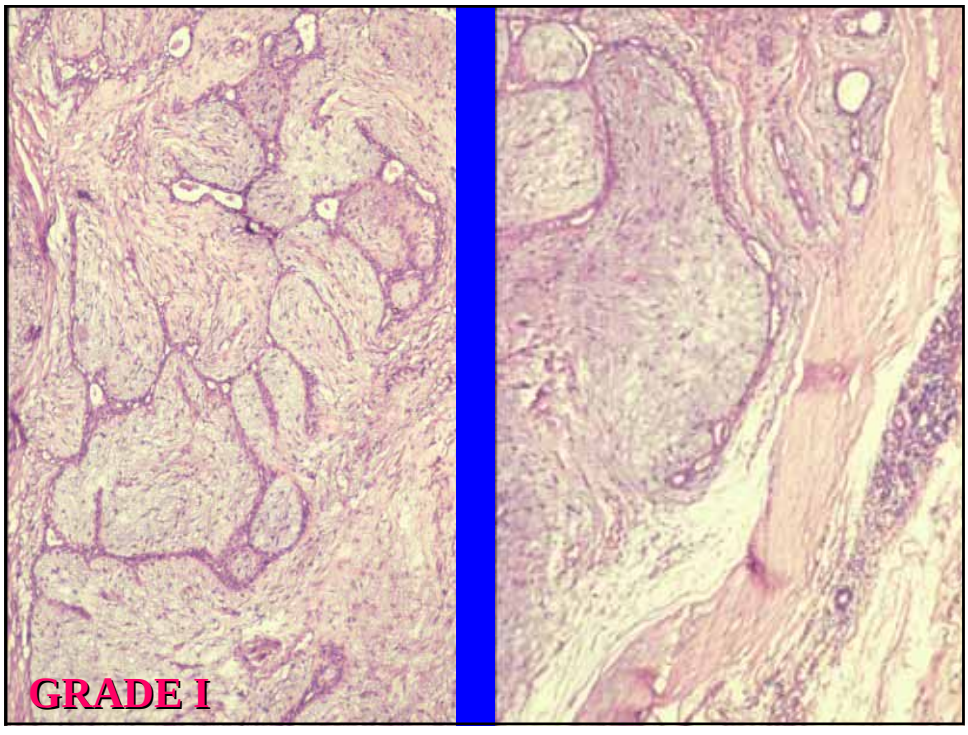
Histological subtypes

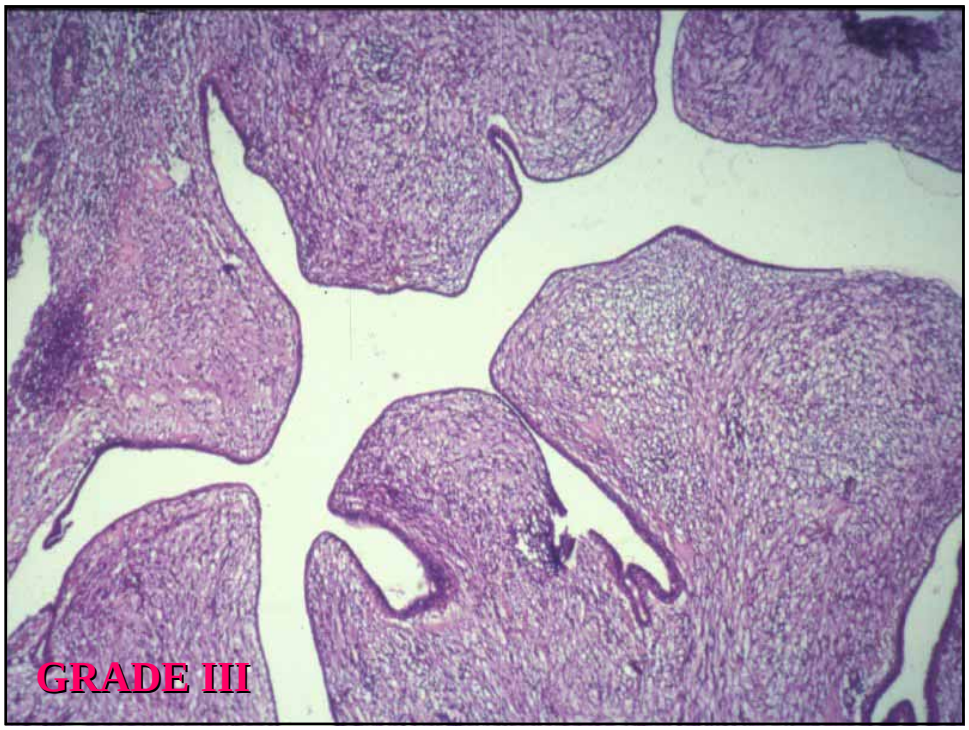
- Fibroadenoma
- Phyllodes tumor
- Pseudoangiomatous stromal hyperplasia
- Hamartoma
- Adenomyoepithelioma
- Metaplastic carcinoma
- Angiosarcoma
- Breast sarcoma

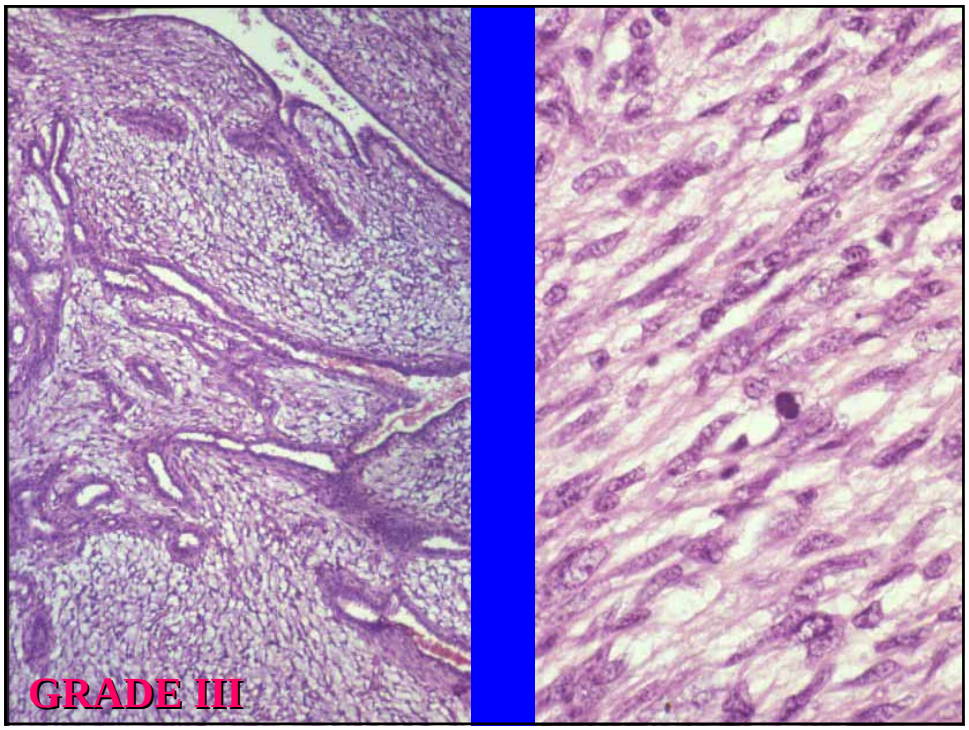
WHO CLASSIFICATION
BREAST TUMOR - 2004

Fibroepithelial tumors

Phyllodes tumor Grade I-III



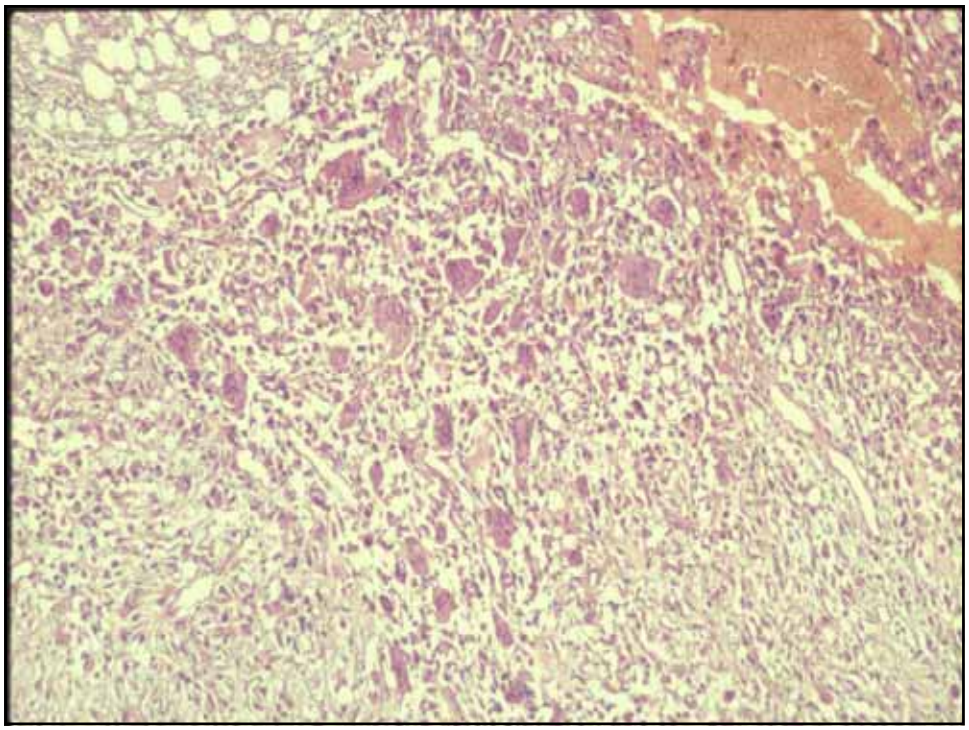

GRADE III

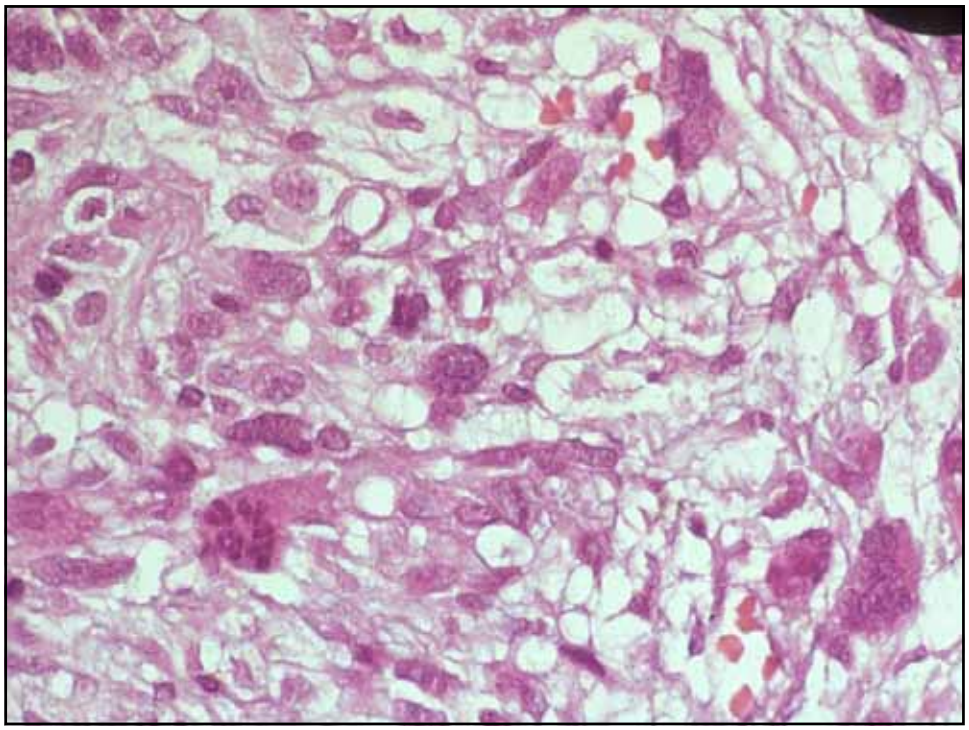

GRADE III

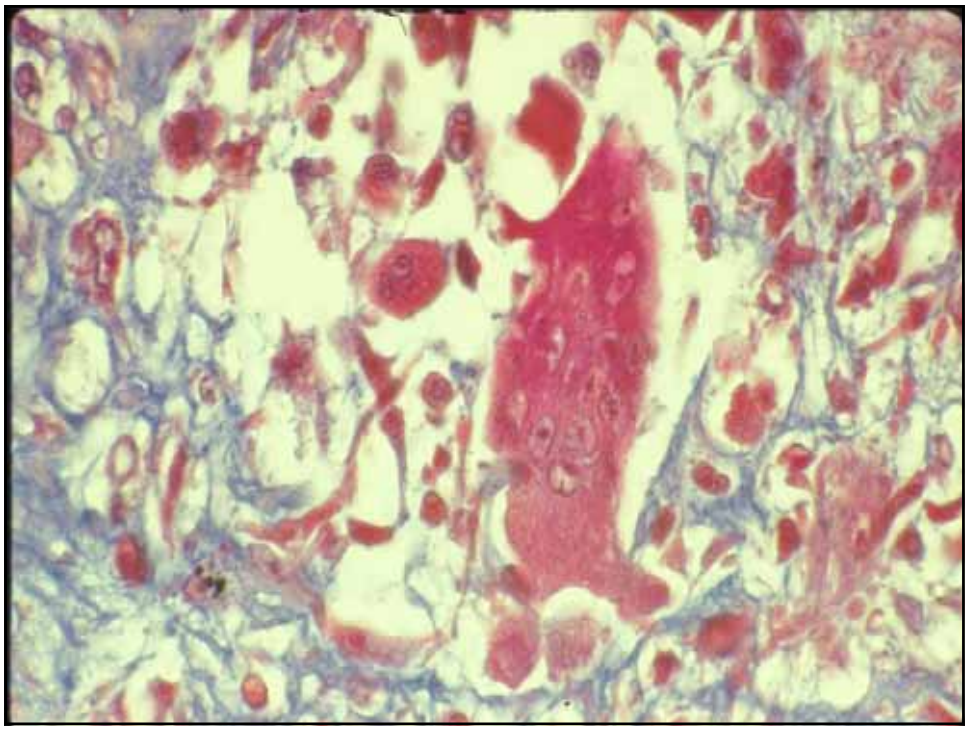
WHO CLASSIFICATION
BREAST TUMOR - 2004

Mesenchymal tumors:

Same classification as bone and soft tissue tumors.





