¿Existe el carcinoma de mama con fenotipo basal?

David Hardisson

Dpt. de Anatomia Patologica

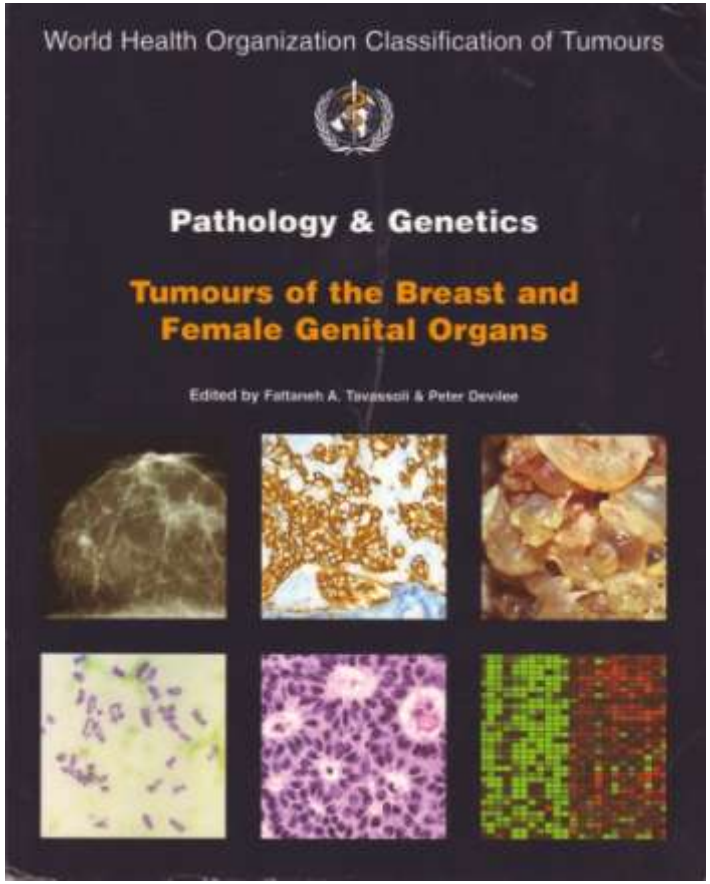
Hospital Universitario La Paz

SaludMadrid

Comunidad de Madrid

UAM UNIVERSIDAD AUTONOMA DE MADRID

IdiPAZ Instituto de Investigación Hospital Universitario La Paz



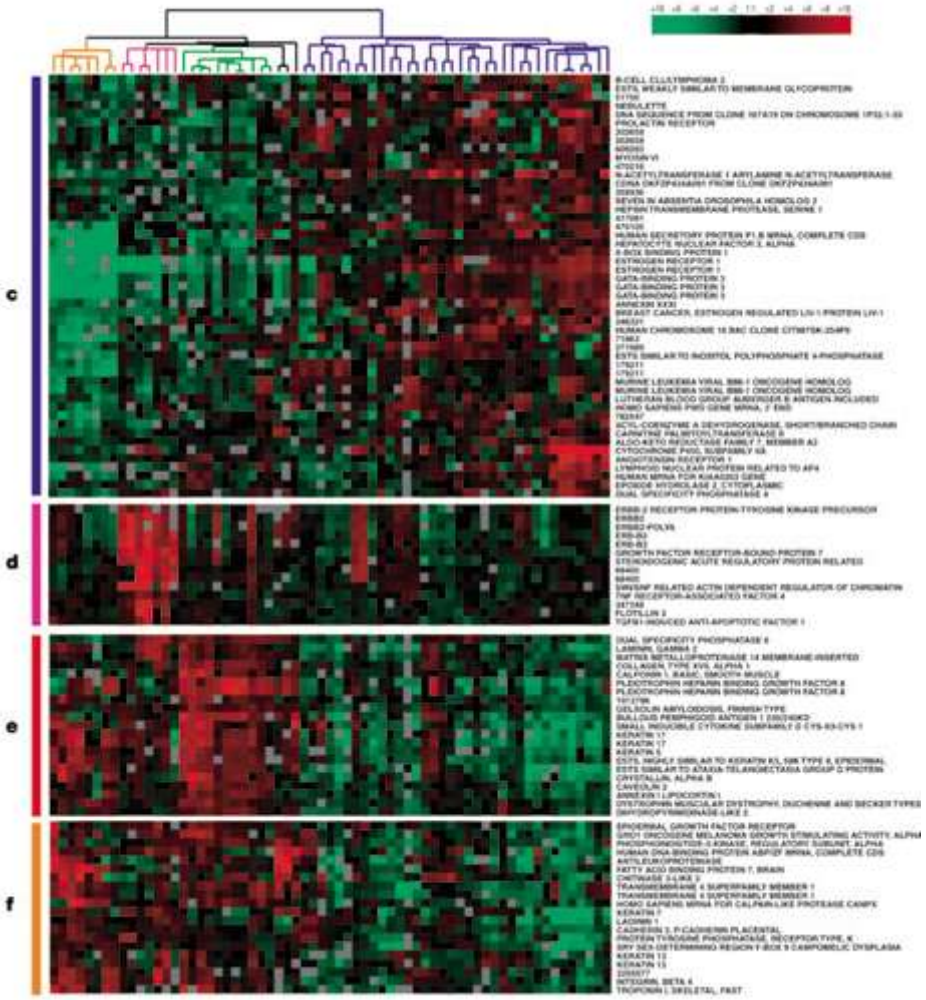
WHO histological classification of tumours of the breast

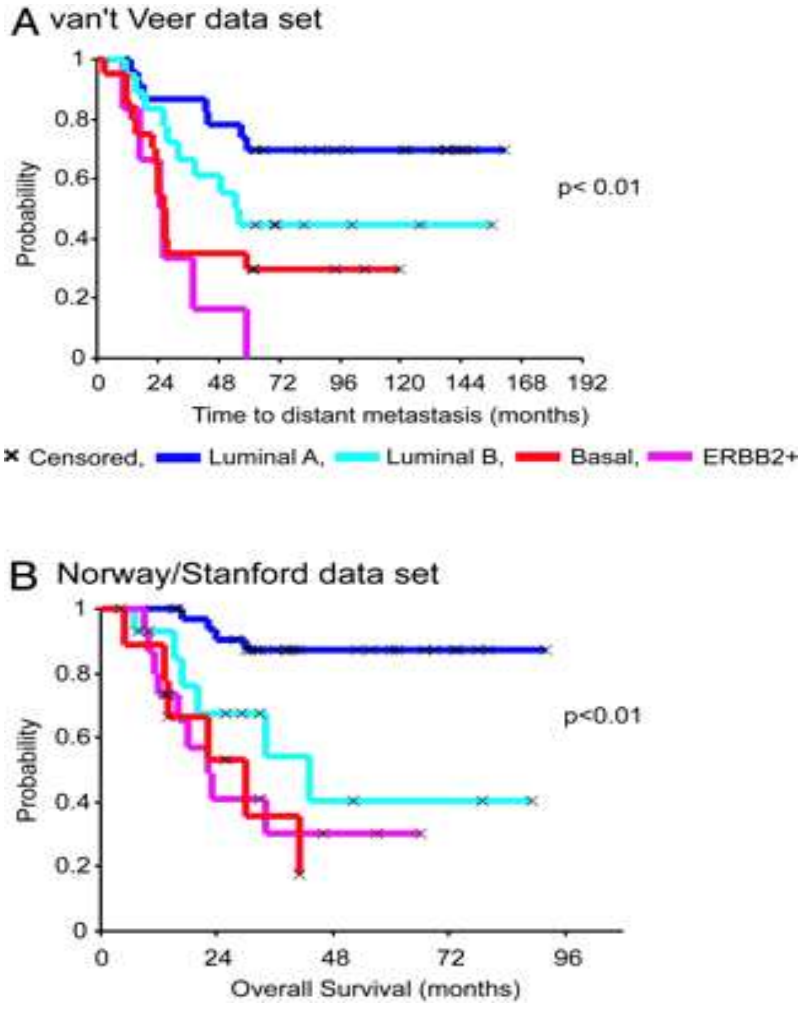
Epithelial tumours	
Invasive ductal carcinoma, not otherwise specified	8500/3
Mixed type carcinoma	
Pleomorphic carcinoma	8022/3
Carcinoma with osteoclastic giant cells	8035/3
Carcinoma with choriocarcinomatous features	
Carcinoma with melanotic features	
Invasive lobular carcinoma	8520/3
Tubular carcinoma	8211/3
Invasive cribriform carcinoma	8201/3
Medullary carcinoma	8510/3
Mucinous carcinoma and other tumours with abundant mucin	
Mucinous carcinoma	8480/3
Cystadenocarcinoma and columnar cell mucinous carcinoma	8480/3
Signet ring cell carcinoma	8490/3
Neuroendocrine tumours	
Solid neuroendocrine carcinoma	
Atypical carcinoid tumour	8249/3
Small cell / oat cell carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Invasive papillary carcinoma	8503/3
Invasive micropapillary carcinoma	8507/3
Apocrine carcinoma	8401/3
Metaplastic carcinomas	8575/3
Pure epithelial metaplastic carcinomas	8575/3
Squamous cell carcinoma	8070/3
Adenocarcinoma with spindle cell metaplasia	8572/3
Adenosquamous carcinoma	8560/3
Mucoepidermoid carcinoma	8430/3
Mixed epithelial/mesenchymal metaplastic carcinomas	8575/3
Lipid-rich carcinoma	8314/3
Secretory carcinoma	8502/3
Oncocytic carcinoma	8290/3
Adenoid cystic carcinoma	8200/3
Acinic cell carcinoma	8550/3
Glycogen-rich clear cell carcinoma	8315/3
Sebaceous carcinoma	8410/3
Inflammatory carcinoma	8530/3
Lobular neoplasia	
Lobular carcinoma in situ	8520/2
Intraductal proliferative lesions	
Usual ductal hyperplasia	
Flat epithelial atypia	
Atypical ductal hyperplasia	
Ductal carcinoma in situ	8500/2
Microinvasive carcinoma	
Intraductal papillary neoplasms	
Central papilloma	8503/0
Peripheral papilloma	8503/0
Atypical papilloma	
Intraductal papillary carcinoma	8503/2
Intracystic papillary carcinoma	8504/2
Benign epithelial proliferations	
Adenosis including variants	
Sclerosing adenosis	
Apocrine adenosis	
Blunt duct adenosis	
Microglandular adenosis	
Adenomyoepithelial adenosis	
Radial scar / complex sclerosing lesion	
Adenomas	
Tubular adenoma	8211/0
Lactating adenoma	8204/0
Apocrine adenoma	8401/0
Pleomorphic adenoma	8940/0
Ductal adenoma	8503/0
Myoepithelial lesions	
Myoepitheliosis	
Adenomyoepithelial adenosis	
Adenomyoepithelioma	8983/0
Malignant myoepithelioma	8982/3
Mesenchymal tumours	
Haemangioma	9120/0
Angiomatosis	
Haemangiopericytoma	9150/1
Pseudoangiomatous stromal hyperplasia	
Myofibroblastoma	8825/0
Fibromatosis (aggressive)	8821/1
Inflammatory myofibroblastic tumour	8825/1
Lipoma	8850/0
Angiolipoma	8861/0
Granular cell tumour	9580/0
Neurofibroma	9540/0
Schwannoma	9560/0
Angiosarcoma	9120/3
Liposarcoma	8850/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Fibroepithelial tumours	
Fibroadenoma	9010/0
Phyllodes tumour	9020/1
Benign	9020/0
Borderline	9020/1
Malignant	9020/3
Periductal stromal sarcoma, low grade	9020/3
Mammary hamartoma	
Tumours of the nipple	
Nipple adenoma	8506/0
Syringomatous adenoma	8407/0
Paget disease of the nipple	8540/3
Malignant lymphoma	
Diffuse large B-cell lymphoma	9680/3
Burkitt lymphoma	9687/3
Extranodal marginal-zone B-cell lymphoma of MALT type	9699/3
Follicular lymphoma	9690/3
Metastatic tumours	
Tumours of the male breast	
Gynaecomastia	
Carcinoma	
Invasive	8500/3
In situ	8500/2

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) (921) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /2 for in situ carcinomas and grade 3 intraepithelial neoplasia, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*





c Luminal, ER+

d ERBB2

e Basal

f Normal

CÁNCER DE MAMA CON FENOTIPO BASAL

- **Definición, espectro morfológico.**
- **Marcadores, origen.**
- **Relación con *BRCA1*.**
- **Significado clínico.**