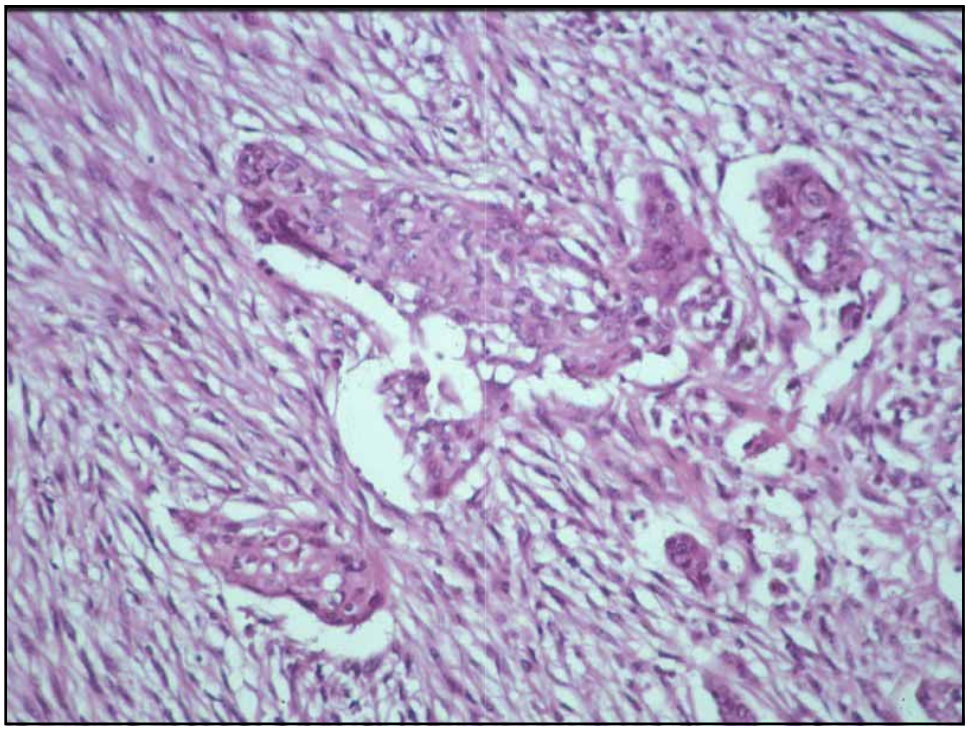


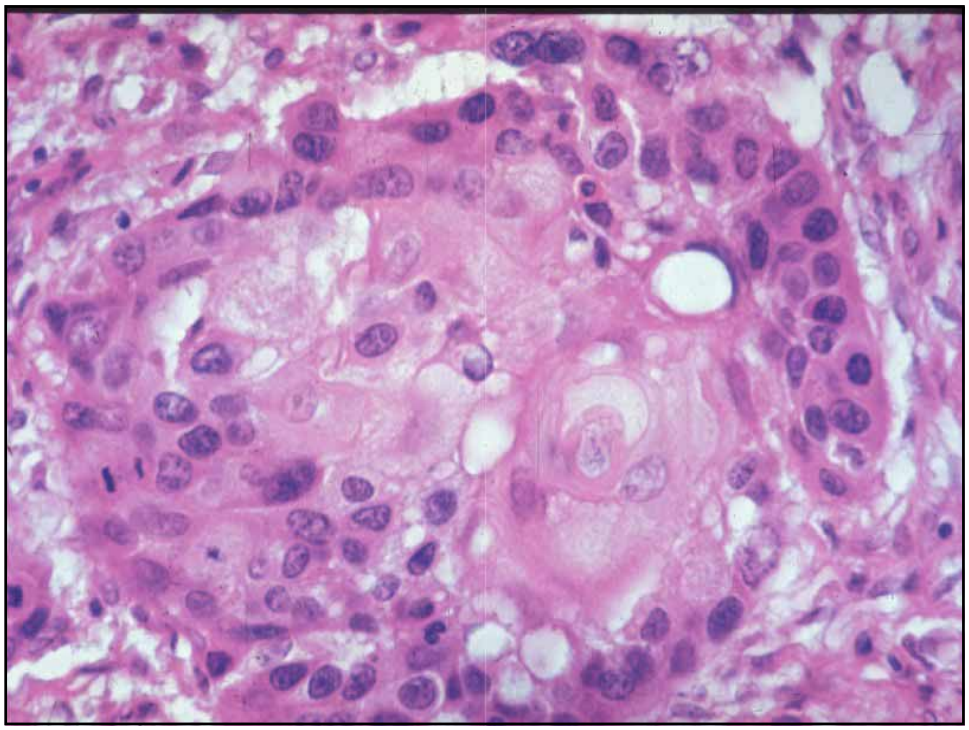
CASE 2

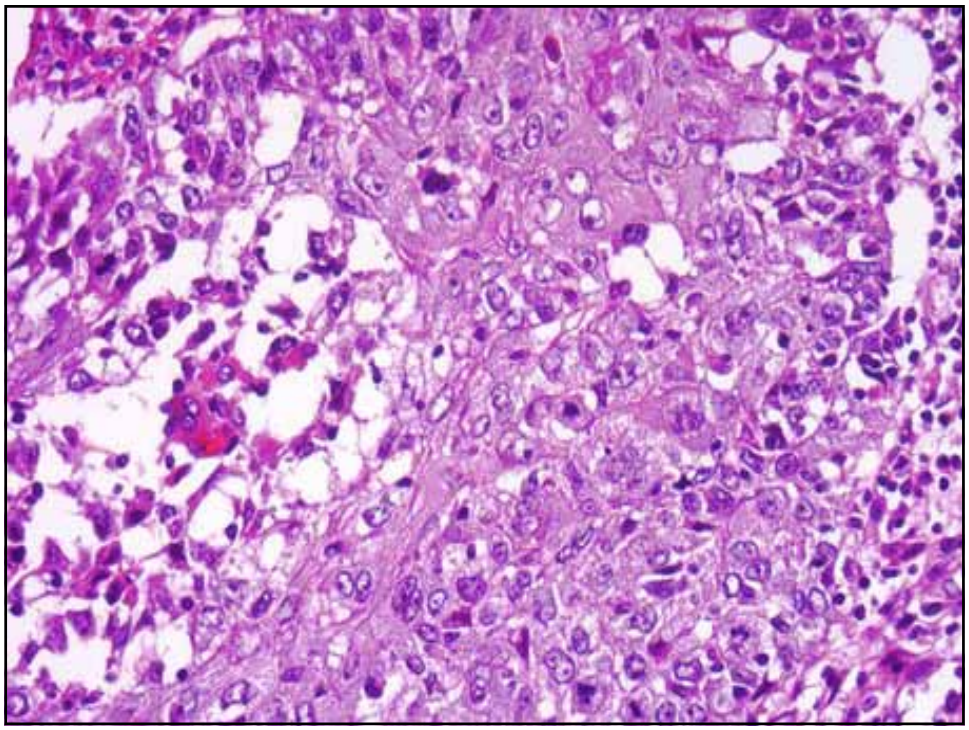
Antonio Llombart-Bosch

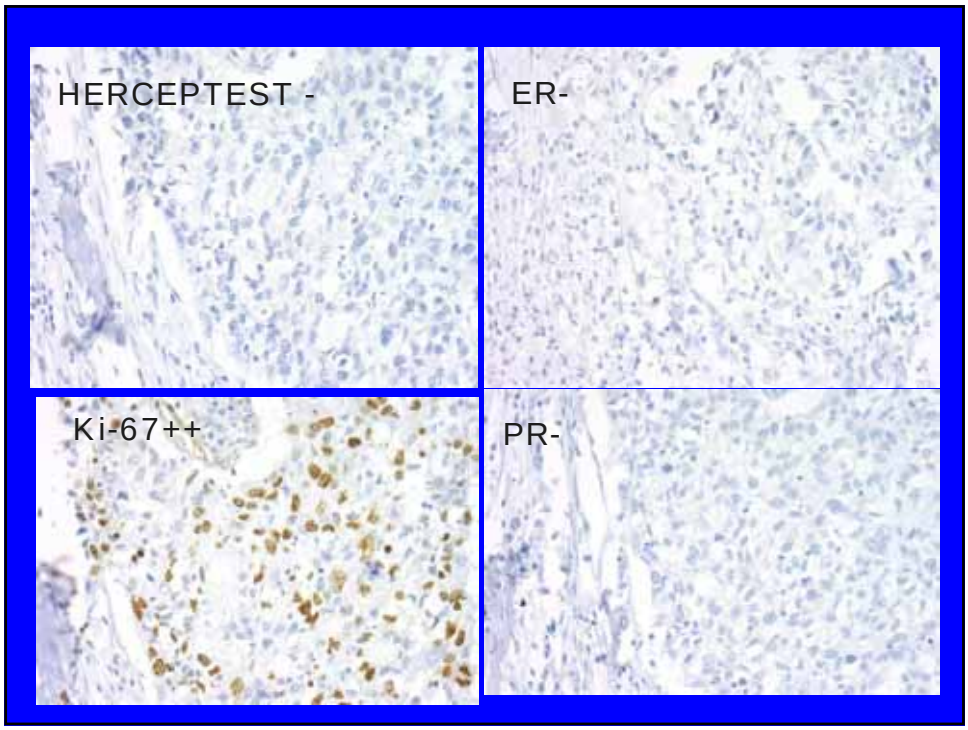
CLINICAL DATA

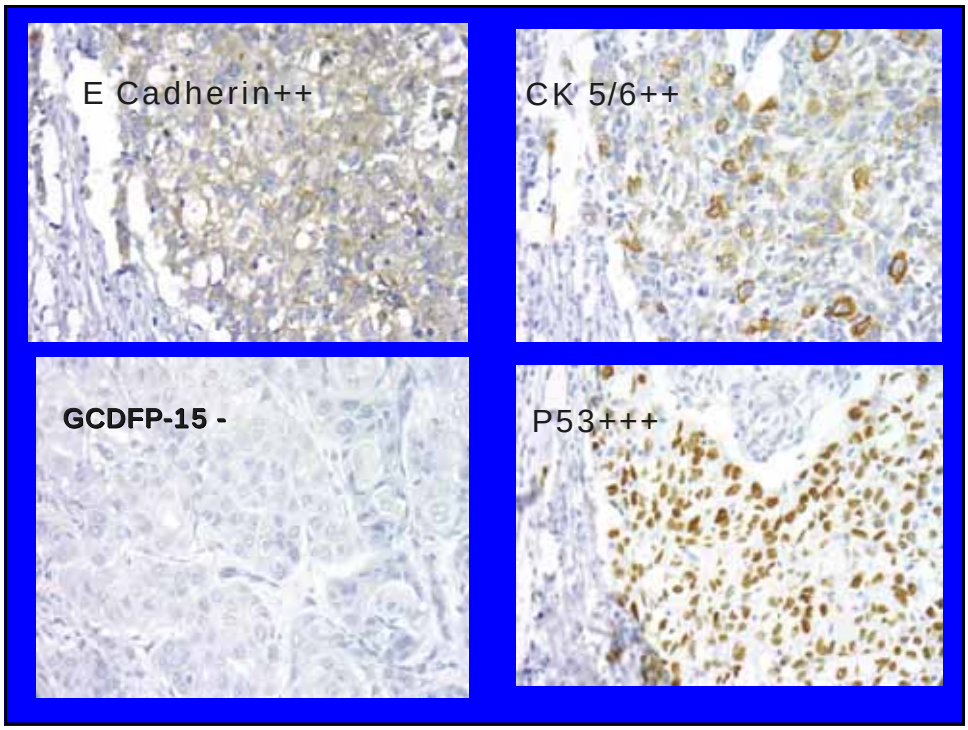
- ✓ 63-year-old woman with a nodule in left breast (ESQ)
- ✓ The tumor measured 3cms
- ✓ Fine needle aspiration cytology (positive for malignancy).
- ✓ Frozen biopsy and quadrantectomy
- ✓ Sentinel lymph node positive
- ✓ 3 positive for metastasis lymph nodes from 16
- ✓ Radiotherapy and chemotherapy.
- ✓ Follow up, 2 years, free of disease.








HERCEPTEST -
ER-
Ki-67++
PR-


E Cadherin++
CK 5/6++
GCDFP-15 -
P53+++

DIAGNOSIS

SQUAMOUS METAPLASTIC CARCINOMA
OF THE BREAST

TRIPLE NEGATIVE

Squamous metaplastic carcinoma of the breast. Study of 11 cases.

WHO 2003 Classification. Metaplastic carcinoma.

- Exclusively epithelial
  - Squamous
    - Large cells queratinizing
    - Spindle cells
    - Acantholytic
  - Adenocarcinoma with spindle cell differentiation
  - Adenosquamous including mucoepidermoid
- Mixed epithelial/mesenchymal
  - Carcinoma with chondroid metaplasia
  - Carcinoma with osseous metaplasia
  - Carcinosarcoma (with specific components)

Incidence

- Squamous metaplastic carcinoma of the breast are rare and represent from 0.06% to 1.1% of invasive carcinomas.

Diagnosis Criteria. Squamous metaplastic breast carcinoma.

- Absence of others neoplastic components in the tumor.
- The tumor is not related to adjacent cutaneous structures.
- Absence of primary squamous carcinoma in other locations outside the breast.

Clinicopathological summarized

Variable	Value
Total of patients	11
Age	62.5 (49-89)
Clinical presentation Breast nodule Cystic nodule	 11 (100%) 7 (63.6%)
FNAB results Positive Suspicious Negative Not performed	 7 (63.6%) 2 (18.2%) 1 (9.1%) 1 (9.1%)

Clinicopathological summarized

Variable	Value
Location	
Left breast	8 (72,7%)
Right breast	3 (27,3%)
Surgical type	
Radical Mast + lymph nodes exeresis	8 (72,7%)
Mastectomy	1 (9,1%)
Quadrantec + lymph nodes exeresis	1 (9,1%)
Quadrantec without lymph nodes exer	1 (9,1%)
Tumor measure cms	3,3 (1,5-5)

Clinico-pathological summarized

Variable	Value
Histological grade	
1	0
2	2 (18.2%)
3	9 (81.8%)
Nuclear grade	
1 y 2	0
3	11 (100%)
Insitu ductal component	
absent	5 (45.5%)
Poor	4 (36.4%)
Extensive	2 (18.2%)

Clinico-pathological summarized

Variable	Value
Lymph node status 1 2 3 No lymph node exeresis	 5 (45.5%) 3 (27.3%) 1 (9.1%) 2 (18.2%)
I IIA IIB No	1 (9.1%) 4 (36.4%) 4 (36.4%) 2 (18.2%)

Clinicopathological summarized

Variable	Value
Local and distance metastasis Yes No	 4 (36.3%) 7 (63.7%)
Metastasis sites •Axillary lymph nodes •Brain and bone marrow •Osseous	 1 (9.1%) 1 (9.1%) 2 (18.2%)

Follow-up

Variable	Value
• Died •Alive	3 (27.3%) 8 (72.7%)
Free survival (5 years)	2 (18.2%)

Conclusions.
Squamous breast carcinoma

- Incidence 2.5 %
- Average age 62.5 years (49-89)
- Clinical presentation with breast nodule and cystic fluid in 7 cases.
- FNAB positive for malignancy in 7 cases (63.6%)
- Tumor incidence predominant in left breast.
- Tumor measurement (average 3.3 / 1.5-5 cm

Conclusions case 2

- The histological grade (Bloom–Richardson) and nuclear grade (Fisher) was high in all cases.
- IIA and IIB were the predominant pathological status.
- Two tumors were negative for estrogen, progesterone and Her-2 neu (null) and FISH analysis confirmed no Her2 amplification.
- From 11 patients, 3 died and 8 are alive, free of disease (72.7%).

Case 3

Antonio Llombart-Bosch

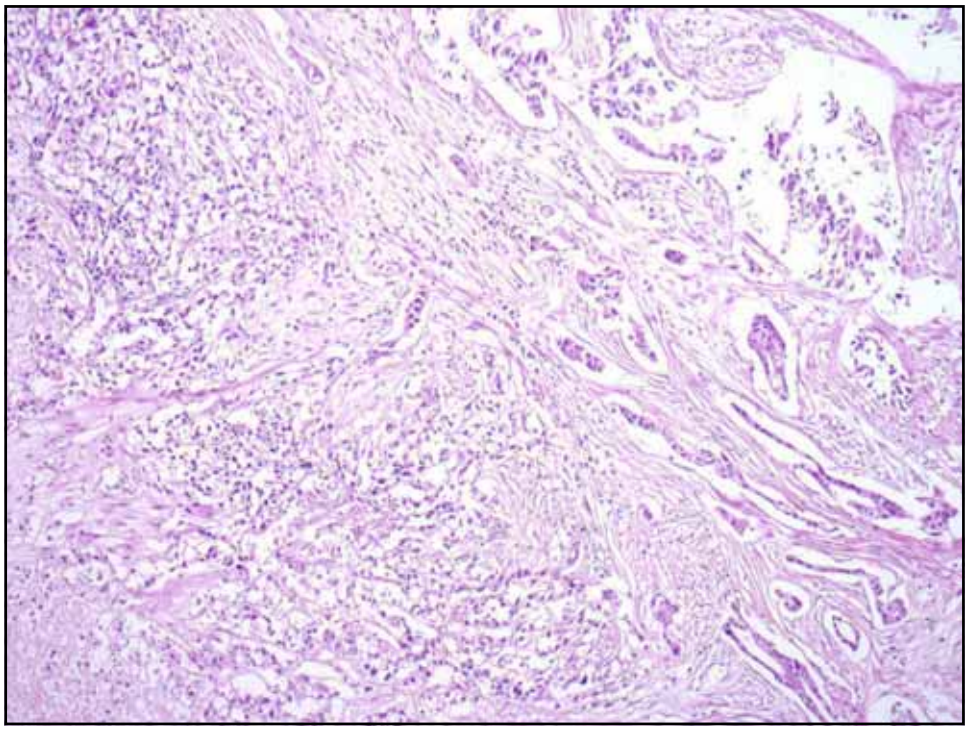
CASE Nº3

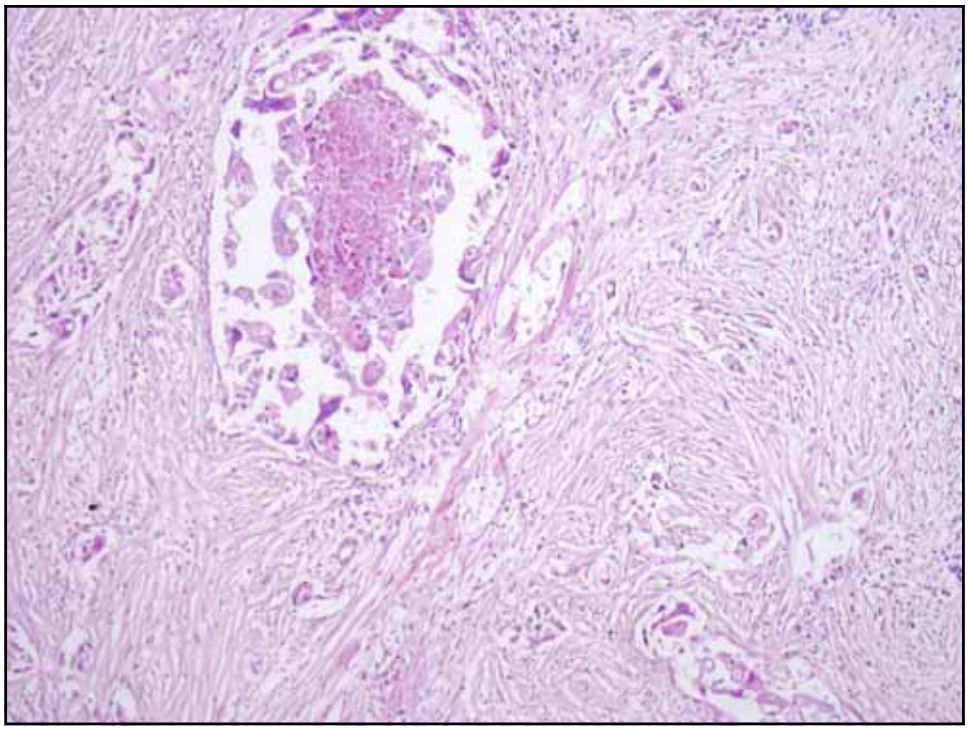
72-year-old woman with a nodule in the left breast. Radical mastectomy. The tumor measured 5.3 cm, 6 lymph nodes were involved..

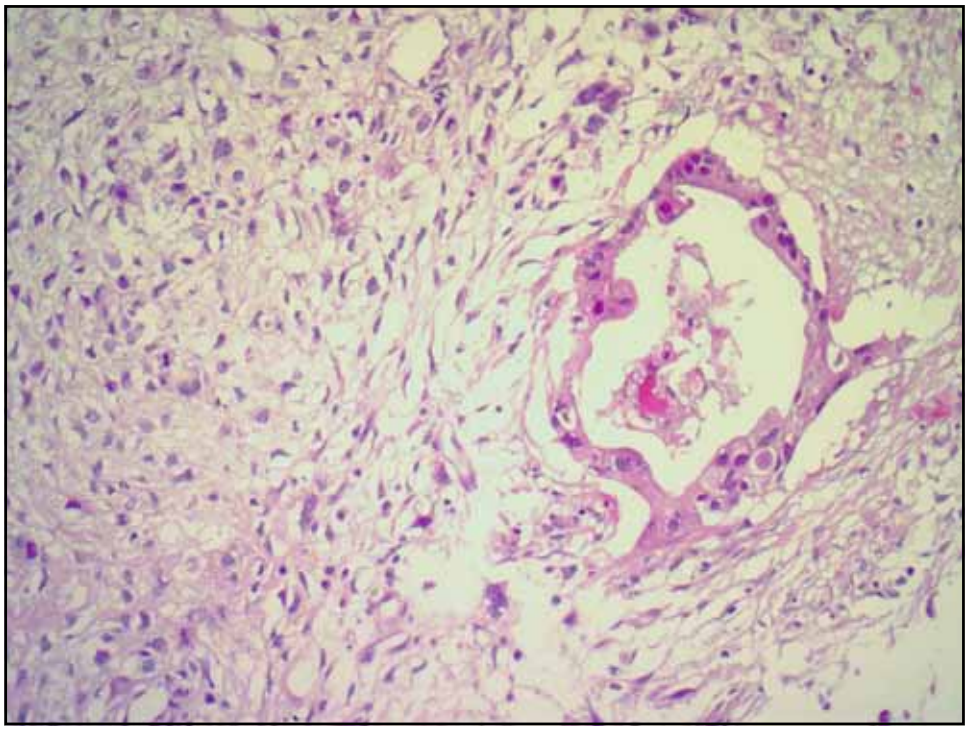
Adjuvant systemic chemotherapy, loco regional radiotherapy and hormonal therapy.

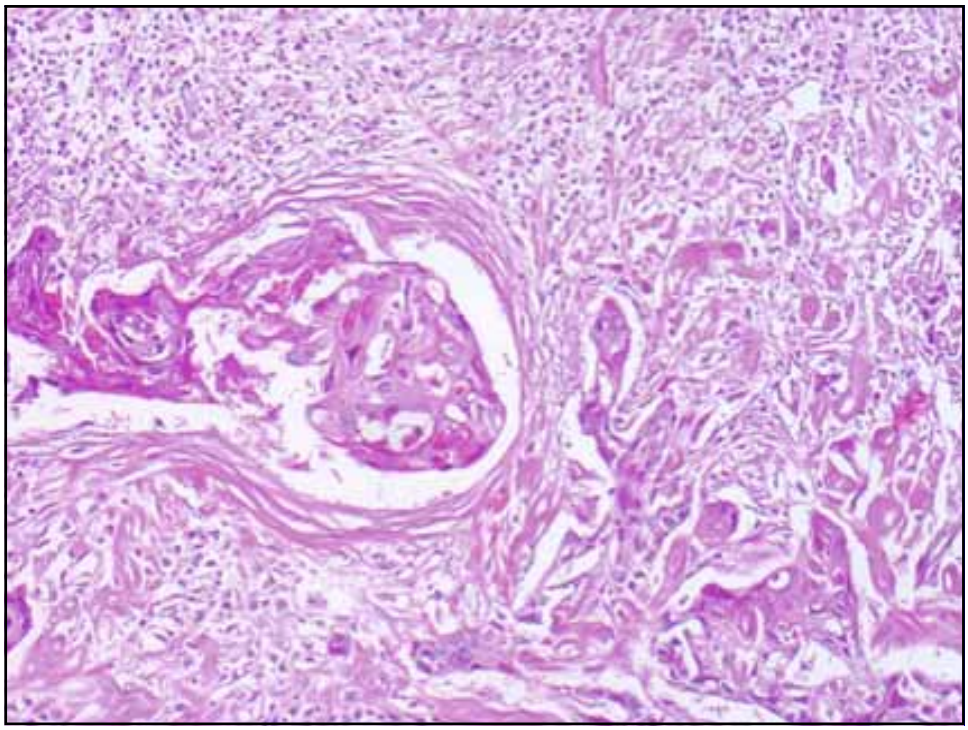
Thirty-one months after diagnosis, metastases in lung and brain. Further chemotherapy and radiotherapy failed to prevent a second relapse. The patient died 35 months after diagnosis.

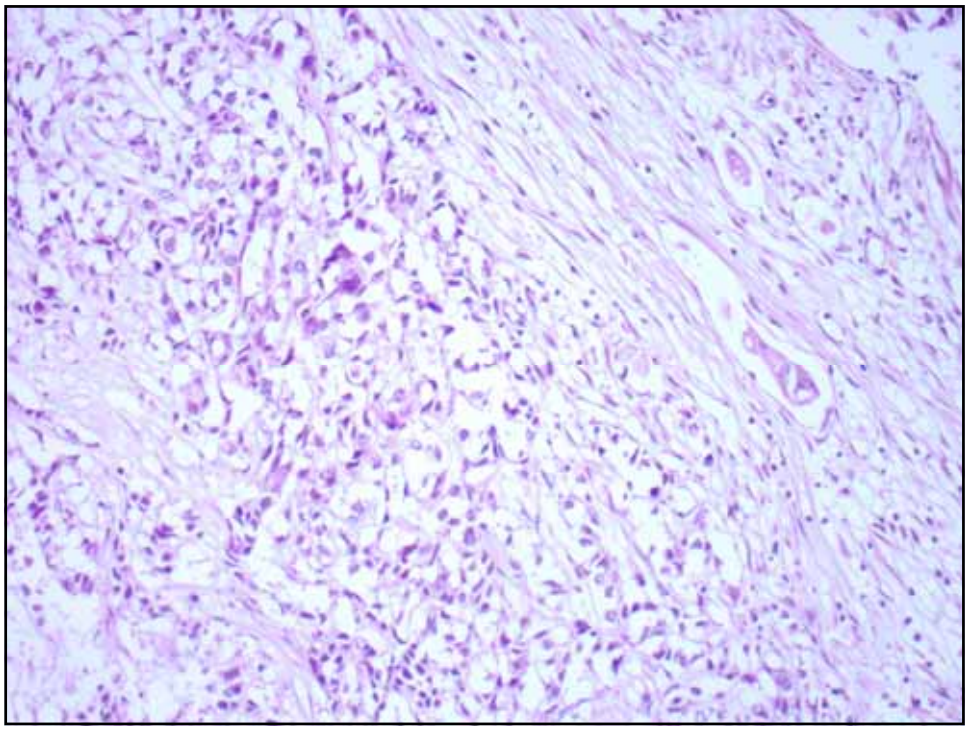
Grossly, showed a double nodule: a round, circumscribed, brown-reddish nodule measuring 5.3 cm with an elastic consistency and micro cystic areas; it merged together with a second whitish, hard, satellite tumor of 2.2 cm.