CÁNCER DE MAMA CON FENOTIPO BASAL

- **Definición, espectro morfológico.**
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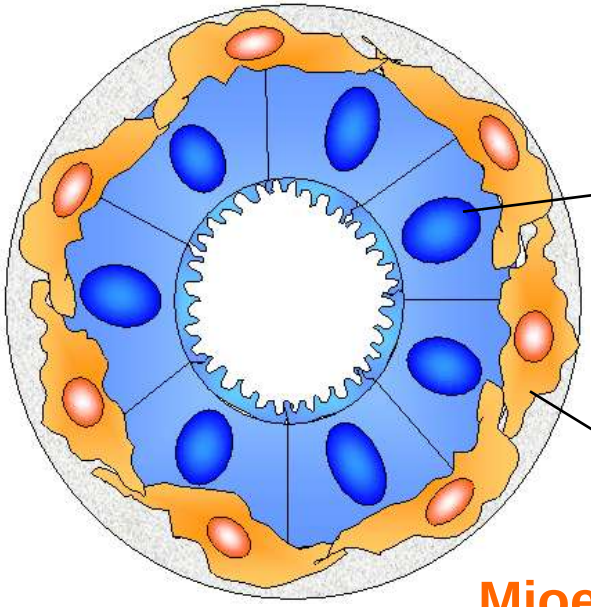
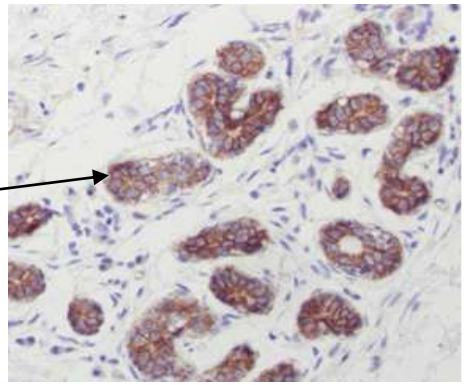


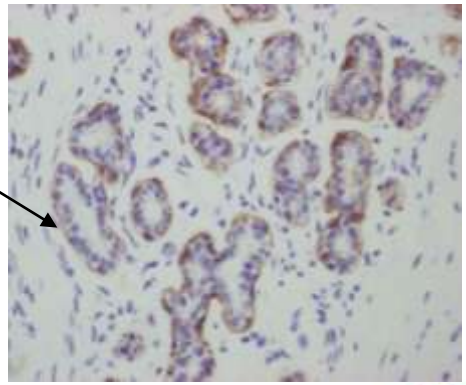
Epitelial



CK8, 18, 19

Cadherina-E

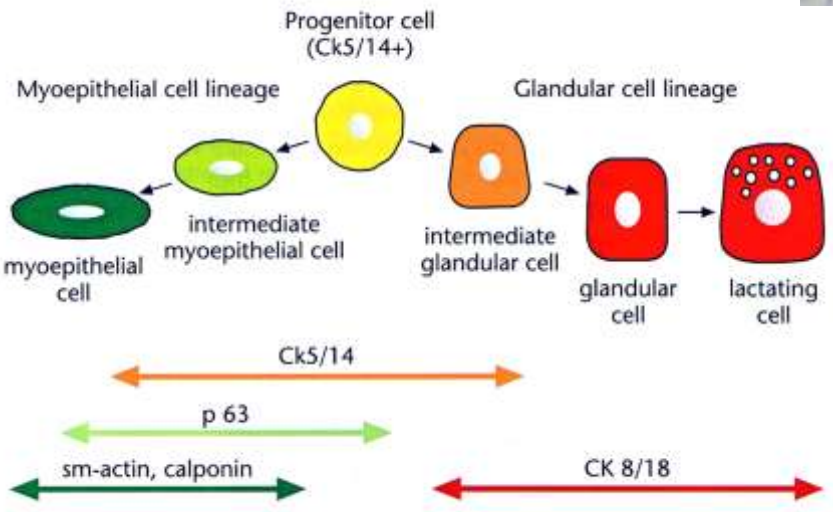
Mioepitelial (basal?)

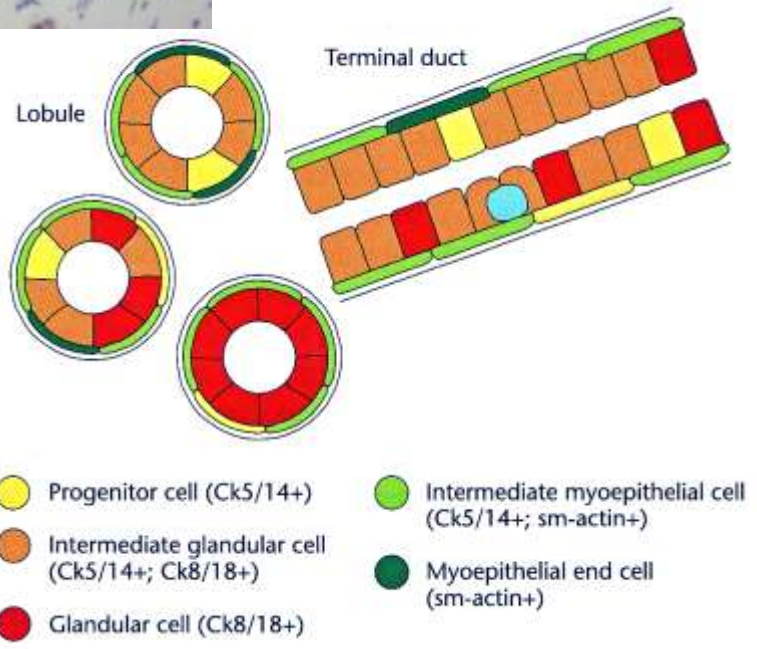


CK5/6, 14, 17

Cadherina P

p63, CD10, actina…





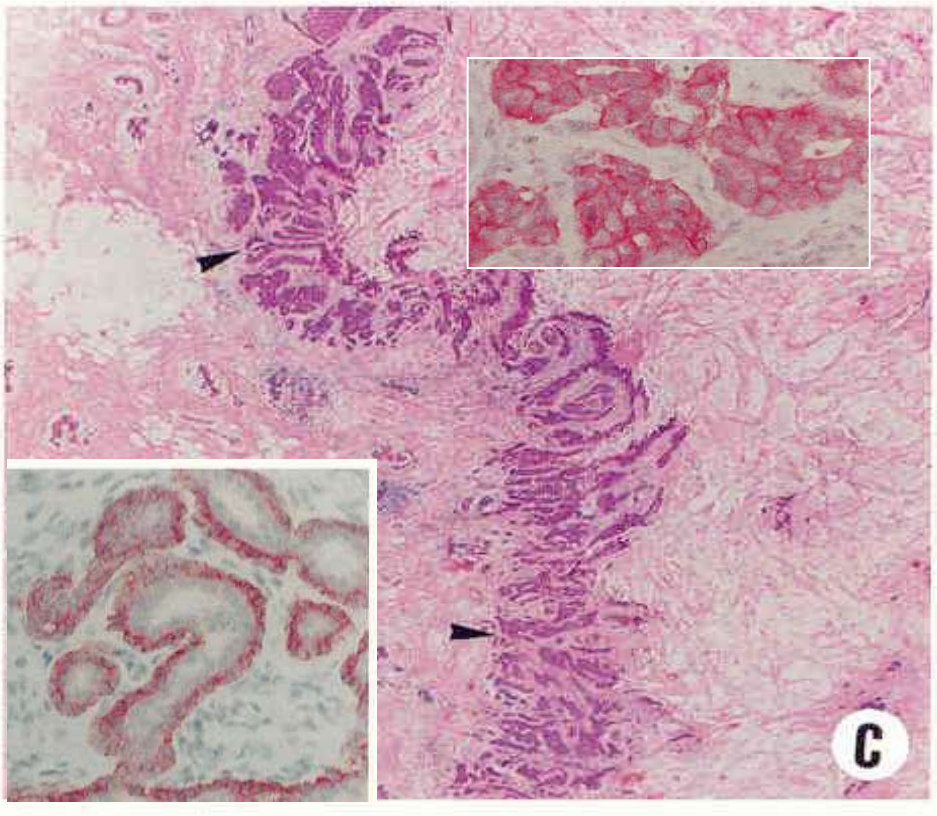
Boecker W. Preneoplasia of the breast, 2007

CÁNCER DE MAMA Y FENOTIPO BASAL

Anomalous Expression of P-Cadherin in Breast Carcinoma

Correlation with E-Cadherin Expression and Pathological Features

Palacios et al; Am J Pathol 1995



Large, Central Acellular Zones Indicating Myoepithelial Tumor Differentiation in High-Grade Invasive Ductal Carcinomas as Markers of Predisposition to Lung and Brain Metastases

Hitoshi Tsuda, M.D., Teruko Takarabe, C.T., Fumio Hasegawa, M.T., Takashi Fukutomi, M.D., and Setsuo Hirohashi, M.D.