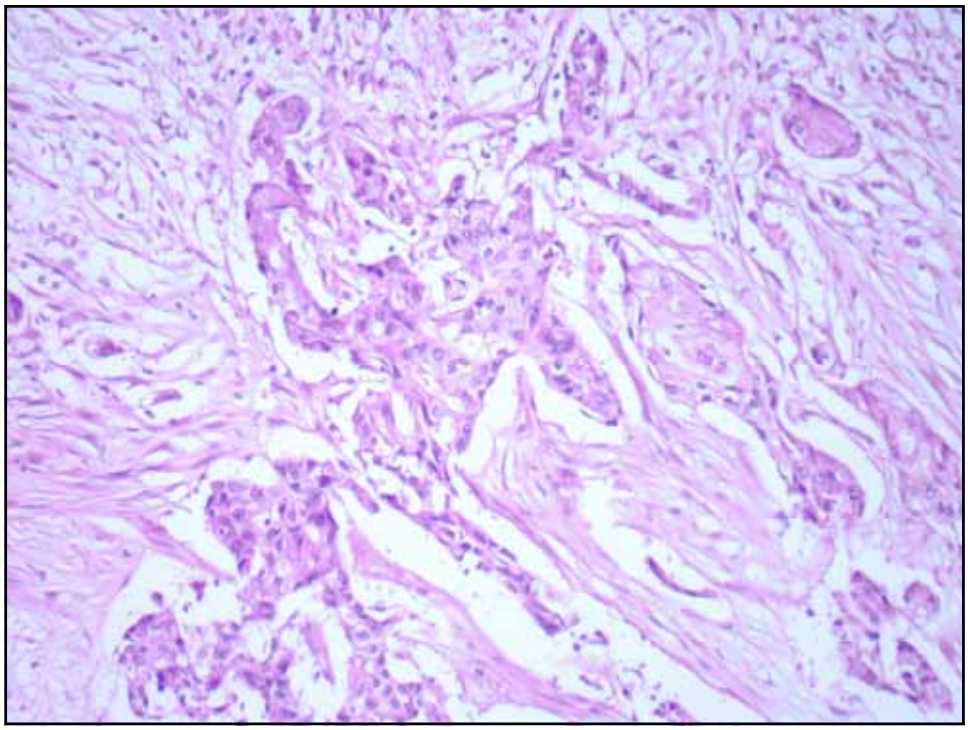


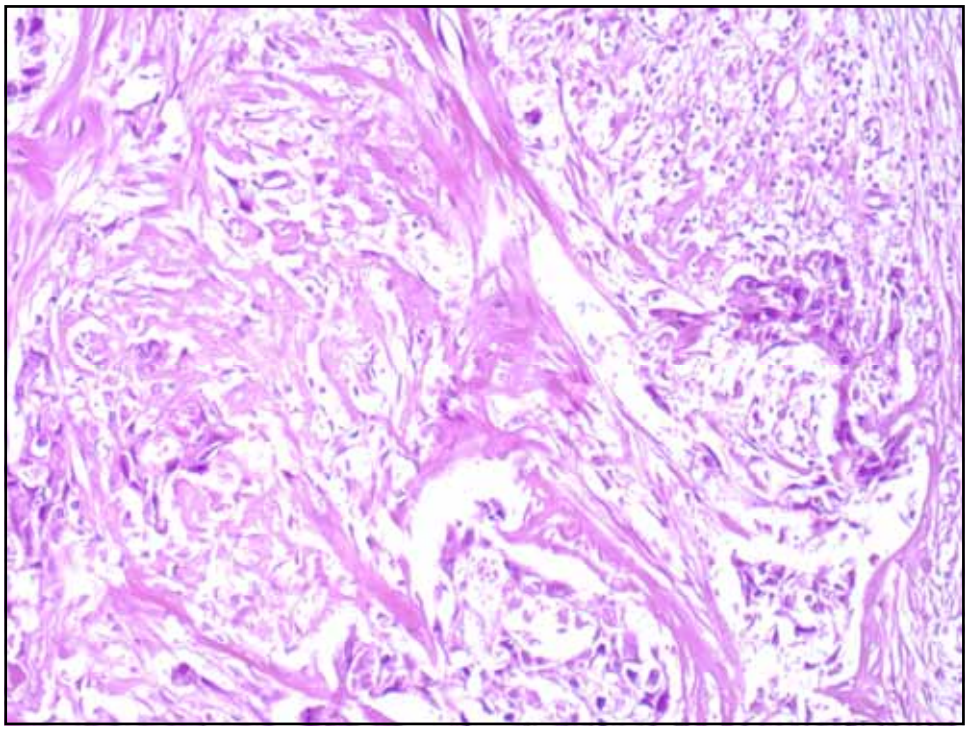


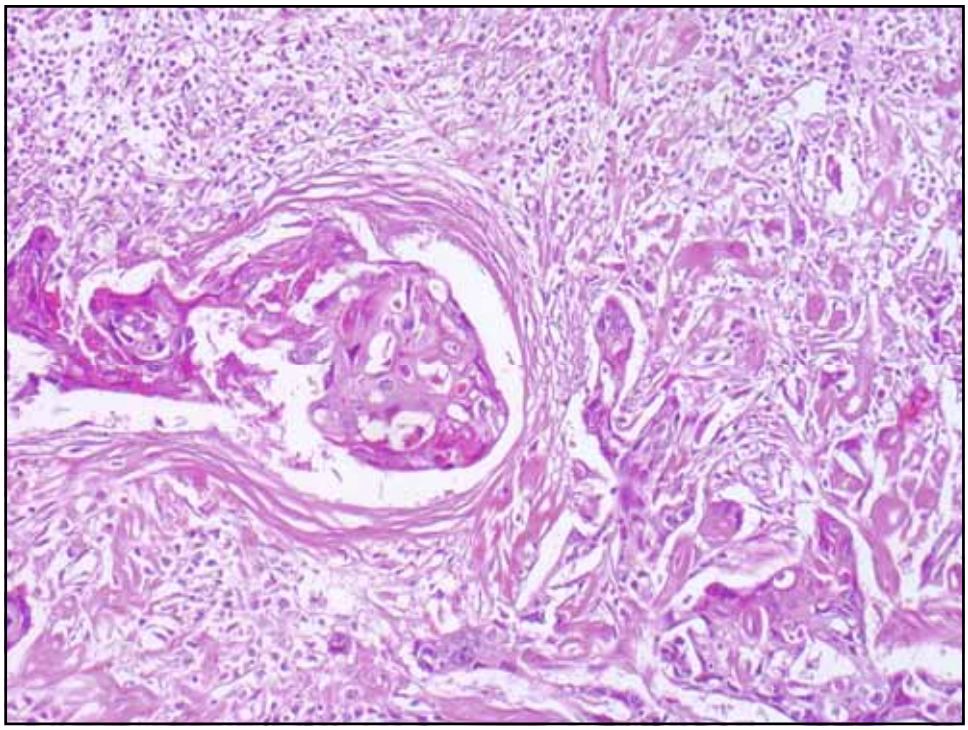


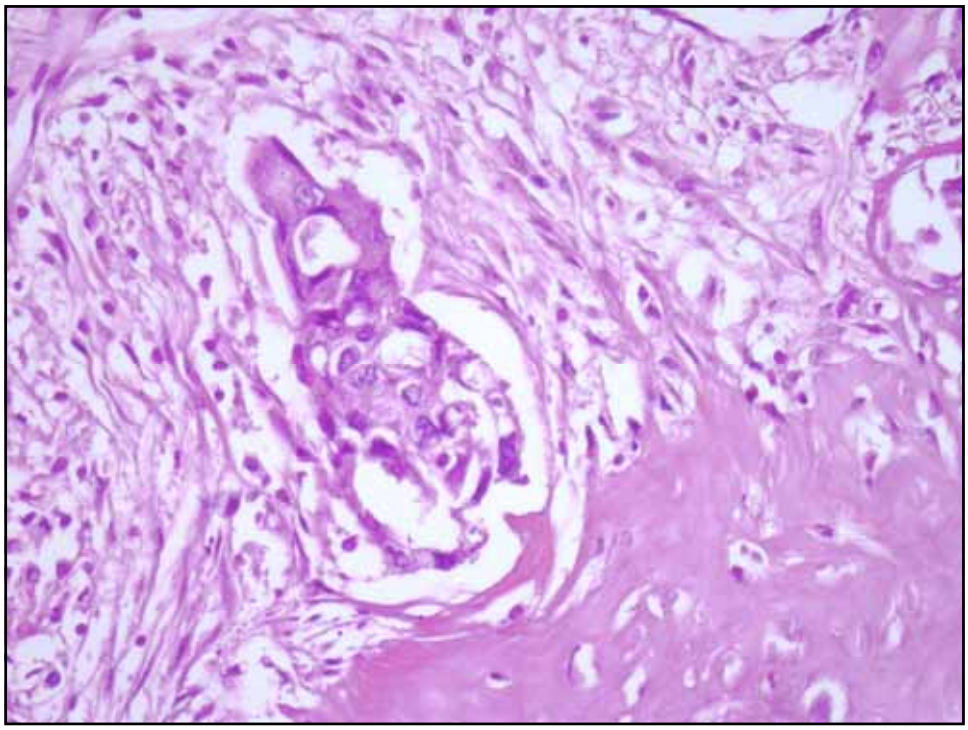


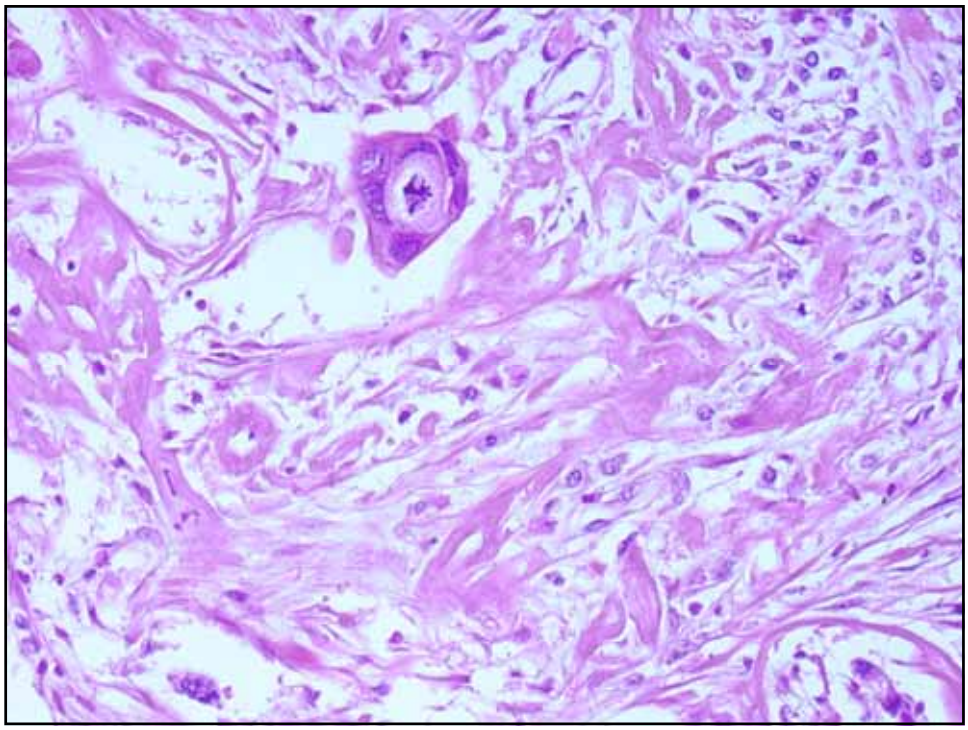








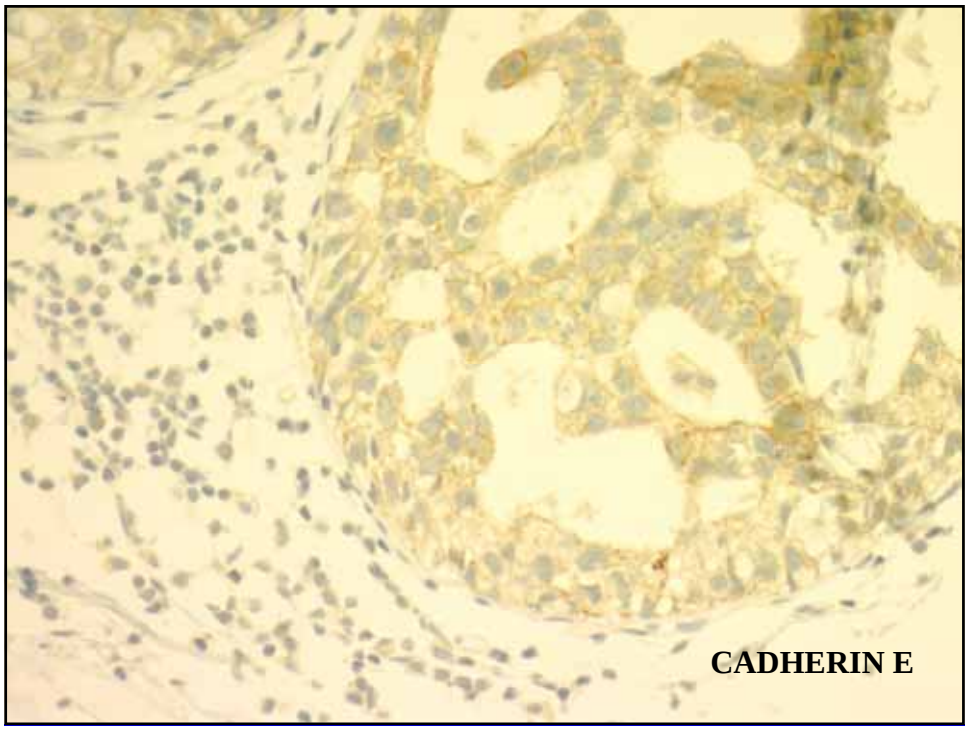




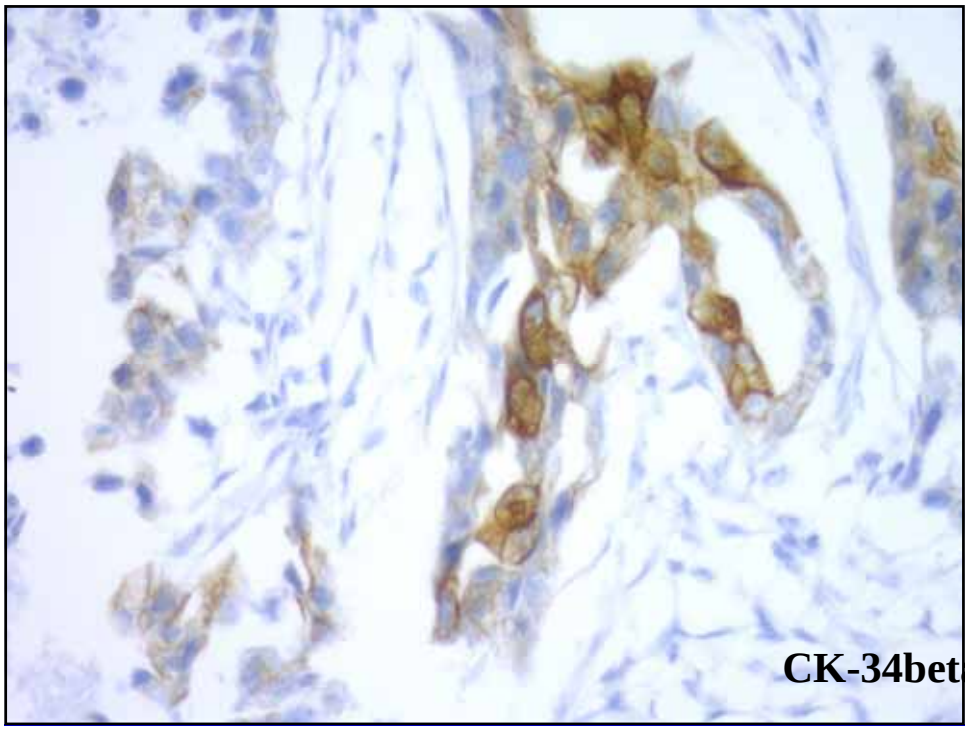
IMMUNOHISTOCHEMY

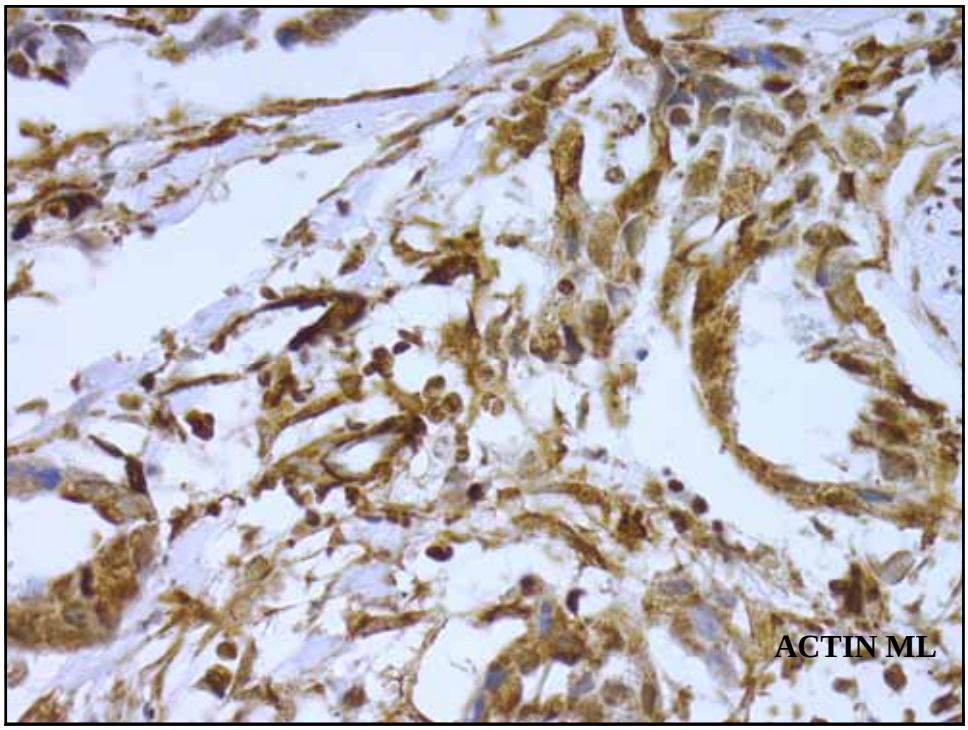
Antibody	Source	Dilution	Primary Tumor EA/MA	Xenotransplant EA/MA	c.c.
CK1AE1-AE3	DAKO	1:50	+/-	+/+	+/+
EMA	DAKO	1:200	+/+(f)	+/+	+ (f)
Desmin	DAKO	1:100	-/+	+/+	+
Vimentin	Novocastra	1:200	+/+	+/+	+/+
Actin	Biogenex	1:50	+/+	+/+	+
S-100	DAKO	1:200	-/-	-/-	+
E-cadherin	Novocastra	1:20	+/-	+/+	+
Osteocalcin	Chemicon	1:250	+/+	+/+	+/+
Osteonectin	Biogenex	1:300	+/+	+/+	+/+
Cathepsin D	DAKO	1:500	+/+	+/+	+/+
c-erb-B2	Novocastra	1:50	+/+	+(f)/+	+/+
Bcl-2	DAKO	1:50	+/+	-/+	+ (f)
Estrogen receptor	Novocastra	1:40	-/-	-/-	-
Progesterone receptor	Novocastra	1:30	-/-	-/-	-
p53	DAKO	1:50	+/+	+/+	+/+
Ki-67	DAKO	1:50	+/+	+/+	+/+
MDM2	Novocastra	1:50	+	+	+
CD34	Biogenex	1:50	-/-	-/-	-
CD31	DAKO	1:20	-/-	-/-	-

EA: Epithelial areas. MA: Mesenchymal areas. c.c.: cultured cells. (f): focal reactivity



CADHERIN E


CK-34bet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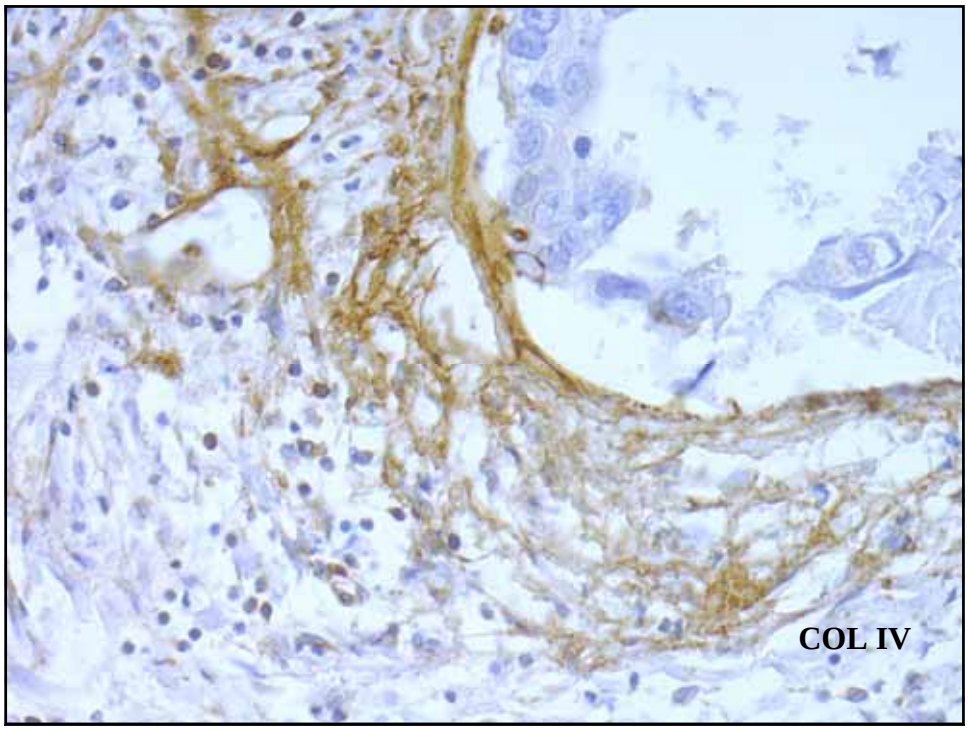
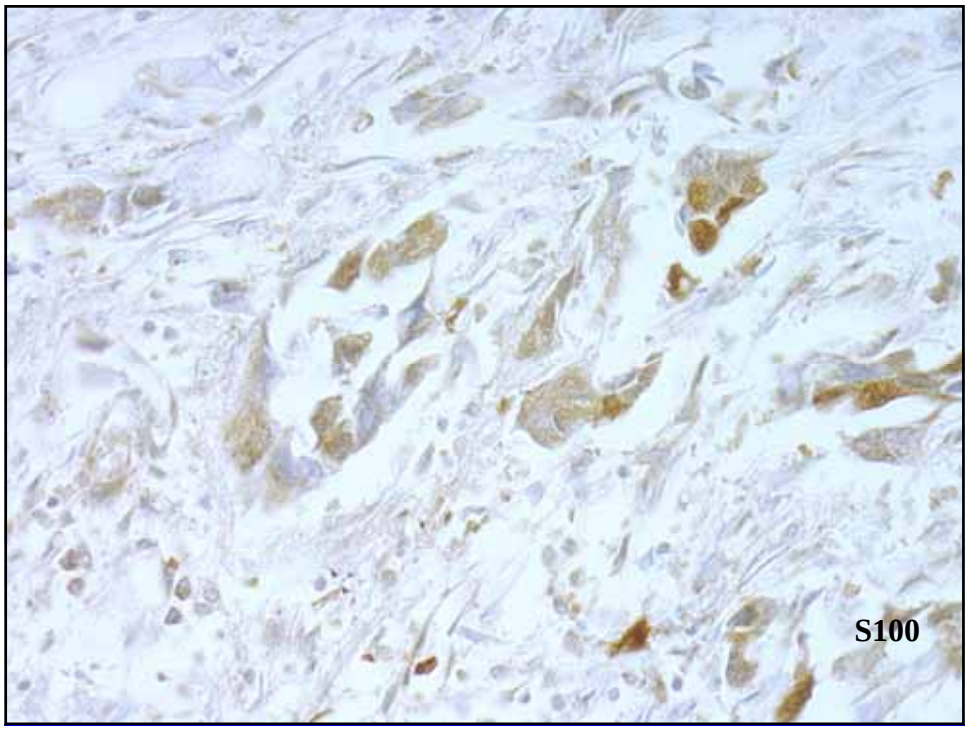
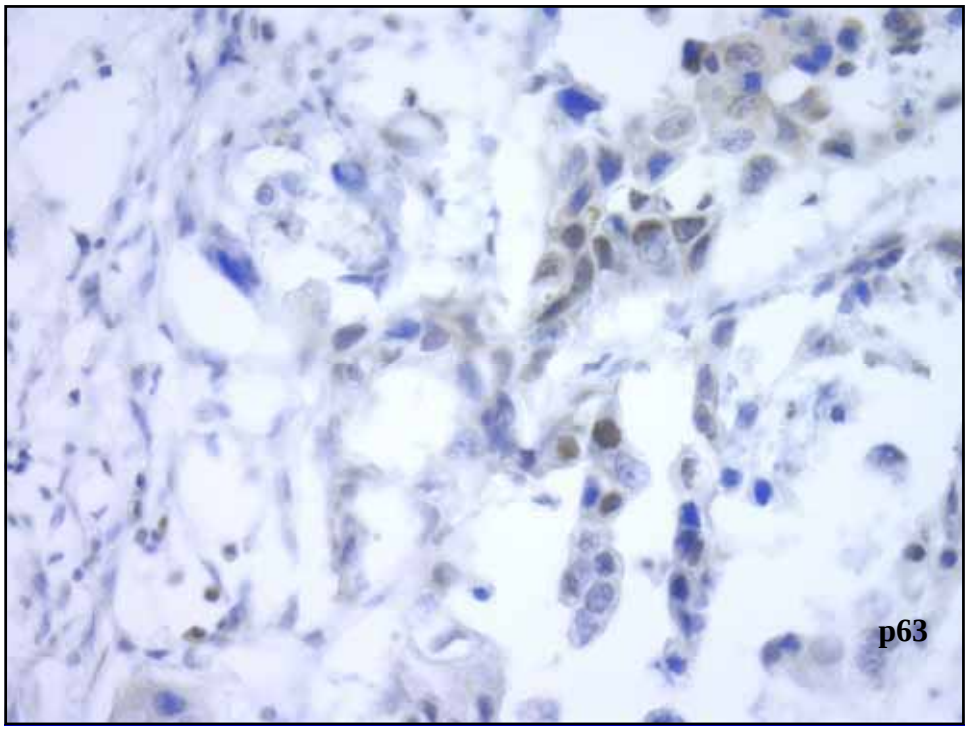
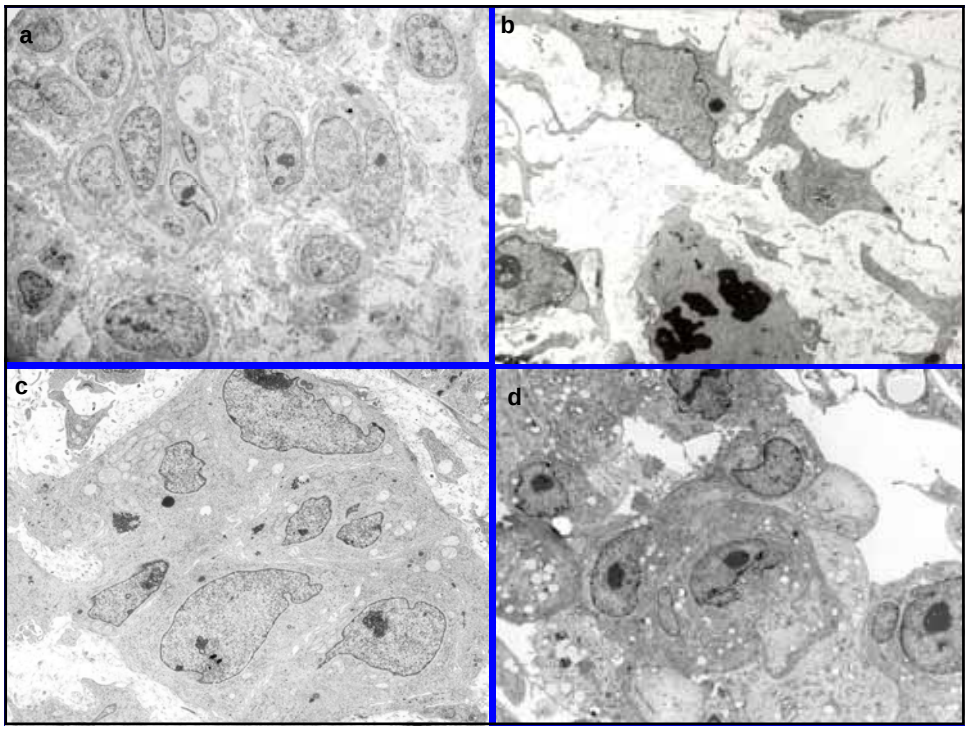