The American Journal of Surgical Pathology 24(2): 197–202, 2000

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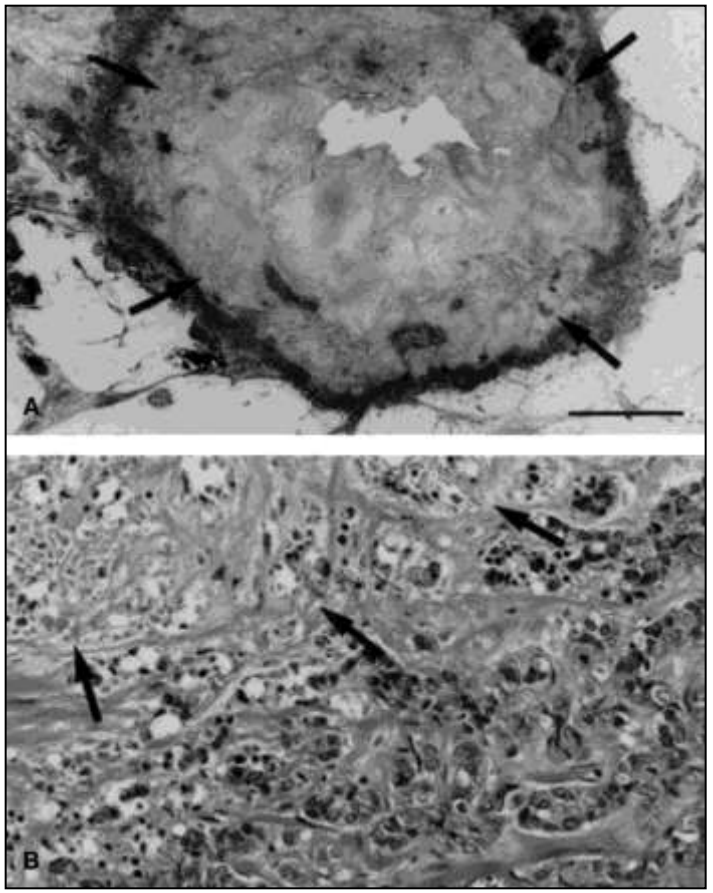
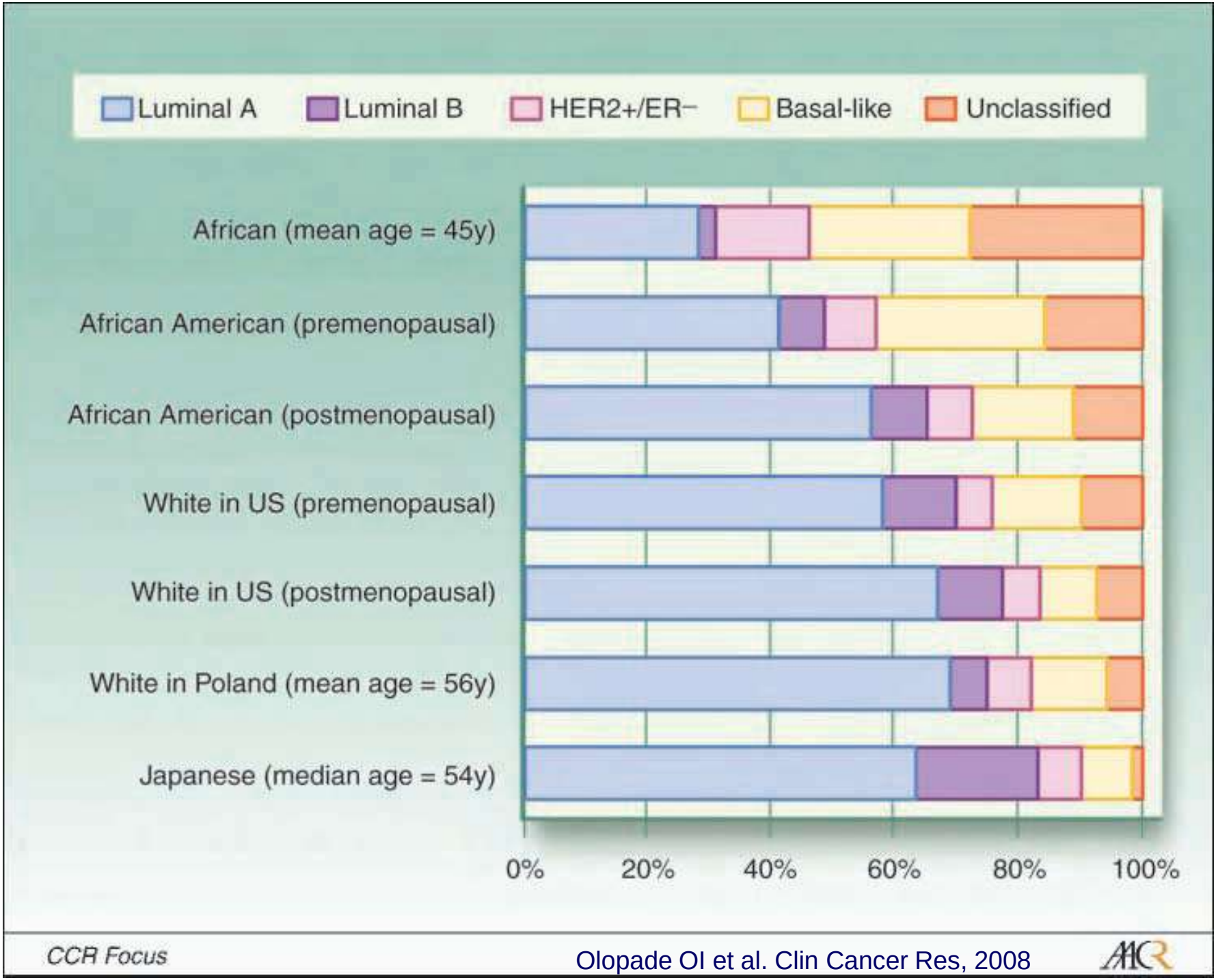
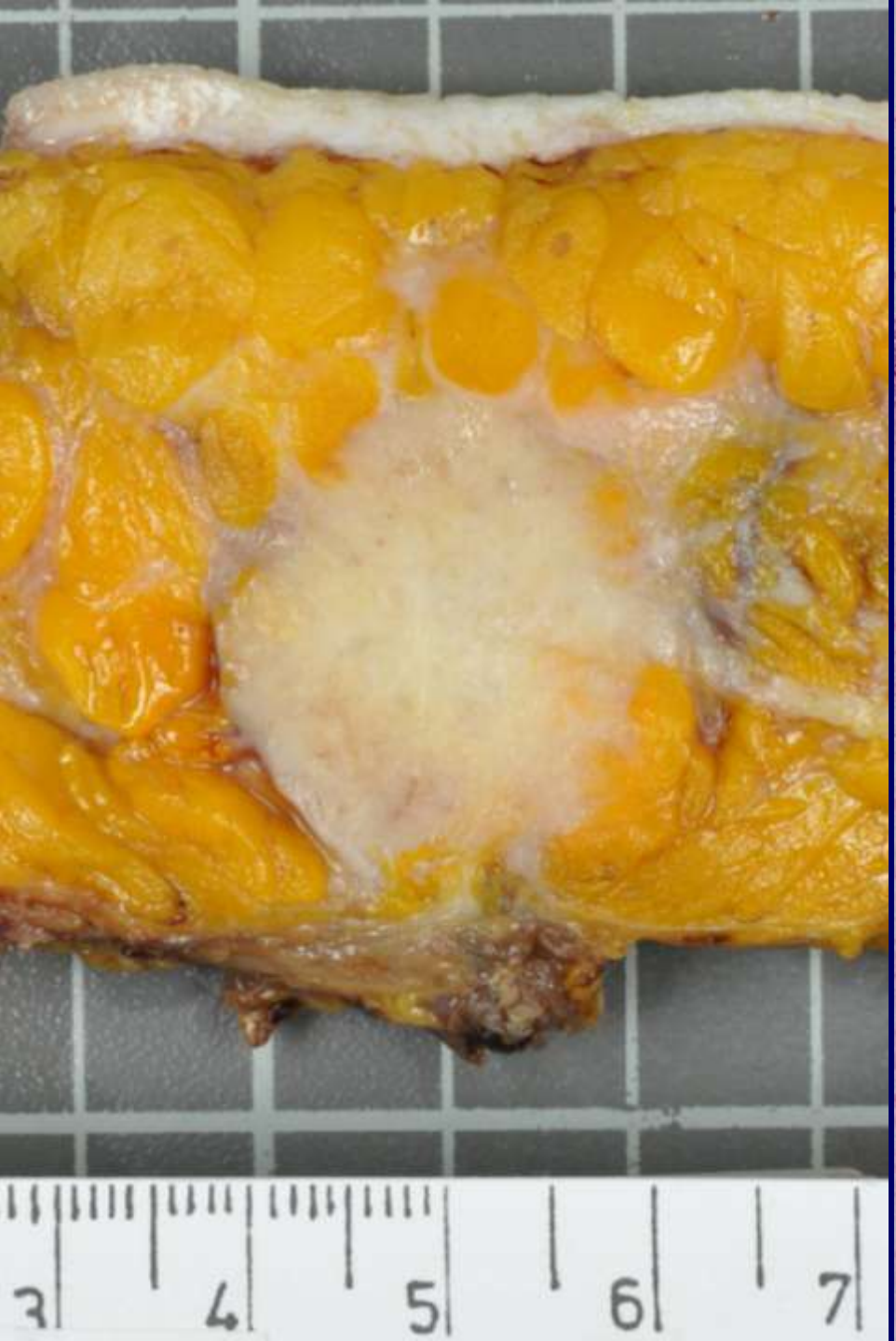




Olopade OI et al. Clin Cancer Res, 2008

Carcinoma de mama con fenotipo basal

Características morfológicas	Características moleculares
Grado 3	RE/RP negativos
Alta proliferación	HER2 negativo
Pleomorfismo nuclear	CK 5/6 positiva
Márgenes expansivos	EGFR positivo
Necrosis geográfica	Vimentina positiva
Ductal, metaplásico…	CD-P positiva
	Otros (c-KIT, laminina, fascina…)
	Mutaciones de *TP53* (hasta 80%)
	Mutaciones de *BRCA1*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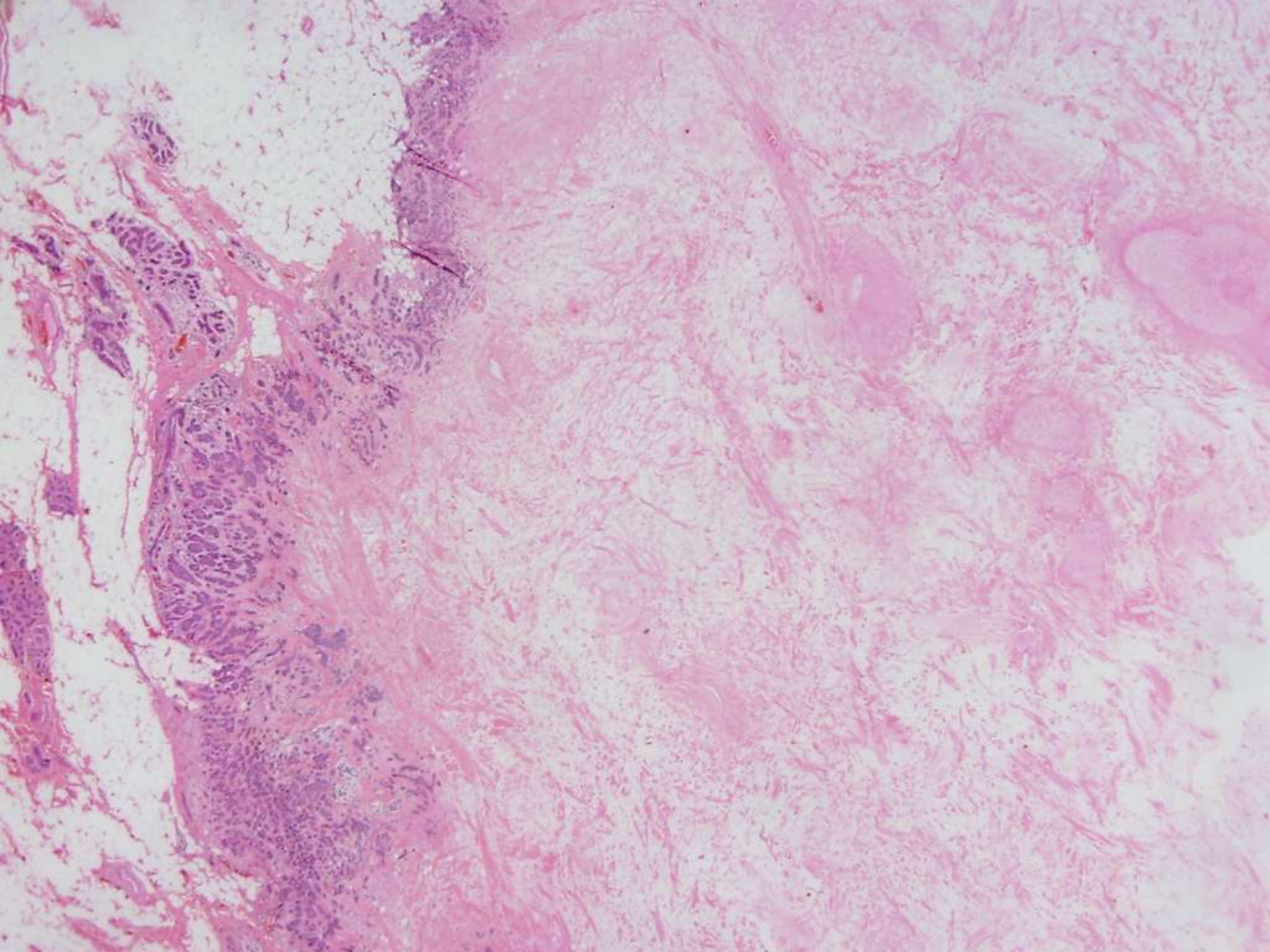
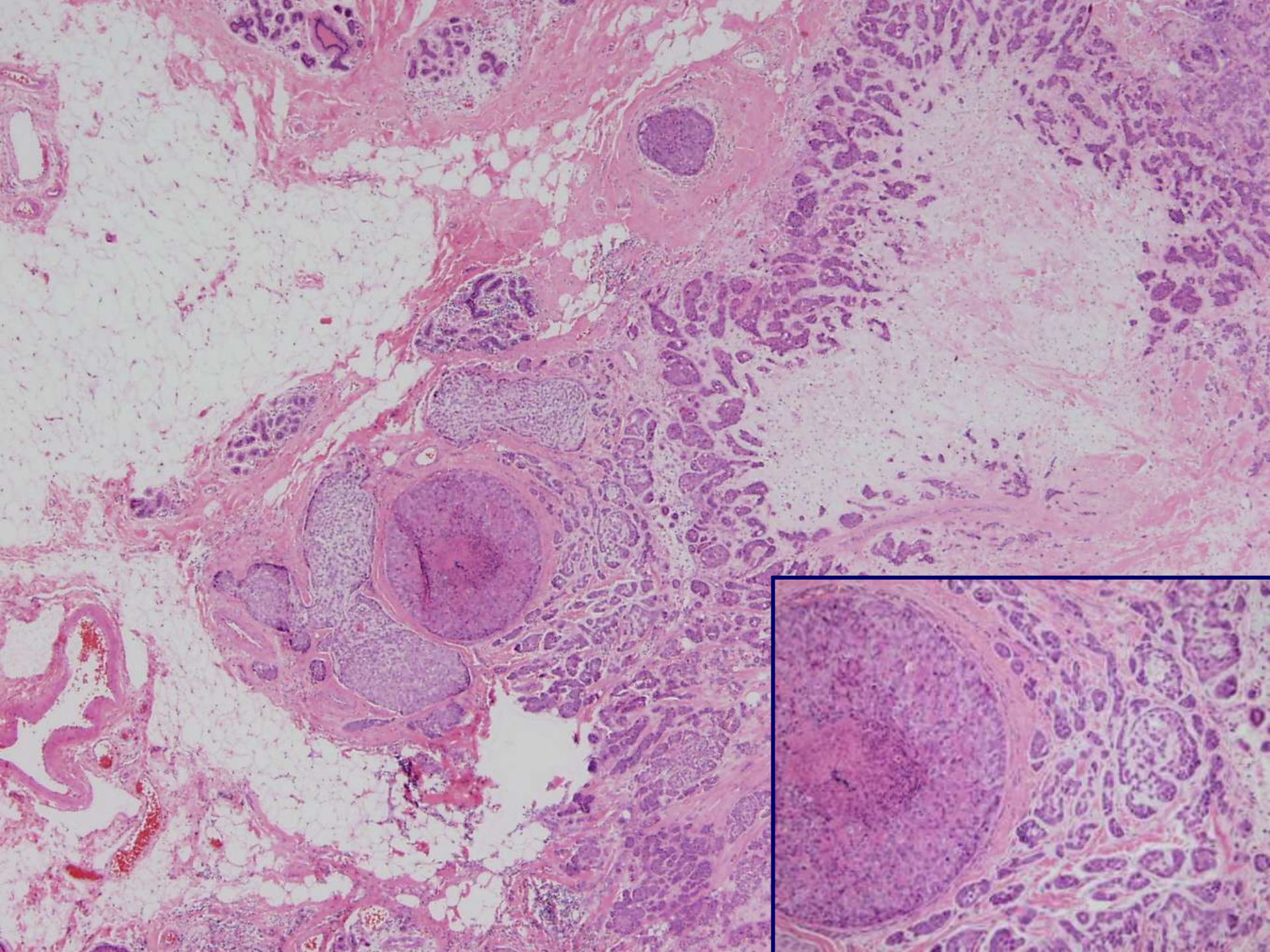
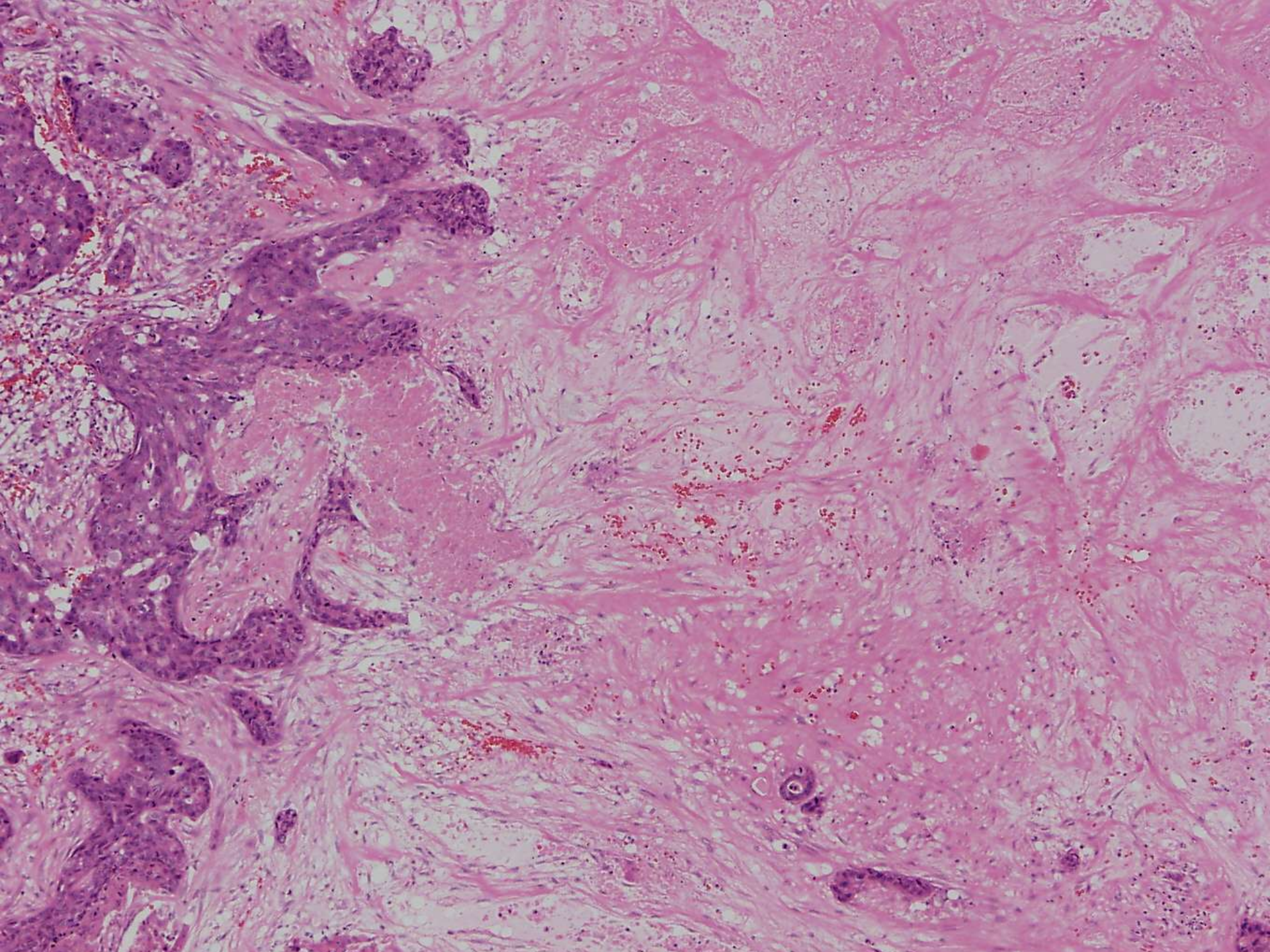
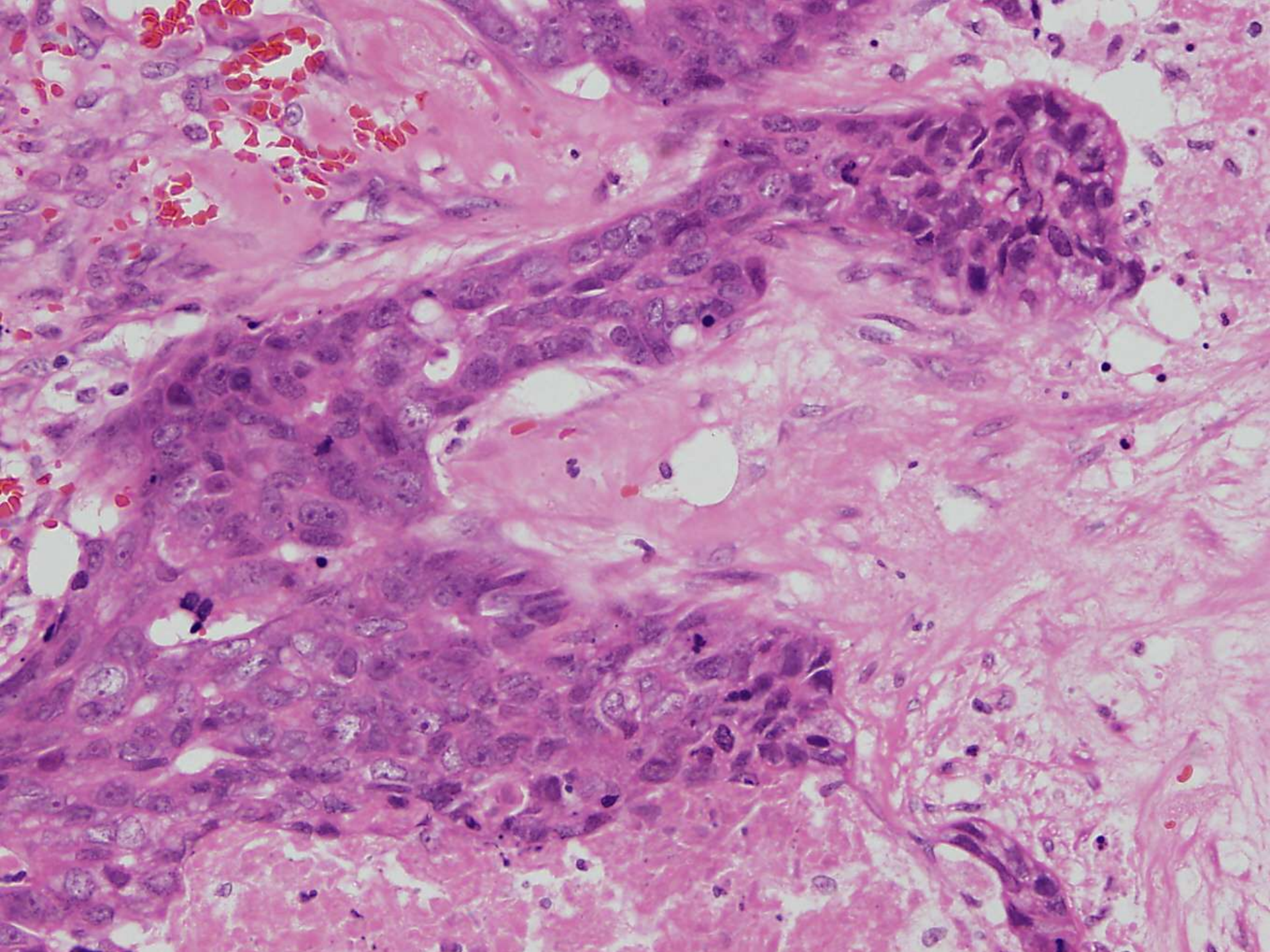
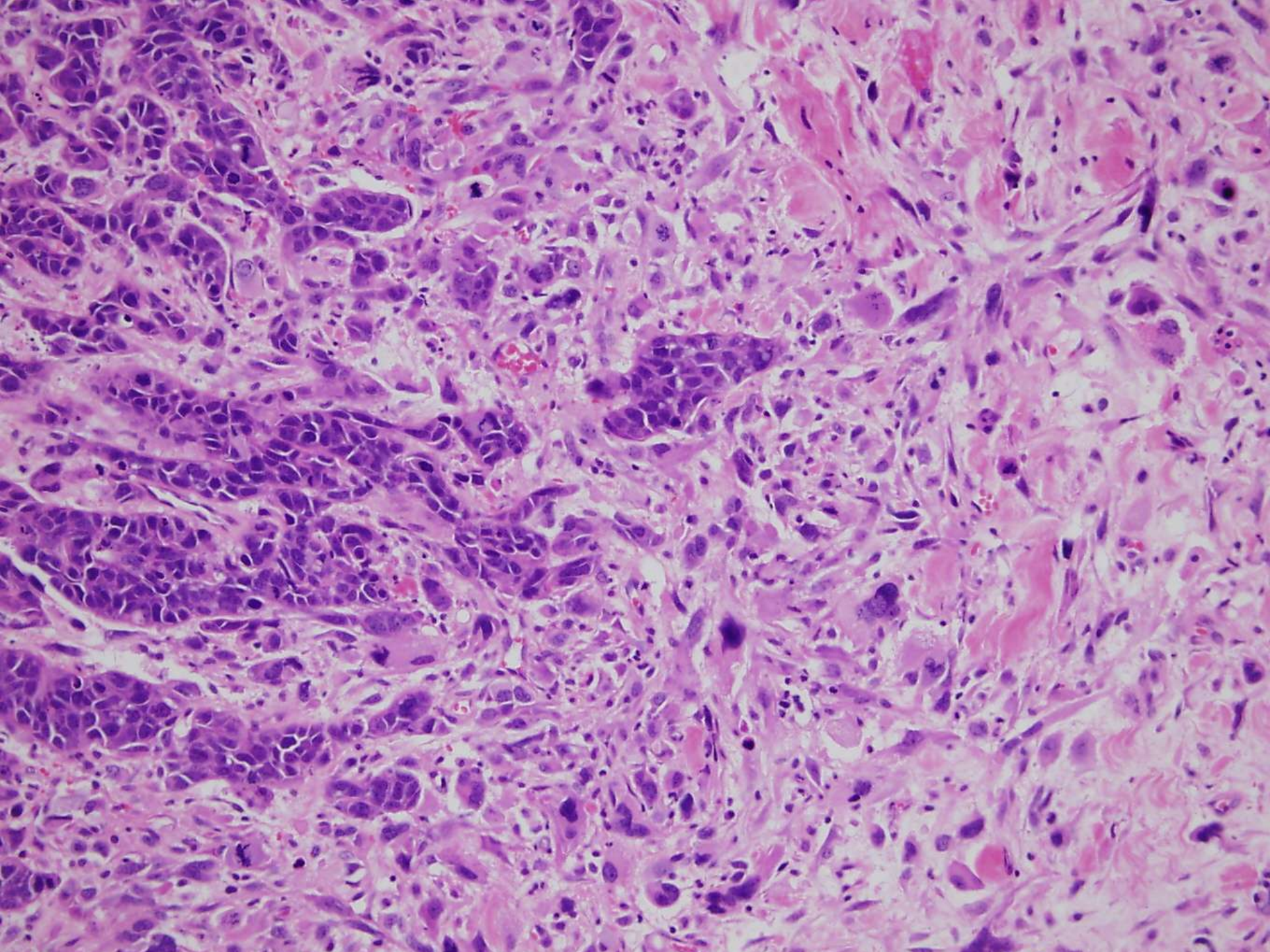
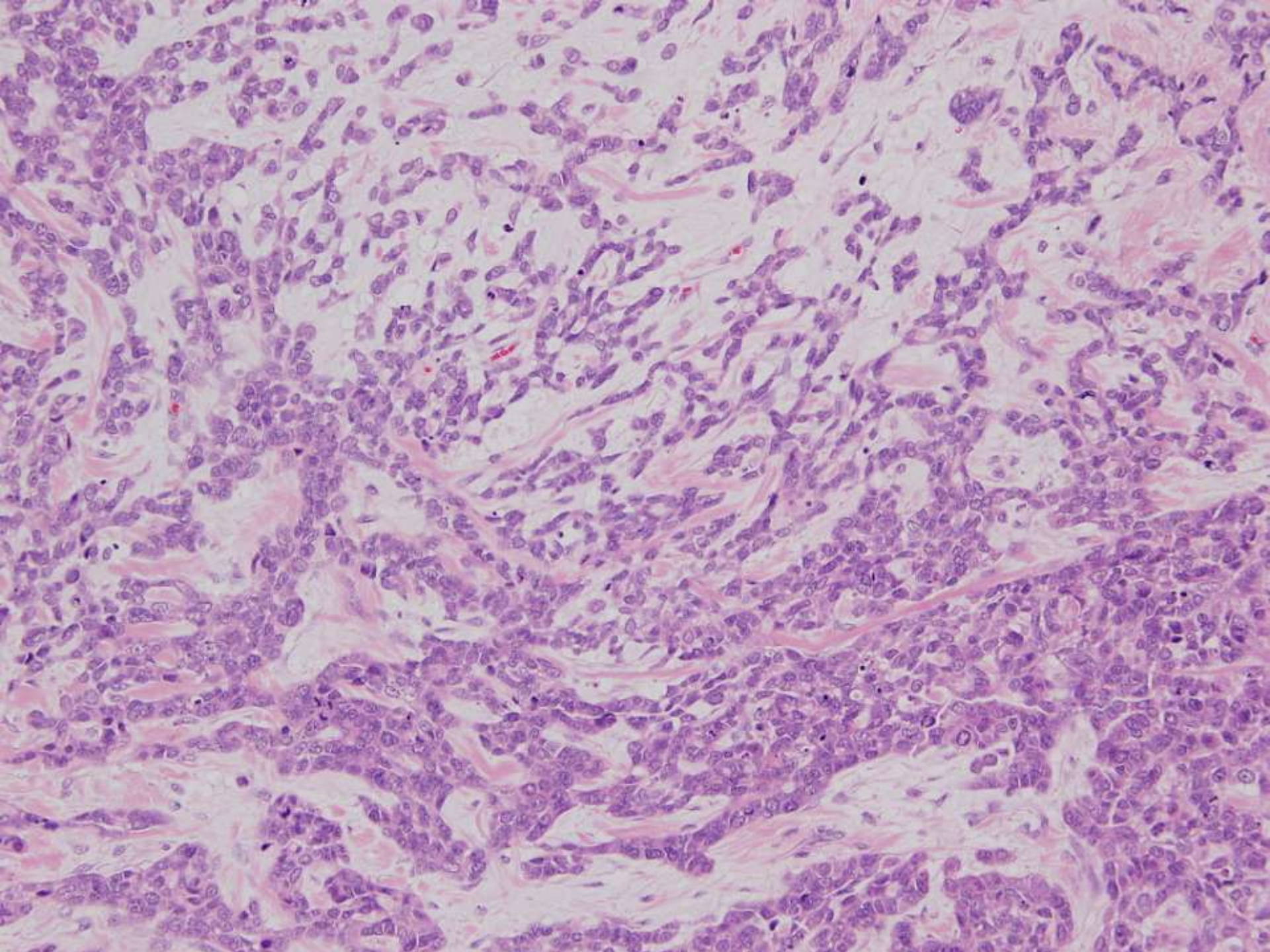