COL IV


S100


p63


a
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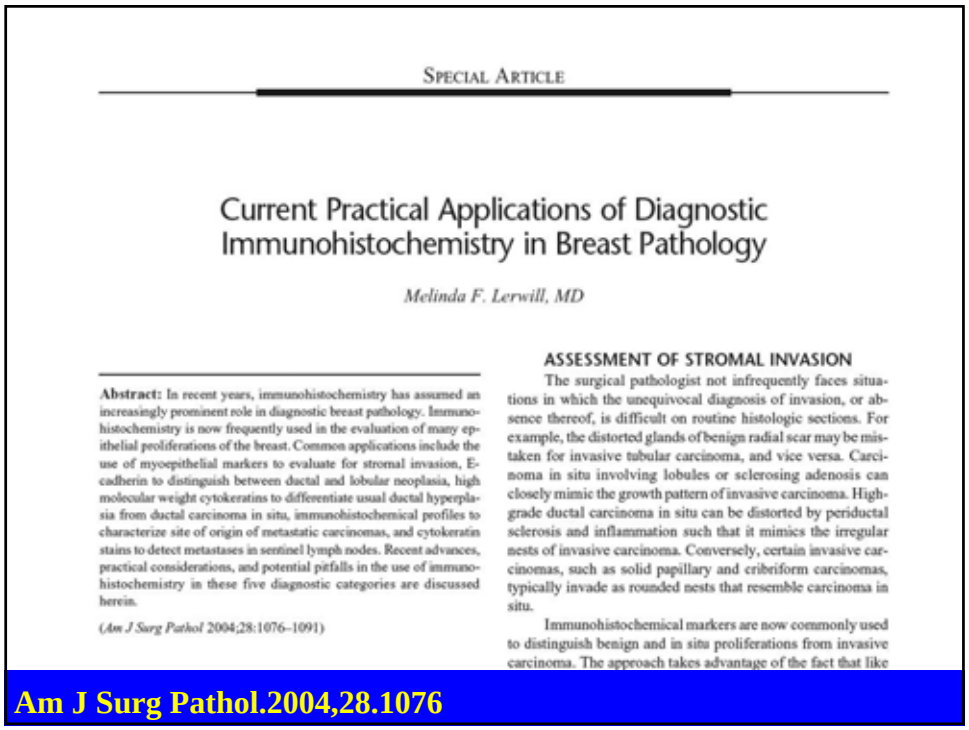
HISTOLOGiCAL DIAGNOSIS

Metaplastic carcinoma of the breast of myoepithelial nature



SPECIAL ARTICLE

Current Practical Applications of Diagnostic Immunohistochemistry in Breast Pathology

Melinda F. Lerwill, MD

Abstract: In recent years, immunohistochemistry has assumed an increasingly prominent role in diagnostic breast pathology. Immunohistochemistry is now frequently used in the evaluation of many epithelial proliferations of the breast. Common applications include the use of myoepithelial markers to evaluate for stromal invasion, E-cadherin to distinguish between ductal and lobular neoplasia, high molecular weight cytokeratins to differentiate usual ductal hyperplasia from ductal carcinoma in situ, immunohistochemical profiles to characterize site of origin of metastatic carcinomas, and cytokeratin stains to detect metastases in sentinel lymph nodes. Recent advances, practical considerations, and potential pitfalls in the use of immunohistochemistry in these five diagnostic categories are discussed herein.

(*Am J Surg Pathol* 2004;28:1076–1091)

ASSESSMENT OF STROMAL INVASION

The surgical pathologist not infrequently faces situations in which the unequivocal diagnosis of invasion, or absence thereof, is difficult on routine histologic sections. For example, the distorted glands of benign radial scar may be mistaken for invasive tubular carcinoma, and vice versa. Carcinoma in situ involving lobules or sclerosing adenosis can closely mimic the growth pattern of invasive carcinoma. High-grade ductal carcinoma in situ can be distorted by periductal sclerosis and inflammation such that it mimics the irregular nests of invasive carcinoma. Conversely, certain invasive carcinomas, such as solid papillary and cribriform carcinomas, typically invade as rounded nests that resemble carcinoma in situ.

Immunohistochemical markers are now commonly used to distinguish benign and in situ proliferations from invasive carcinoma. The approach takes advantage of the fact that like

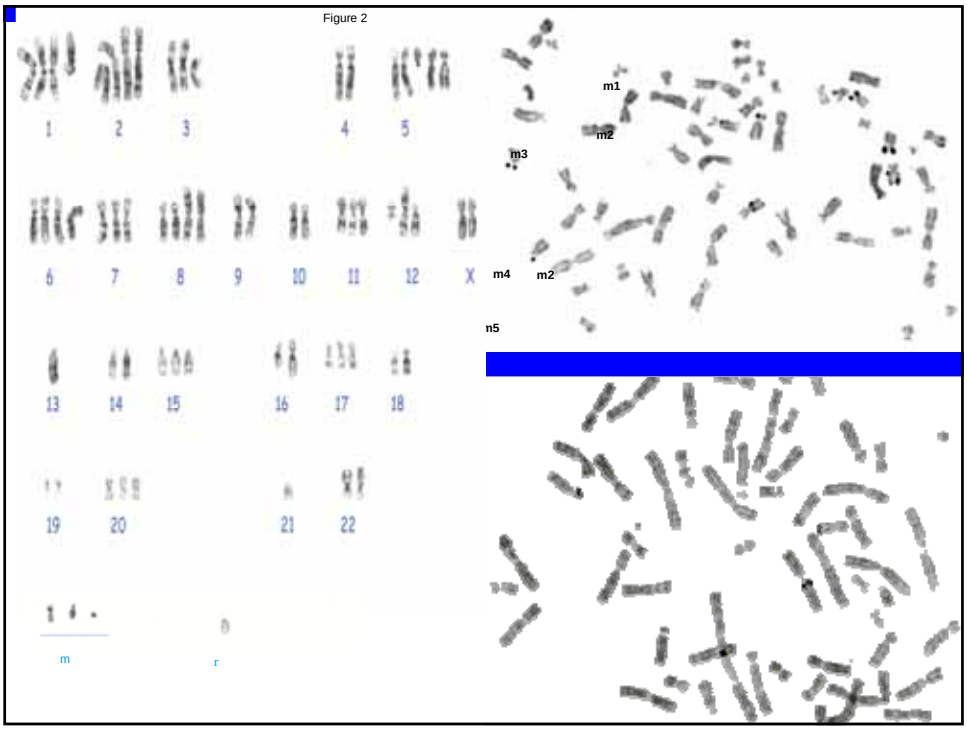
Am J Surg Pathol.2004,28.1076

Immunohistochemical analysis confirmed the participation of myoepithelial cells as the major component of the tumor, expressing positively for p63,CK 34beta and E12 cytokeratin that have also been observed in myoepithelial cells derived metaplastic carcinomas of the breast (**Koker and Leer (Am. J. Surg.Pathol. 28,11,1506-1512. 2004**).

CYTOGENETICS

All samples analyzed showed **abnormal karyotypes in the triploid range**, with many complex structural clonal abnormalities. **No modal number** was found, the majority of cells were between 64 and 69. A high number of metaphases showed abnormalities such as: **dicentric chromosomes, acentric fragments, telomeric associations, breaks or dmin**.
6 cells showed a **ring chromosome of double the normal size.**

Figure 2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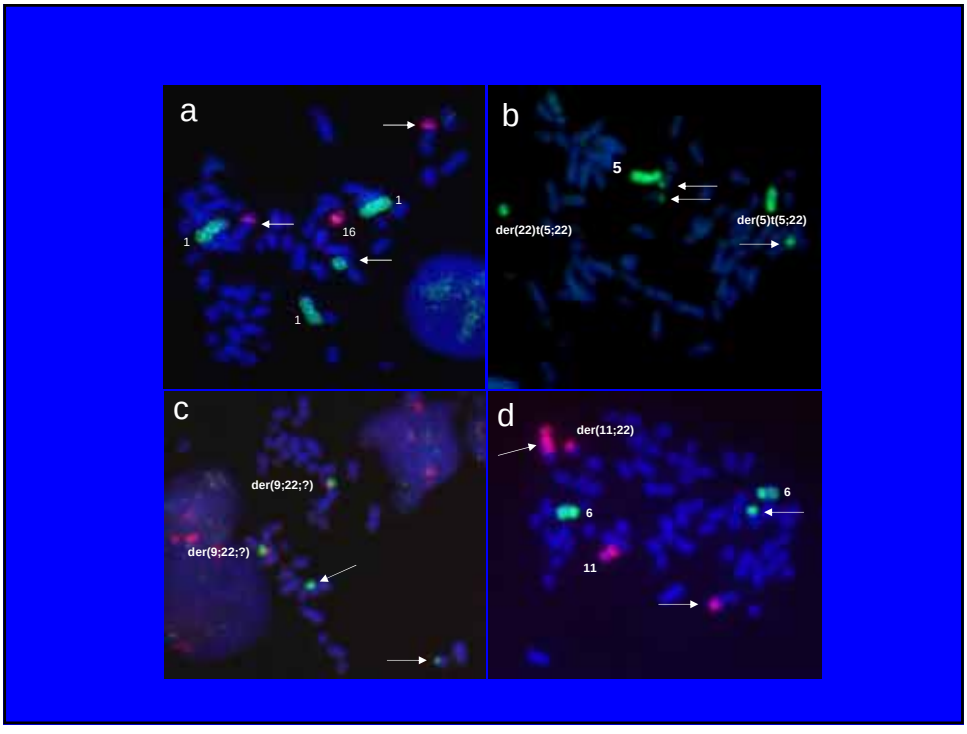
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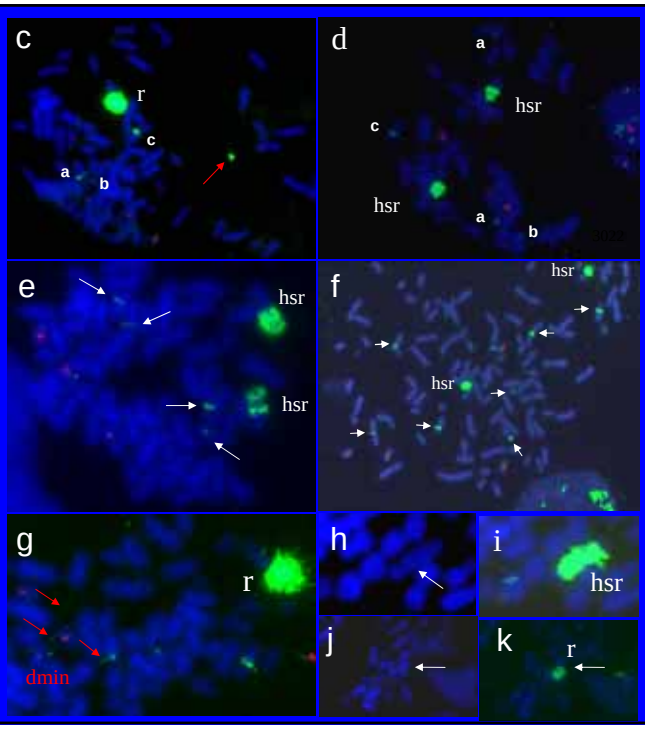
der(5)t(5;22)
c
der(9;22;?)
der(9;22;?)
d
der(11;22)
6
6
11