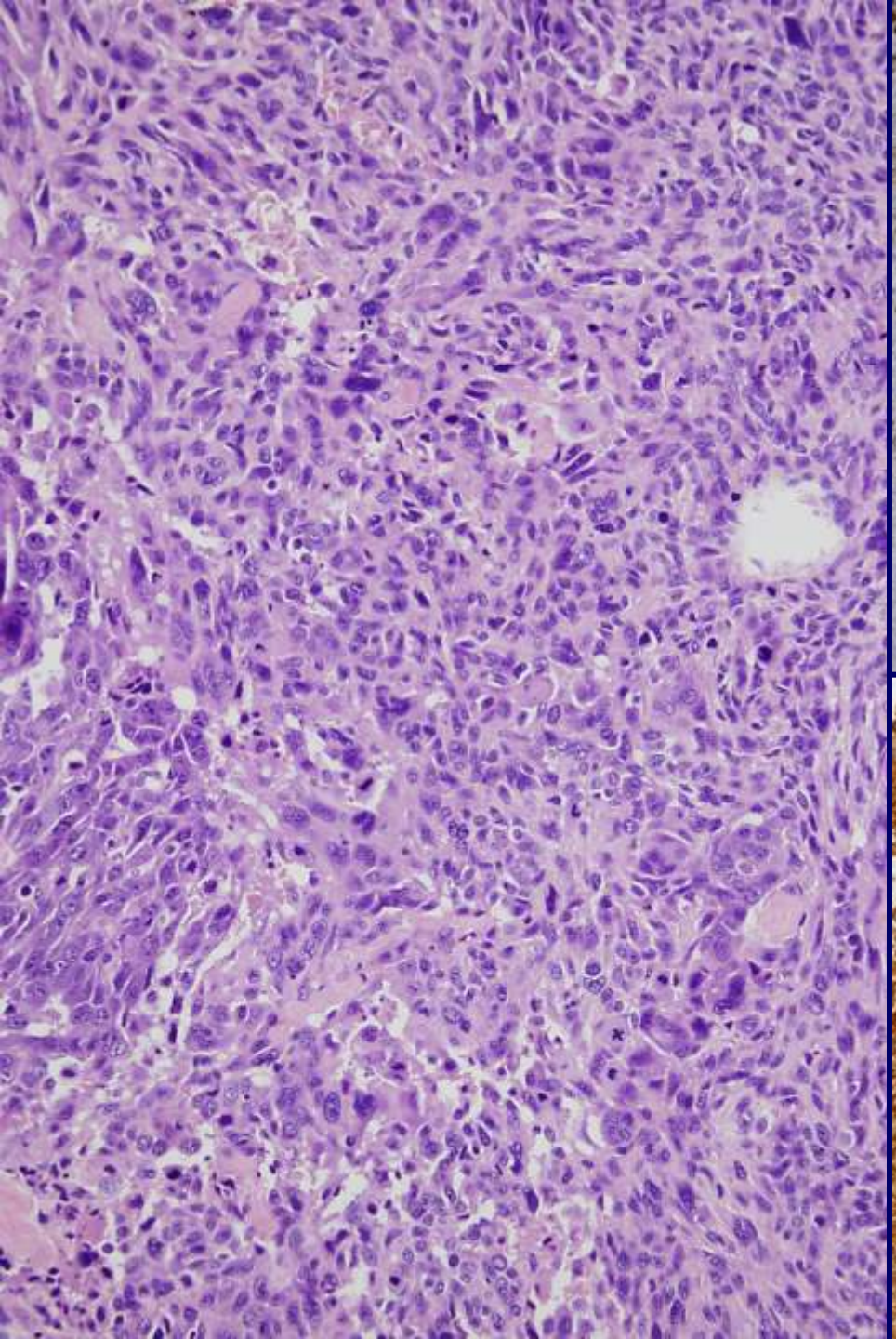


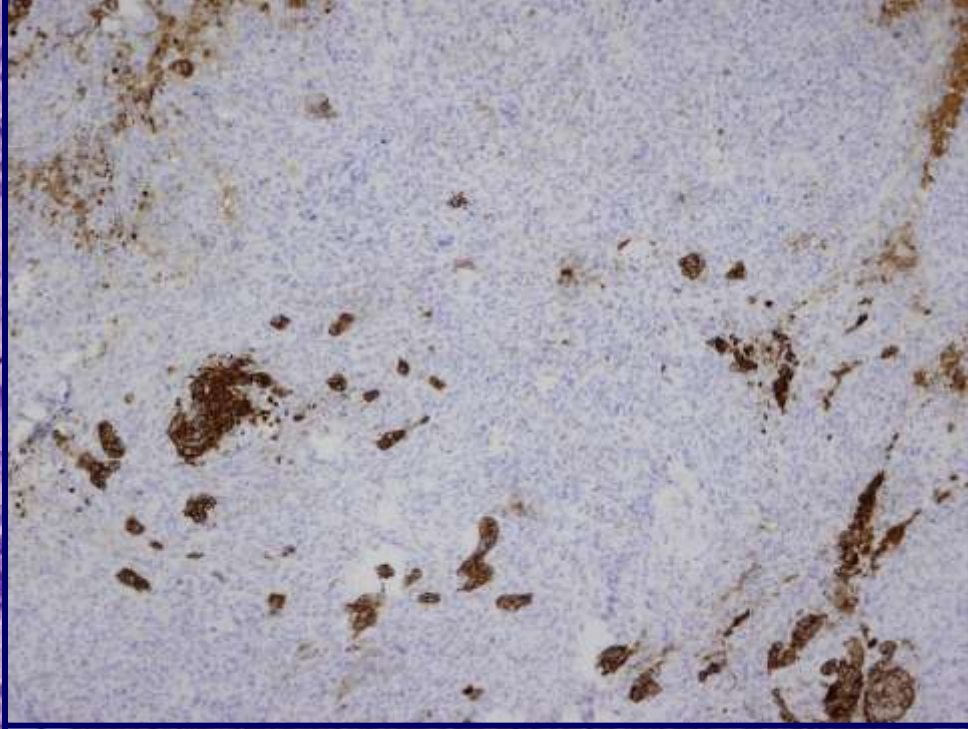


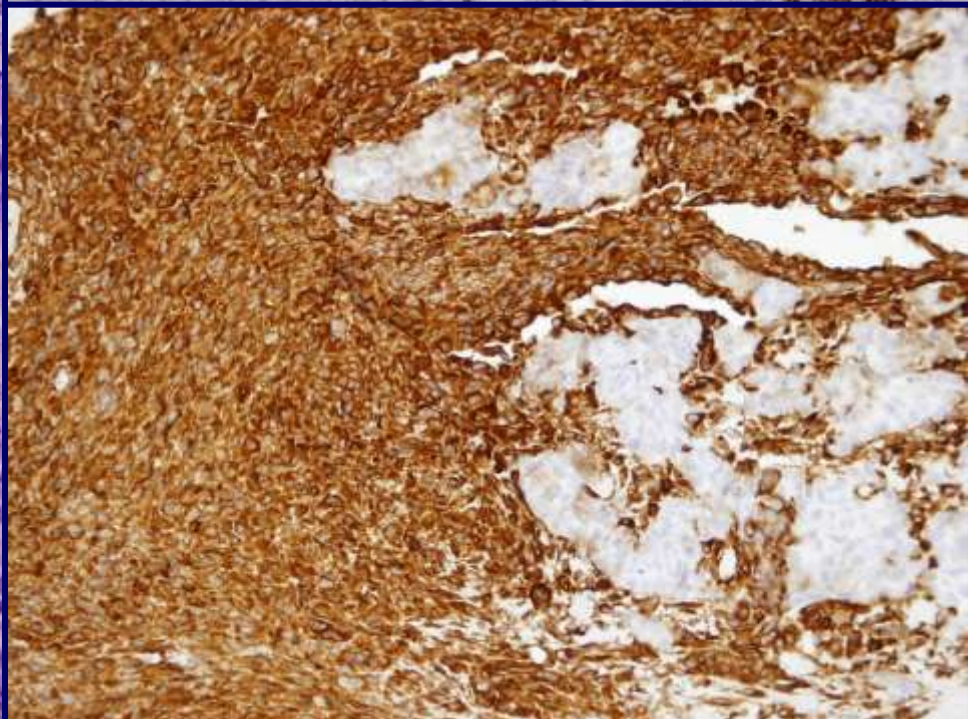


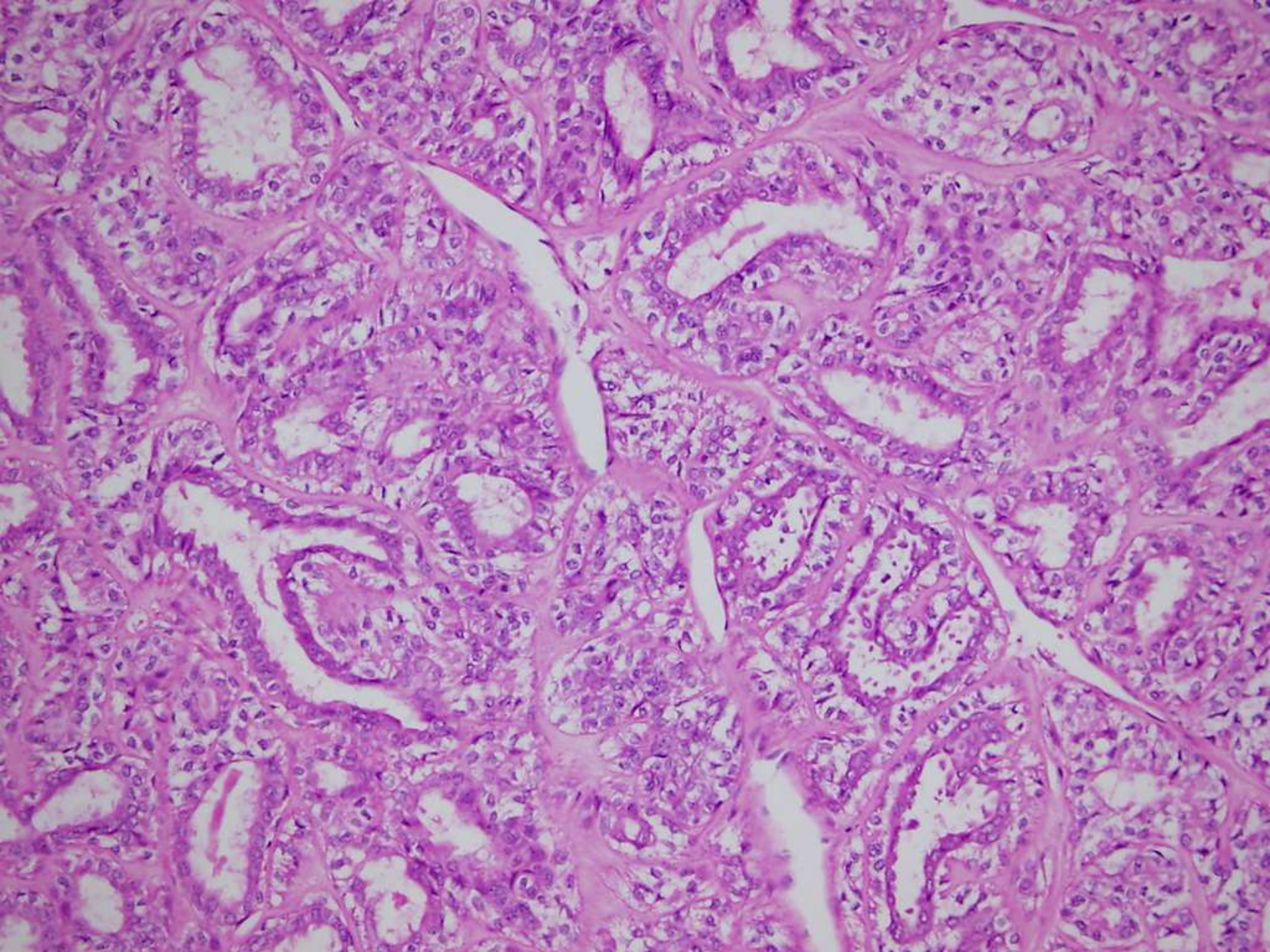




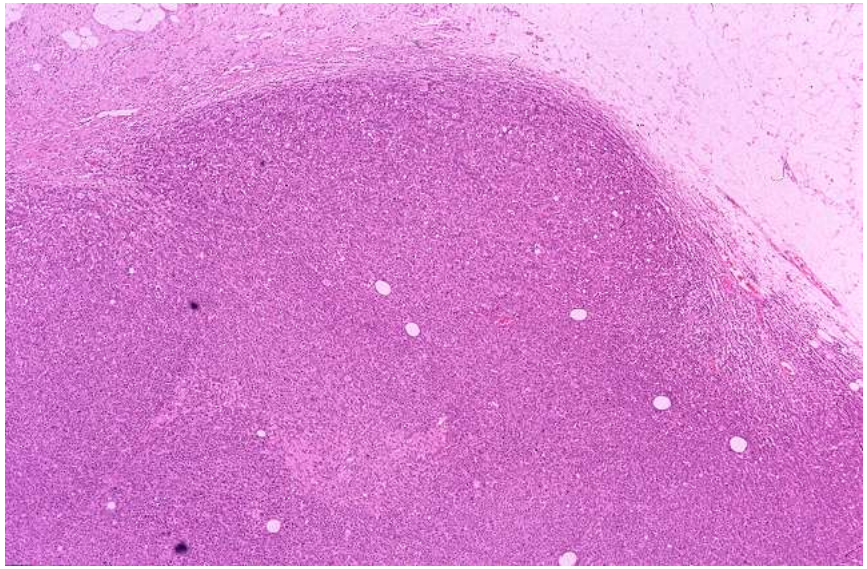


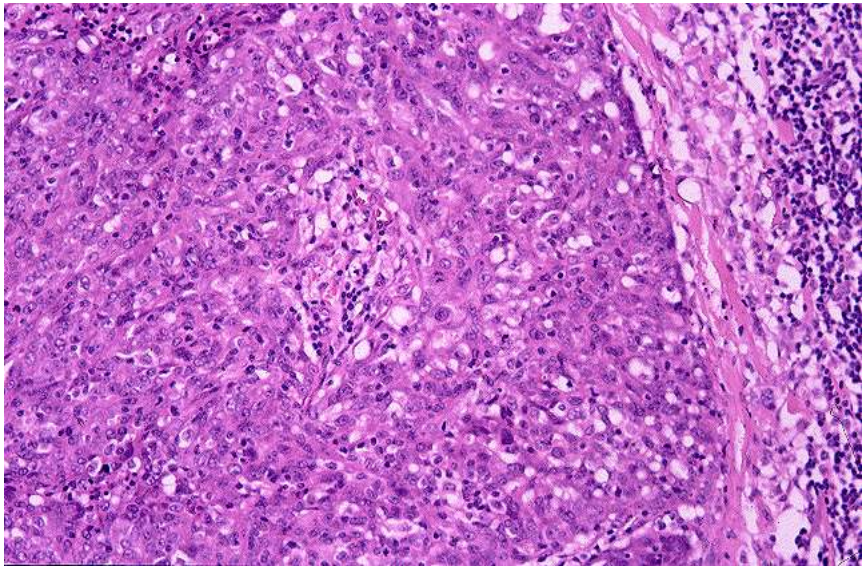


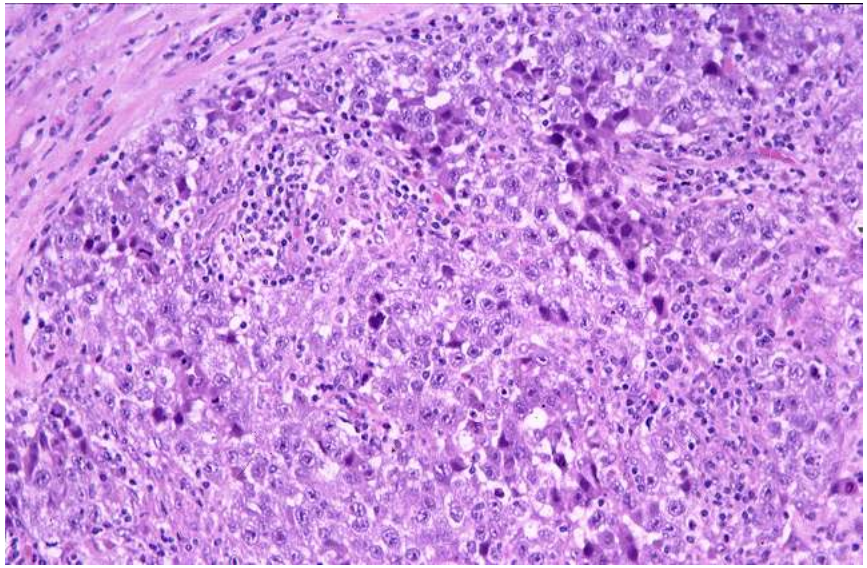


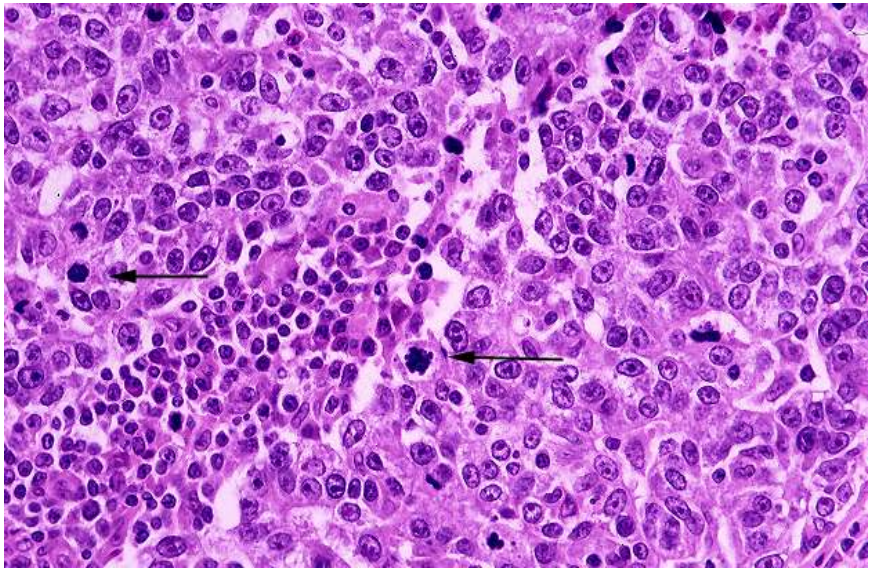


Carcinoma medular

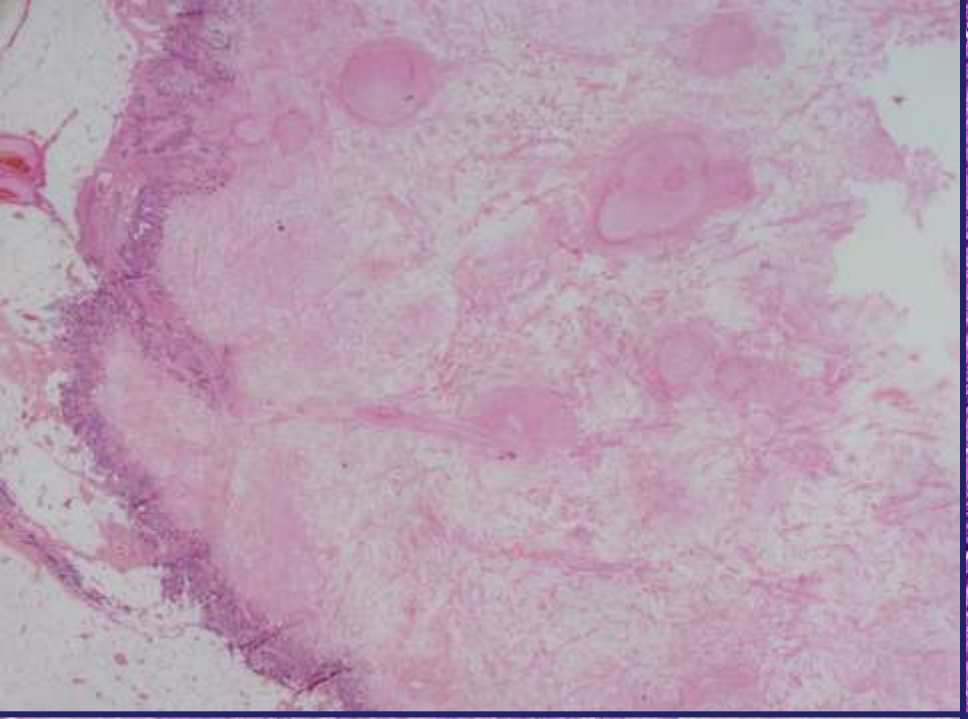


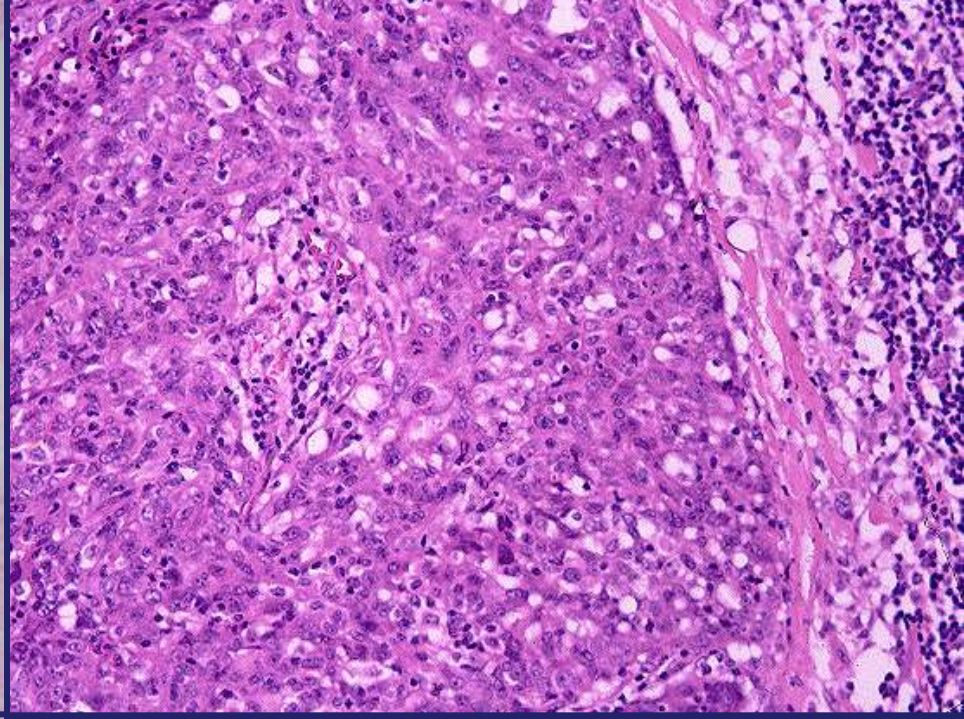


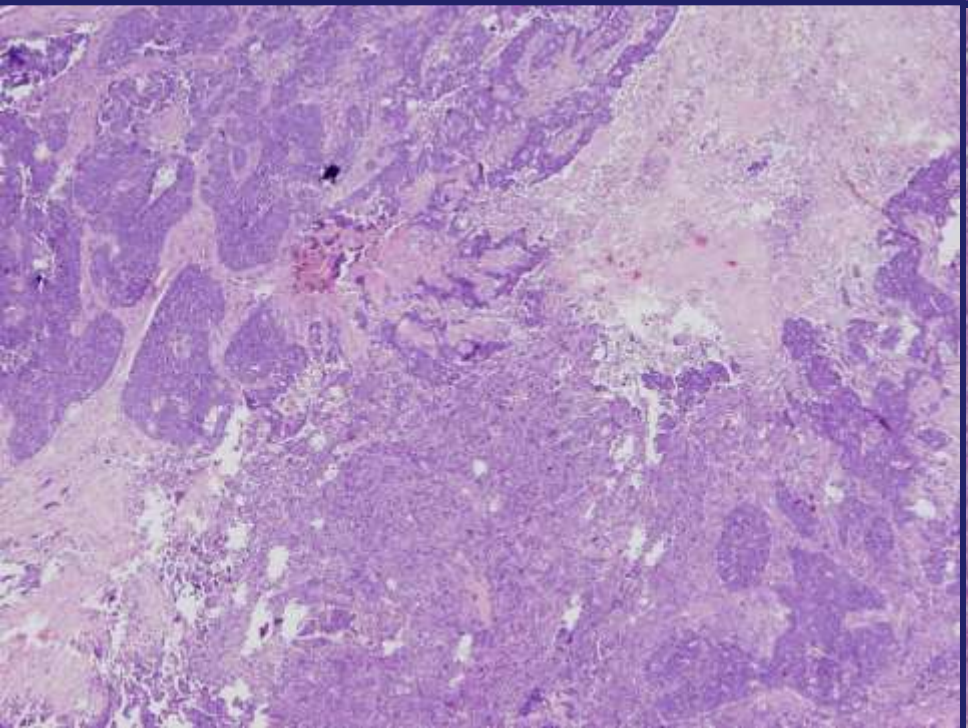


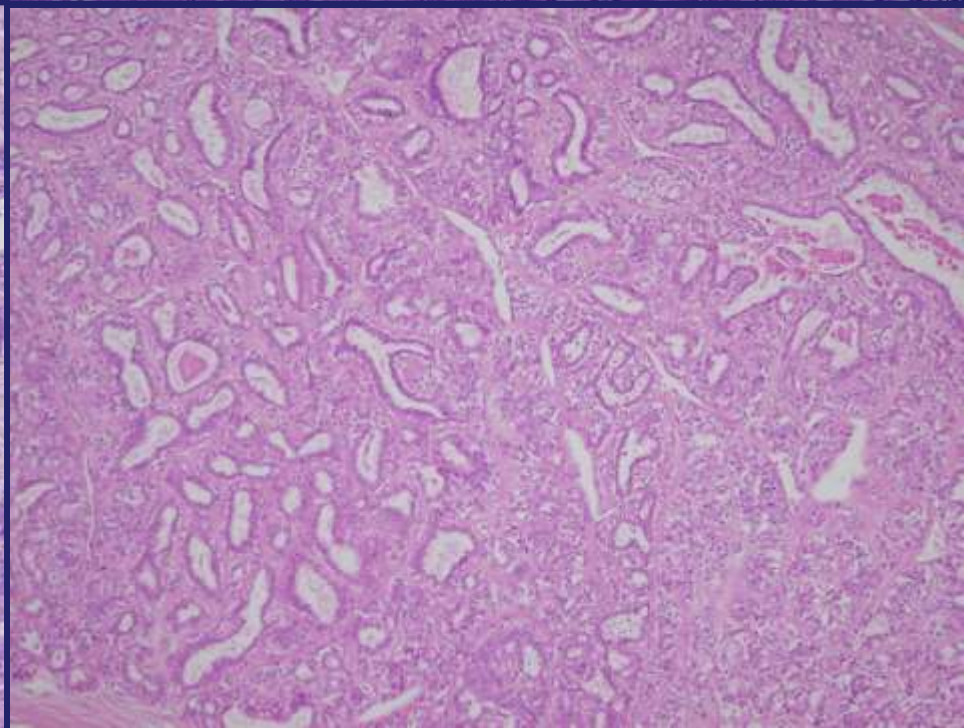


Cortesía Dr. J. Palacios, HU Virgen del Rocío, Sevilla









Variedades de carcinoma de mama “triple negativos”

Poor prognosis
Invasive ductal carcinoma NOS – high grade
Invasive lobular carcinoma – high grade
Metaplastic carcinoma – high grade
Myoepithelial carcinoma
High grade neuroendocrine (oat-cell) carcinoma
Good prognosis
Apocrine carcinoma – low grade
Medullary carcinoma
Secretory breast carcinoma
Adenoid cystic carcinoma
Metaplastic carcinoma – low grade (adenosquamous and fibromatosis-like)

Oakman C et al. The Breast 2010

Pathobiology

Review

Pathobiology 2008;75:119–131
DOI: 10.1159/000123850

Is 'Basal-Like' Carcinoma of the Breast a Distinct Clinicopathological Entity? A Critical Review with Cautionary Notes

Farid Moinfar

Unit of Breast and Gynecologic Pathology, Department of Pathology, Medical University of Graz, Graz, Austria