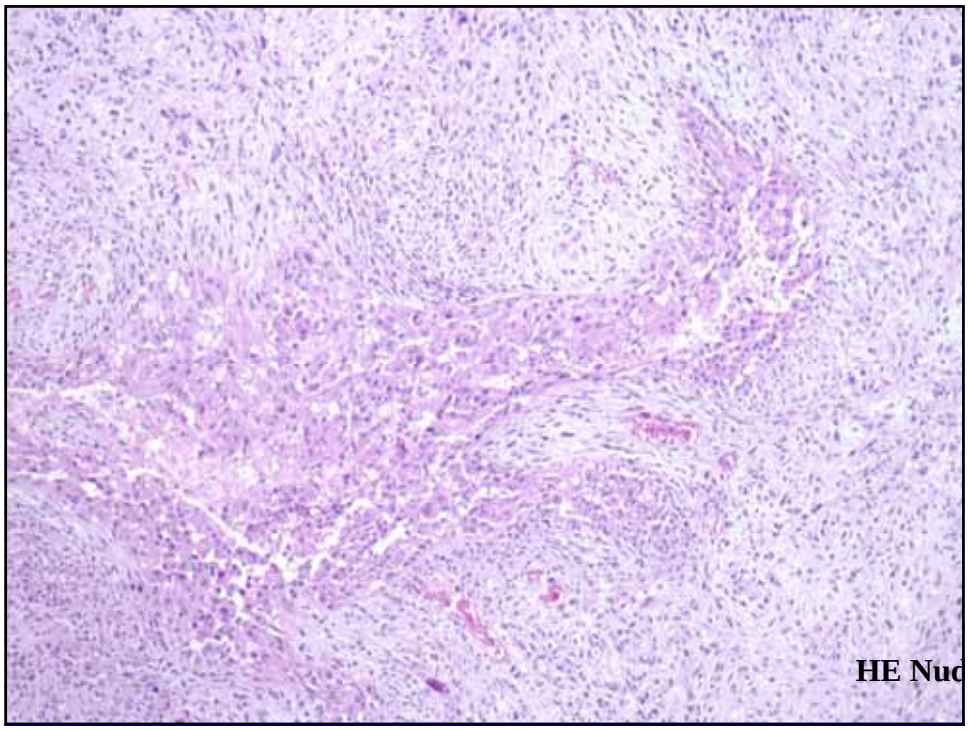


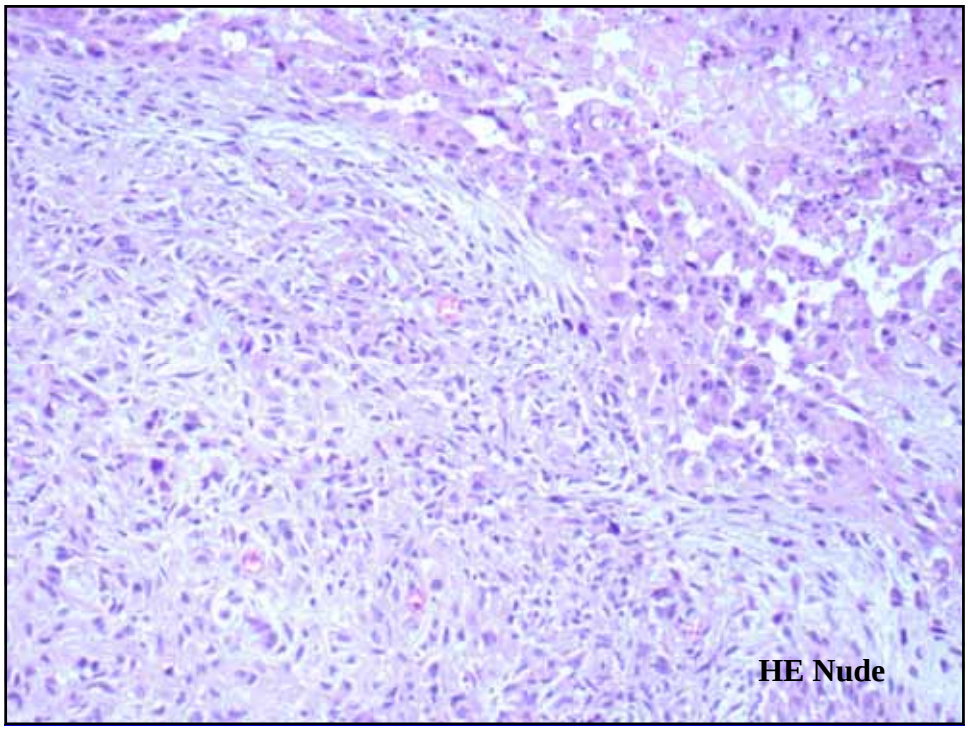
NUDE MICE TRANSFER

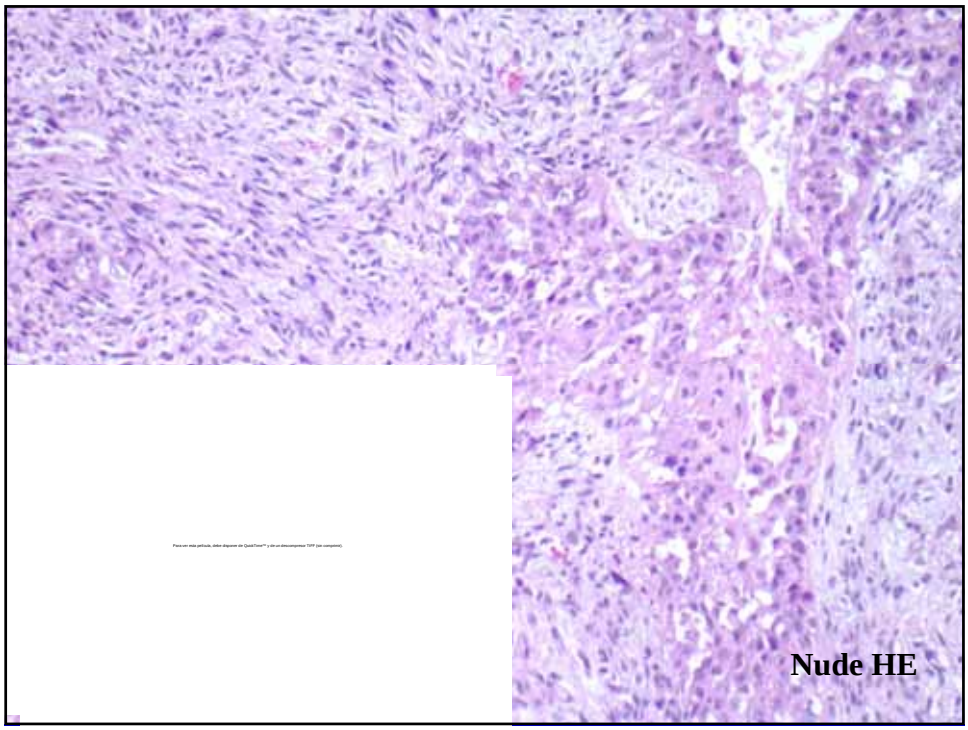
Fragments of primary tumor were inoculated into the backs of 4 to 6-week-old male BALB/c nude mice.

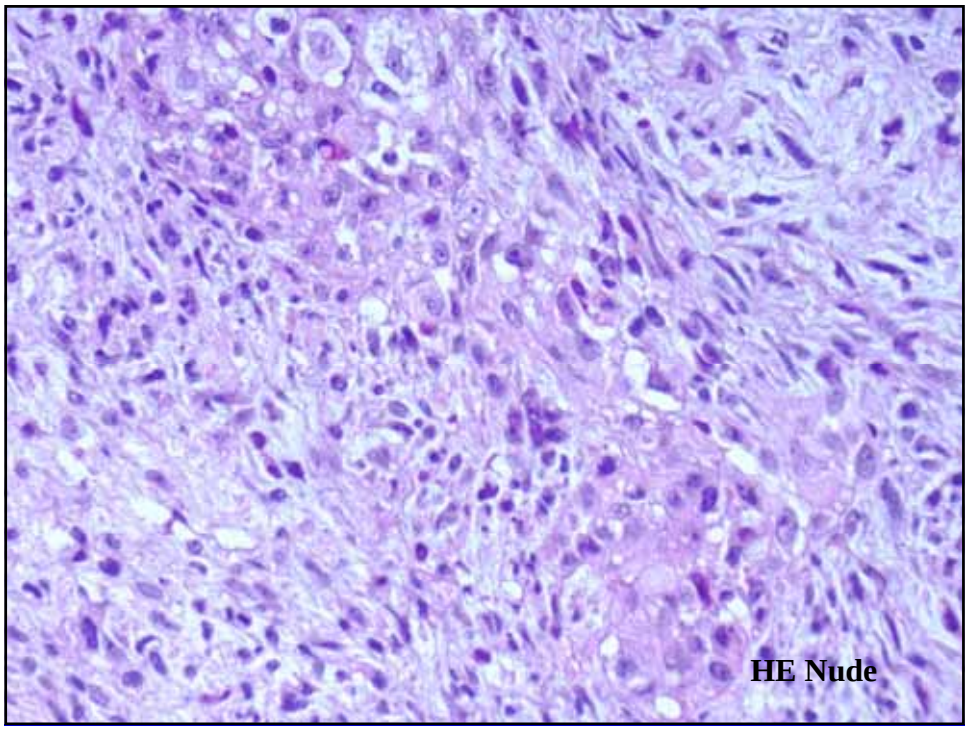
Tumors were transplanted again to other nude mice for serial heterotransplantation.

Samples of the tumors were processed for the histological, immunohistochemical, ultrastructural and genetic studies.


HE Nud


HE Nude


Nude HE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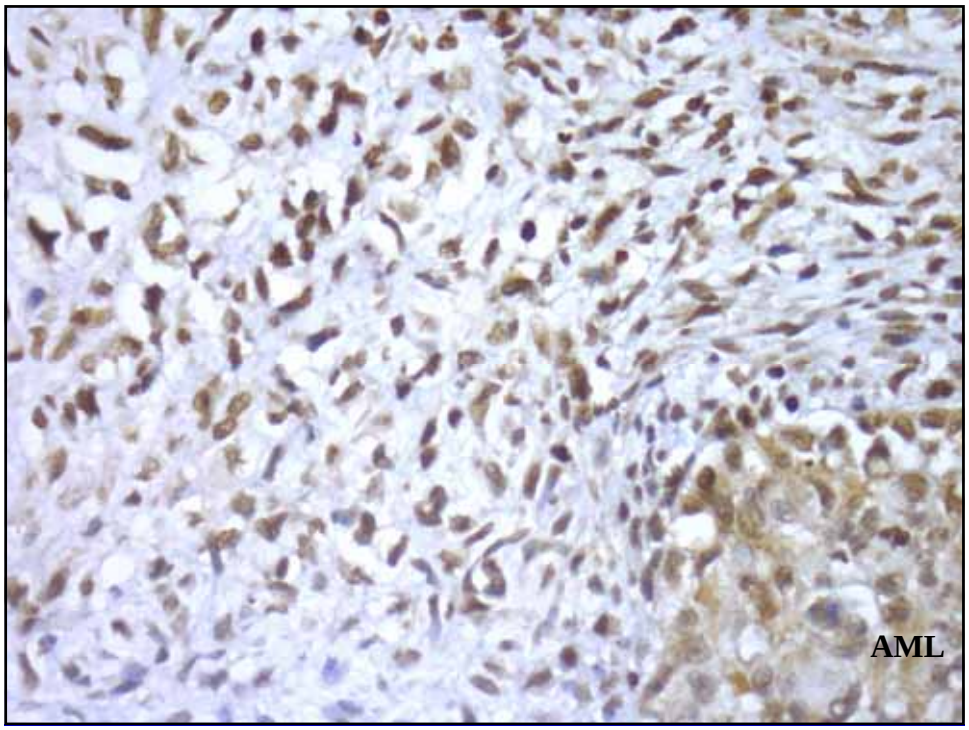
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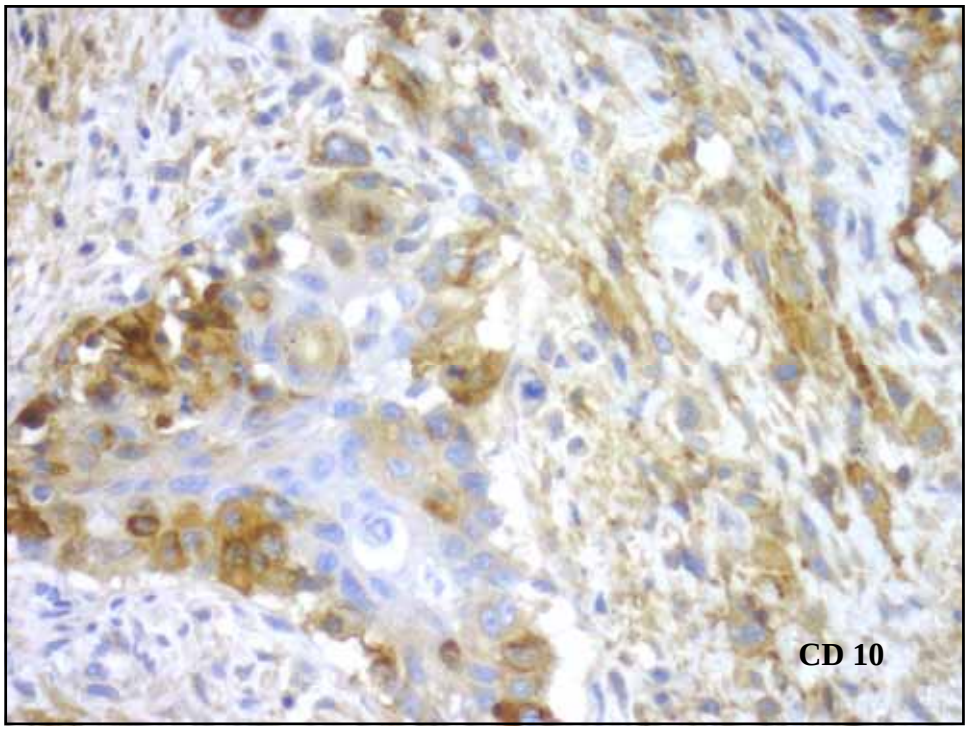
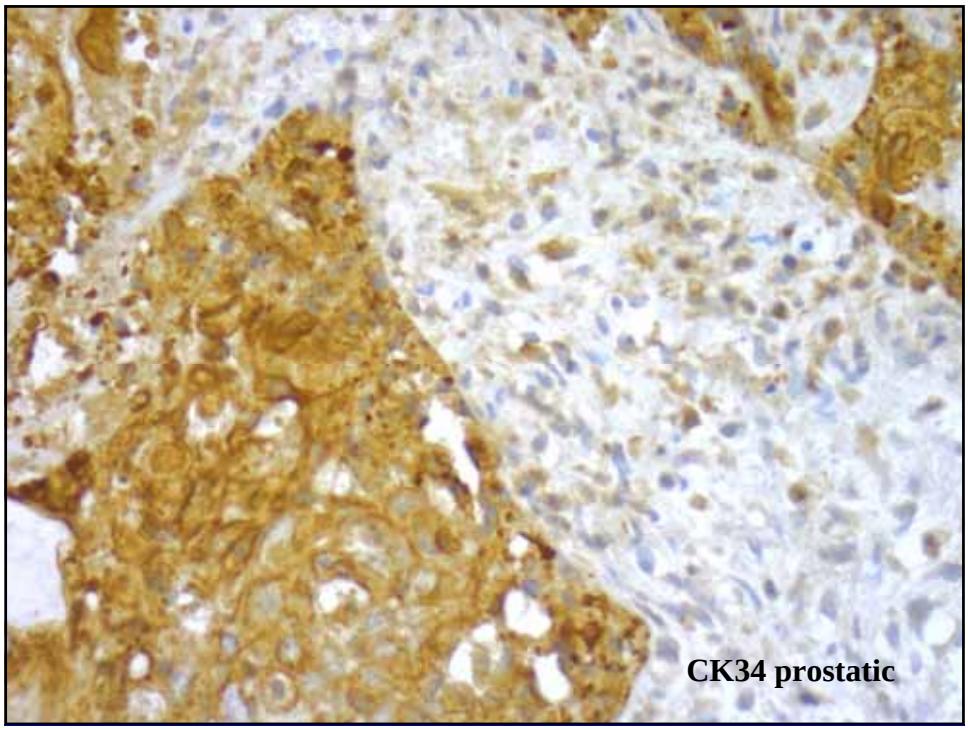
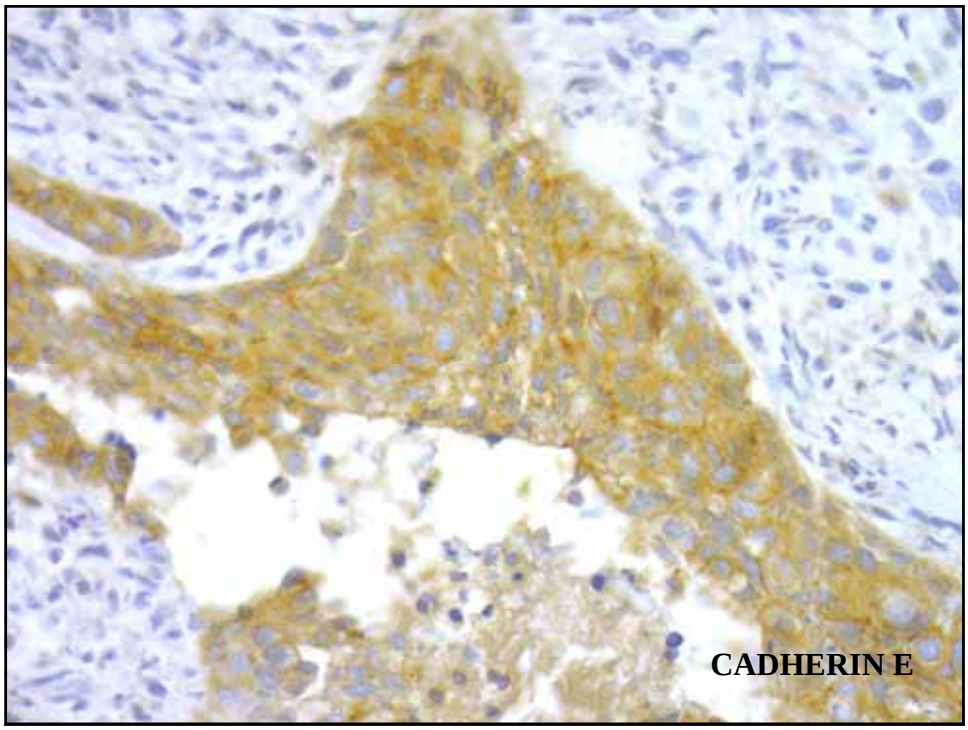