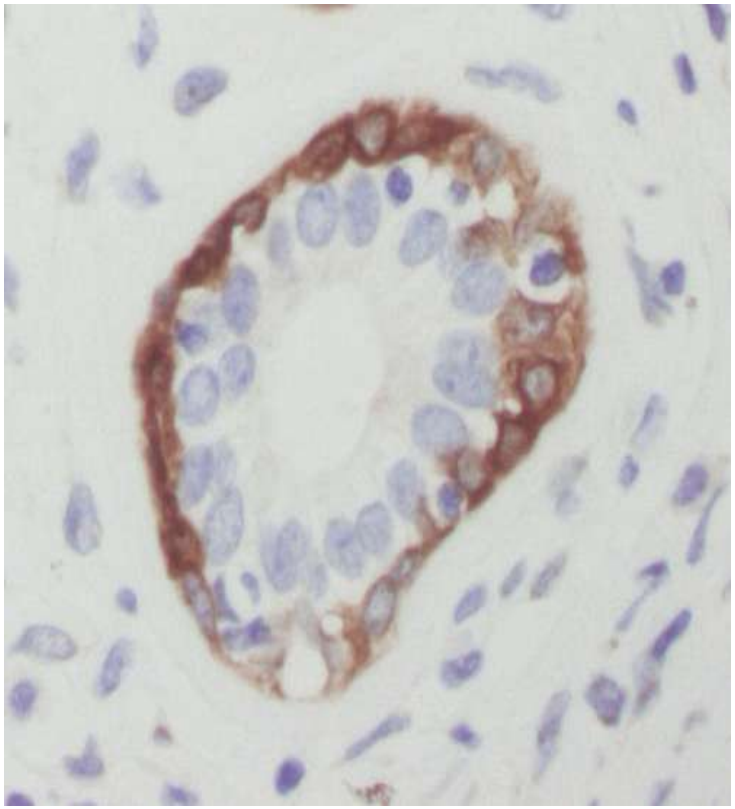
Abstract

This review deals with studies that have used cDNA microarrays and immunohistochemistry to identify a subtype of breast carcinoma known as basal-like carcinoma. The key breast carcinoma studies are critically discussed to highlight methodological problems in cohort selection, definitions, interpretation of results and statistical analysis. The review concludes that basal-like carcinomas do not reflect a single, biologically uniform group of breast cancers, but show significant variations in their phenotypes, grades, immunoprofiles and clinical behavior, just as a wide range of subtypes and behaviors is observed among epithelial/luminal-derived breast carcinomas. Well-designed studies with comparison of low-grade nonbasal versus low-grade basal and high-grade nonbasal versus high-grade basal carcinomas are necessary before one can be convinced that this subtype represents a distinct clinicopathological entity.

CÁNCER DE MAMA CON FENOTIPO BASAL

- **Definición, espectro morfológico.**
- **Marcadores, origen.**
- **Relación con *BRCA1*.**
- **Significado clínico.**

MARCADORES MIOEPITELIALES



CALPONINA

CK5

CK14

CDH3

SMA

CALPONINA

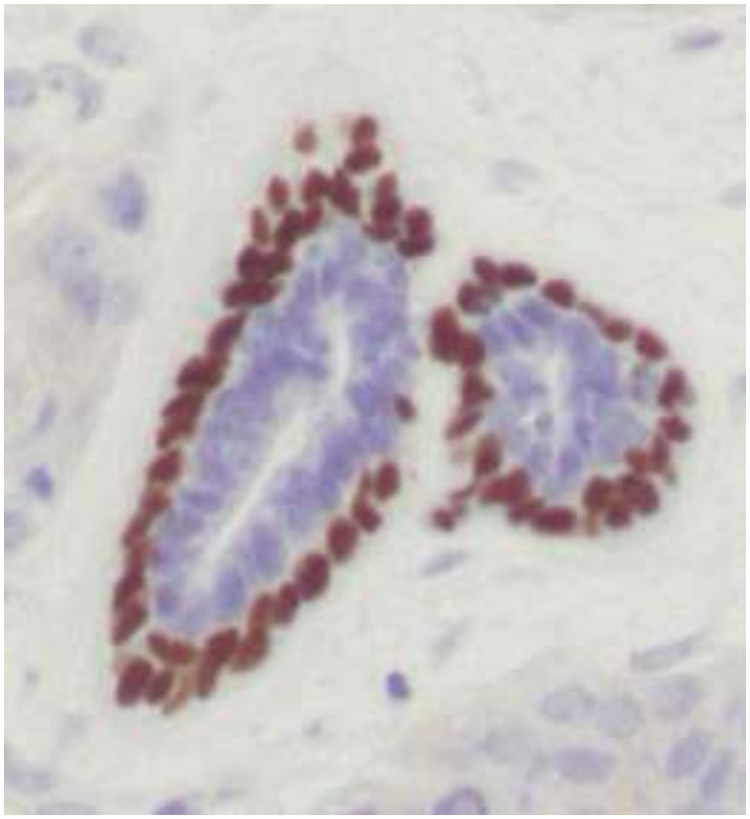
p63

H-CALDESMON

S100

CD10

CD44



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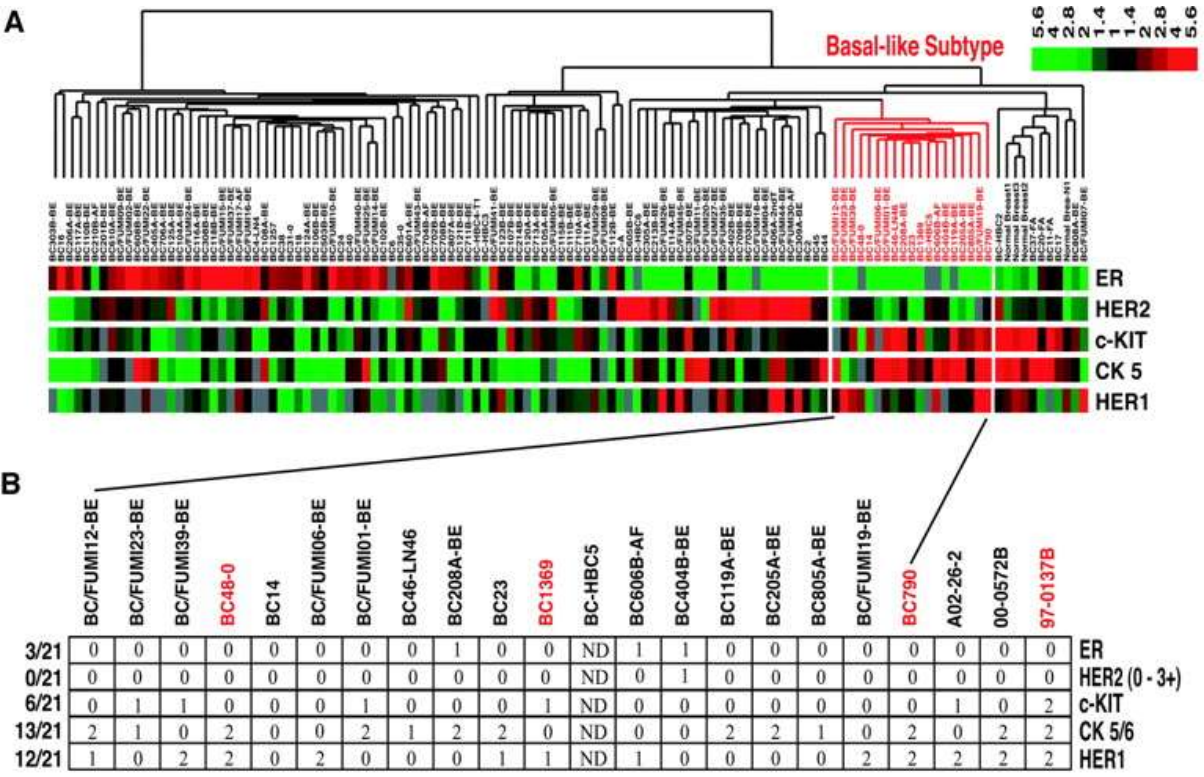
Cortesía Dr. J. Palacios, HU Virgen del Rocío, Sevilla