CD 10


CK34 prostatic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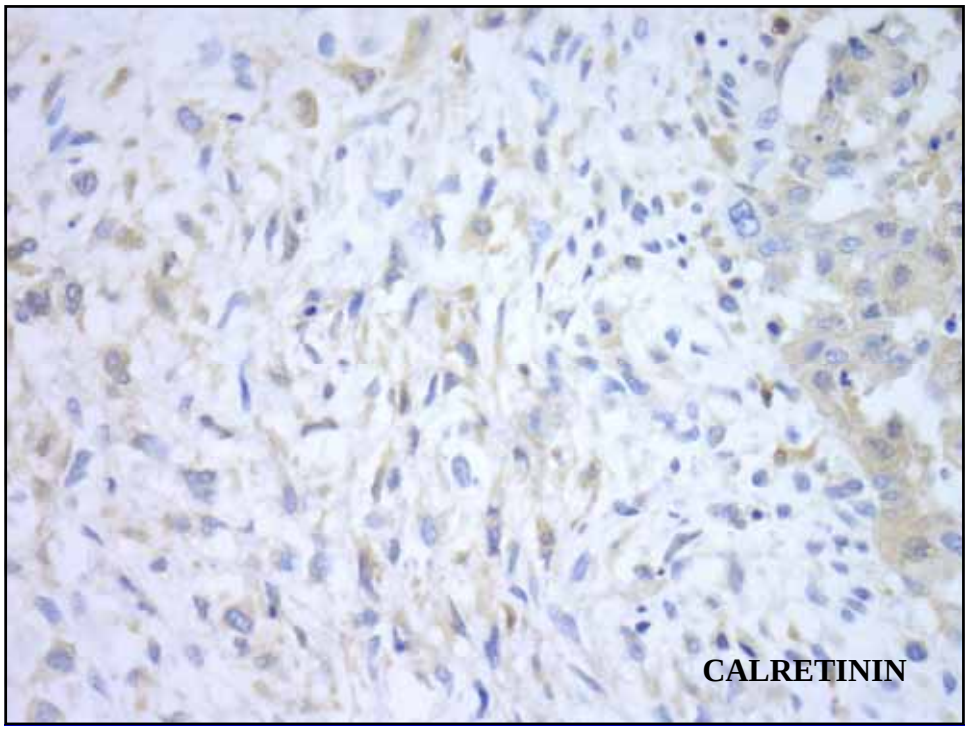
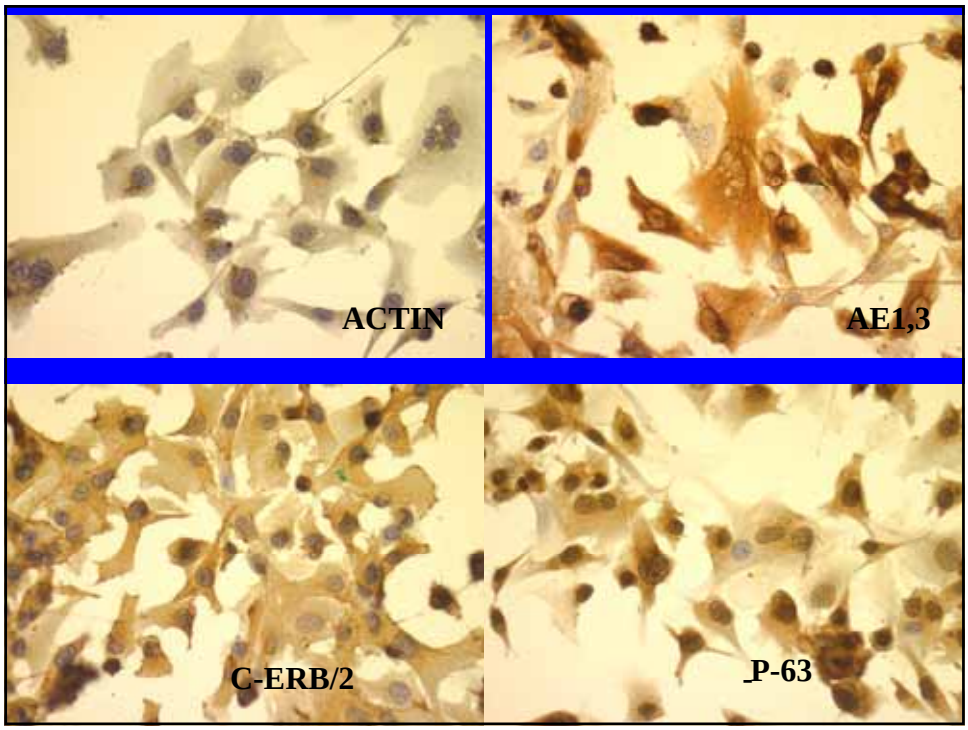
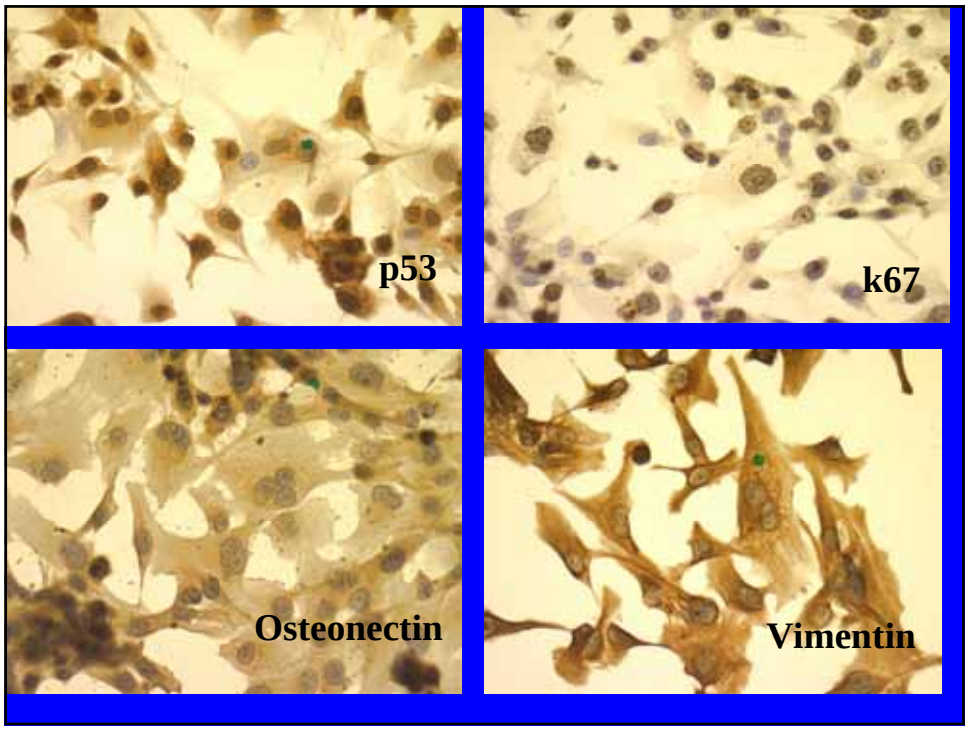
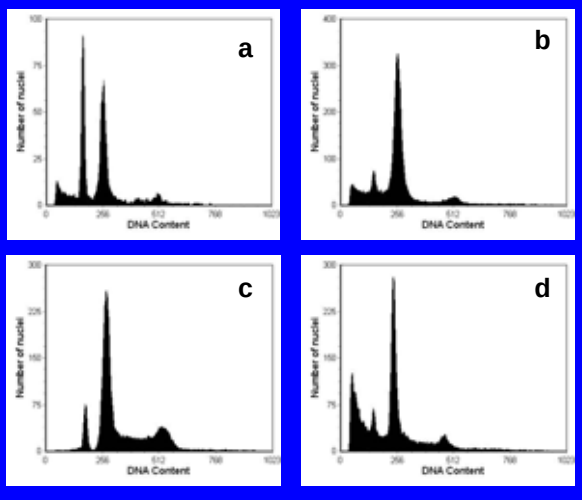

CALRETININ


ACTIN
AE1,3
C-ERB/2
P-63



FLOW CYTOMETRY



G1/S checkpoint: homozygous deletion of the 9p21 locus genes loss of $p16^{INK4A}$, $p14^{ARF}$, and $p15^{INK4B}$ transcripts

No *p53* point mutations or *MYCN*, *MDM2*, *cyclin D1* and *CDK4* genetic amplifications.

Amplification of *ERBB2* in the primary tumor, xenografts and cultured cells.

Microdissection: *ERBB2* gene amplification in both epithelial and mesenchymal areas of the primary tumor

***ERBB2* amplification** is an unstable process in which the number of gene copies increases markedly during tumor progression

GENOMIC INSTABILITY

This chromosomal instability is responsible for the phenotypic variability and poor outcome of MBC.

ORIGINAL ARTICLE

Metaplastic Breast Carcinomas: Are They of Myoepithelial Differentiation?

Immunohistochemical Profile of the Sarcomatoid Subtype Using Novel Myoepithelial Markers

Sebastian Leibl, MD, Margit Gogg-Kammerer, MT, Andrea Sommersacher, MT, Helmut Denk, MD, FRCPath, and Farid Moinfar, MD

Abstract: We investigated 20 spindle cell (sarcomatoid) metaplastic carcinomas (MCs) without squamous differentiation. In addition, five high-grade phyllodes tumors were assessed for comparison. Our immunohistochemical antibody panel included pan-cytokeratin (CK), low molecular weight CK (CK8/18), four basal cell type CKs (34βE12, CK5/6, CK14, and CK17), vimentin antibodies, as well as antibodies to established (SMA, CD10, p63, S-100, maspin, calponin, GFAP, SM-myosin), and novel (CD29, 14-3-3σ) myoepithelial markers. Sixteen of the 20 tumors (80%) expressed at least two markers of the combination CD10/p63/SMA. S-100 detected 1 case negative for CD10/p63/SMA and 3 cases that only expressed one marker of this combination. While 18 MCs (90%) were positive for CD29, 14-3-3σ (11 cases) and maspin (9 cases) were observed in 55% and 45%, respectively. Antibodies to pan-CK and the basal cell type CKs were strongly reactive in 12 tumors (60%), but in 6 cases (30%) negativity for these markers was weak and only focal. 2 MCs

matrix-producing carcinoma,[17,27] low-grade fibromatosis-like spindle cell carcinoma,[24] carcinosarcoma,[28] or carcinoma with pseudosarcomatous metaplasia.[9] Although several studies demonstrated a myoepithelial immunophenotype suggesting myoepithelial differentiation at least of some subtypes of MCs,[4,6,17,18,26,28] a thorough immunohistochemical examination using most of the currently available myoepithelial markers has not yet been performed. Moreover, some of these studies included MCs with areas of squamous differentiation,[4,18,26,28] which limits the conclusions drawn by the authors, since many myoepithelial markers are also present in nonneoplastic and neoplastic squamous epithelium. The aim of our study was to examine MCs with pure spindle cell morphology without squamous differentiation, MCs with heterologous elements, and MCs of the carcinosarcoma-subtype for evidence of myoepithelial differentiation. In ad-

Am J Surg Pathol 29,347.2005

The American Journal of Surgical Pathology

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The American Journal of Surgical Pathology: Volume 25(8) August 2001 pp 1054-1060

p63, a p53 Homologue, Is a Selective Nuclear Marker of Myoepithelial Cells of the Human Breast

Barbareschi, Mattia M.D.; Pecciarini, Lorenza Ph.D., Cangi, M. Giulia Ph.D.; Macrì, Ettore M.D.; Rizzo, Aroldo M.D.; Viale, Giuseppe M.D., F.R.C.Path.; Doglioni, Claudio M.D.

From the Departments of Pathology, San Martino Hospital (L.P., M.G.C., E.M., A.R., C.D.), Belluno, Santa Chiara Hospital (M.B.), Trento, and European Institute of Oncology (G.V.), University of Milan School of Medicine, Milan, Italy.

Address correspondence and reprint requests to Claudio Doglioni, MD, Anatomia Patologica Ospedale 32100 Belluno, Italy, e-mail: claudio.doglioni@ulss.belluno.it

(*Am J Surg Pathol* 2004;28:1506–1512)

p63 Expression in Breast Cancer

A Highly Sensitive and Specific Marker of Metaplastic Carcinoma

Meryem M. Koker, MD and Celina G. Kleer, MD

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The American Journal of Surgical Pathology

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The American Journal of Surgical Pathology: Volume 20(3) March 1996 pp 277-285

Monoclonal Origins of Malignant Mixed Tumors (Carcinosarcomas): Evidence for a Divergent Histogenesis

Thompson, Lester M.D.; Chang, Bernard M.D.; Barsky, Sanford H. M.D.

Metaplastic Sarcomatoid Carcinoma of the Breast With Absent or Minimal Overt Invasive Carcinomatous Component

A Misnomer

William G. Davis, MD, Bryan Hennessy, MD,† Gildy Babiera, MD,‡ Kelly Hunt, MD,‡ Vicente Valero, MD,† Thomas A. Buchholz, MD,§ Nour Sneige, MD,* and Michael T. Gilcrease, MD, PhD**

Am J Surg Pathol 2005;29:1456

Para ver esta película, debe disponer de QuickTime™ y de un descompresor TIFF (LZW).

Thanks for your attention