B

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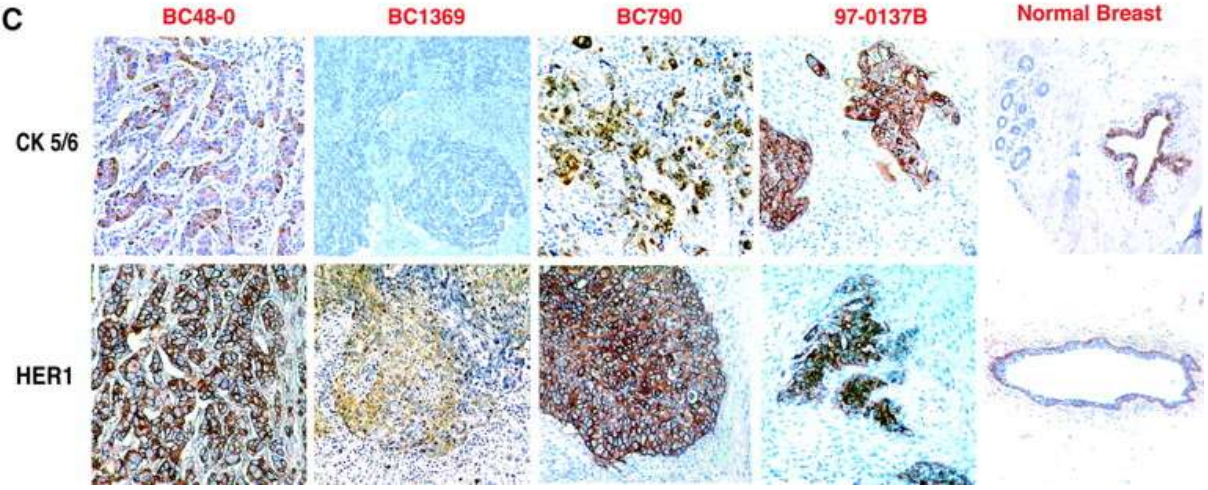
3/21	0	0	0	0	0	0	0	0	1	0	0	ND	1	1	0	0	0	0	0	0	0	0	ER
0/21	0	0	0	0	0	0	0	0	0	0	0	ND	0	1	0	0	0	0	0	0	0	0	HER2 (0 - 3+)
6/21	0	1	1	0	0	0	1	0	0	0	1	ND	0	0	0	0	0	0	0	1	0	2	c-KIT
13/21	2	1	0	2	0	0	2	1	2	2	0	ND	0	0	2	2	1	0	2	0	2	2	CK 5/6
12/21	1	0	2	2	0	2	0	0	0	1	1	ND	1	0	0	0	0	2	2	2	2	2	HER1



FENOTIPO BASAL

ER/HER2-negativo,

CK5 y/o EGFR-positivo

Nielsen el al., Clin Cancer Res 2004

Journal of Pathology
J Pathol 2004; **203**: 661–671
Published online 14 April 2004 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/path.1559

Original Paper

Expression of luminal and basal cytokeratins in human breast carcinoma

Dalia M Abd El-Rehim,[1] Sarah E Pinder,[1] Claire E Paish,[1] J Bell,[1] RW Blamey,[1] John FR Robertson,[2] Robert I Nicholson[3] and Ian O Ellis[1]*

[1]*Department of Histopathology, Breast Unit, Nottingham City Hospital NHS Trust and University of Nottingham, UK*
[2]*Department of Surgery, Breast Unit, Nottingham City Hospital NHS Trust and University of Nottingham, UK*
[3]*Tenovus Institute, Cardiff, UK*

*Correspondence to:
Dr Ian O Ellis, Department of Histopathology, Nottingham City Hospital NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK.
E-mail:
ian.ellis@nottingham.ac.uk

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Accepted: 26 January 2004

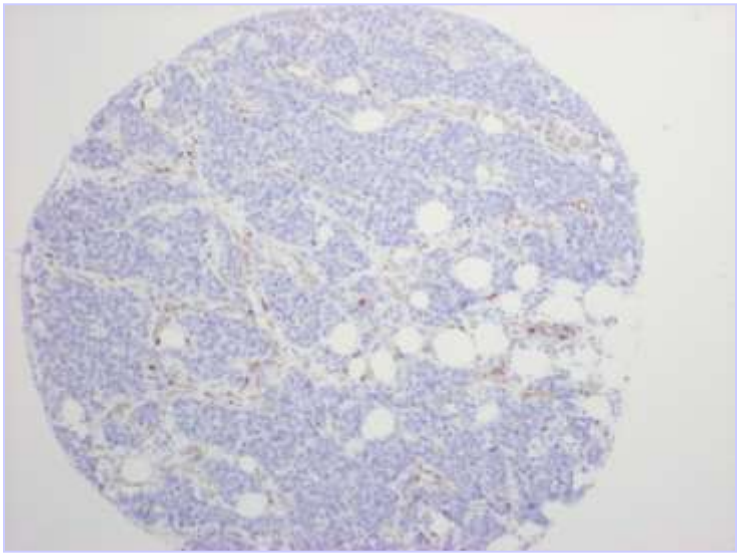
Abstract

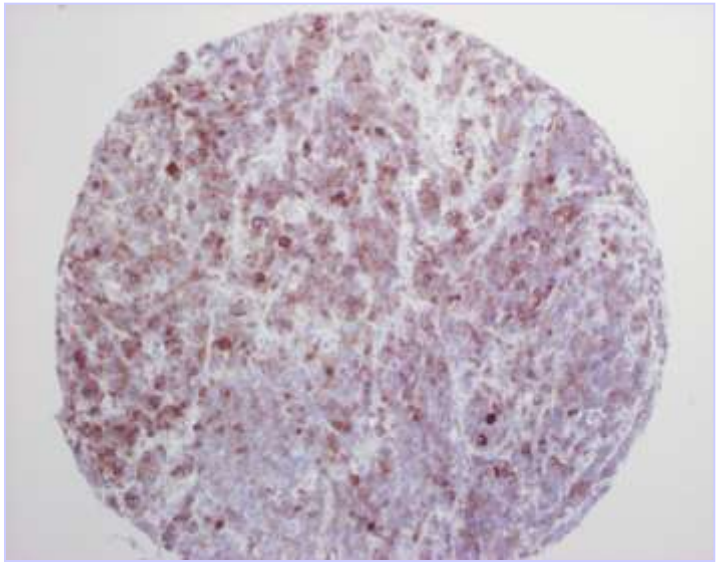
We have examined basal and luminal cell cytokeratin expression in 1944 cases of invasive breast carcinoma, using tissue microarray (TMA) technology, to determine the frequency of expression of each cytokeratin subtype, their relationships and prognostic relevance, if any. Expression was determined by immunocytochemistry staining using antibodies to the luminal cytokeratins (CKs) 7/8, 18 and 19 and the basal markers CK 5/6 and CK 14. Additionally, assessment of α-smooth muscle actin (SMA) and oestrogen receptor status (ER) was performed. The vast majority of the cases showed positivity for CK 7/8, 18 and 19 indicating a differentiated glandular phenotype, a finding associated with good prognosis, ER positivity and older patient age. In contrast, basal marker expression was significantly related to poor prognosis, ER negativity and younger patient age. Multivariate analysis showed that CK 5/6 was an independent indicator for relapse free interval. We were able to subgroup the cases into four distinct phenotype categories (pure luminal, mixed luminal/basal, pure basal and null), which had significant differences in relation to the biological features and the clinical course of the disease. Tumours classified as expressing a basal phenotype (the combined luminal plus basal and the pure basal) were in a poor prognostic subgroup, typically ER negative in most cases. These findings provide further evidence that breast cancer has distinct differentiation subclasses that have both biological and clinical relevance. **Copyright © 2004 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.**

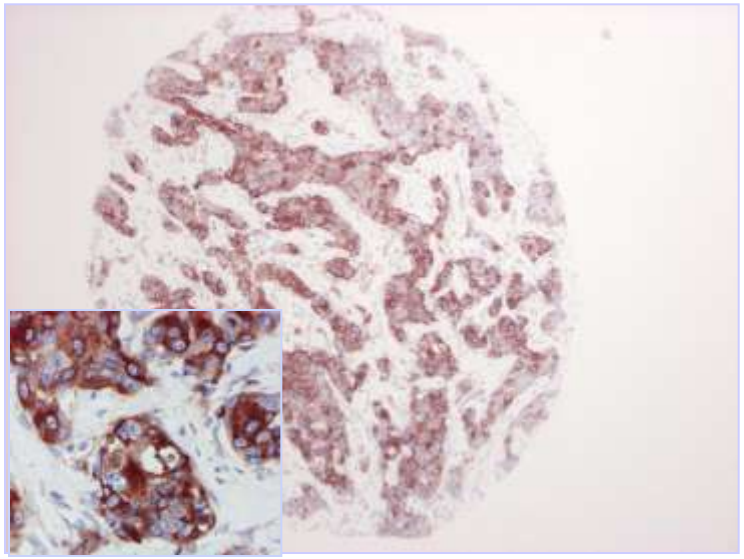
Keywords: tissue microarray; immunohistochemistry; cellular phenotype; invasive breast cancer; cytokeratin; basal and luminal epithelium

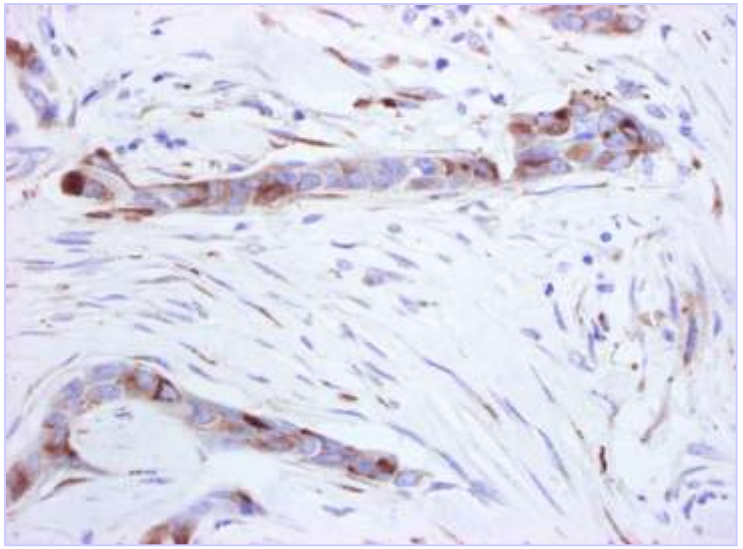
Parámetro	Grupo Basal	Grupo No-basal	X^2 test
Receptor Estrógenos	1/72 (1.4%)	316/407 (77.6%)	p<0,001
Receptor Progesterona	2/72 (2.8%)	264/414 (63.8%)	p<0,001
Cadherina-E	16/69 (23.2%)	205/394 (52.0%)	p<0,001
Cadherina-P	59/65 (90.8%)	82/324 (25.3%)	p<0,001
Cadherina-N	11/64 (17.2%)	27/319 (8.5%)	p=0,033
Cadherina-11	20/68 (29.4%)	44/386 (11.4%)	p<0,001
Citoqueratina 8	39/72 (54.2%)	405/419 (96.7%)	p<0,001
Citoqueratina 19	32/72 (44.4%)	361/415 (87.0%)	p<0,001
Citoqueratina 5/6	45/72 (62.5%)	32/412 (7.8%)	p<0,001
Citoqueratina 14	25/72 (34.7%)	8/417 (2.0%)	p<0,001
Receptor EGF	21/70 (30%)	32/399 (8%)	p<0,001
CD10	19/72 (26.4%)	29/411 (7.1%)	p<0,001
p63	15/71 (21.1%)	40/413 (9.7%)	p=0,005
Caveolina	14/65 (21.5%)	6/410 (1.5%)	p<0,001
Laminina	46/71 (64.8%)	75/410 (18.3%)	p<0,001
Fascina	48/70 (68.6%)	52/412 (12.6%)	p<0,001
Vimentina	59/72 (81.9%)	45/414 (10.9%)	p<0,001
Actina ML	21/72 (29.2%)	7/414 (1.7%)	p<0,001
SPARC	25/71 (35.2%)	26/405 (6.4%)	p<0,001
S100	34/64 (53.1%)	17/397 (4.3%)	p<0,001

VIMENTIN EXPRESSION IN BREAST CANCER









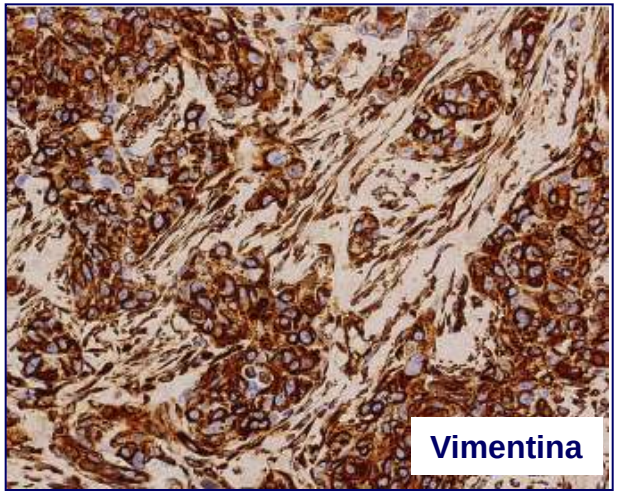
Cortesía Dr. J. Palacios, HU Virgen del Rocío, Sevilla

JCP ONLINE

Vimentin and laminin expression is associated with basal-like phenotype in both sporadic and BRCA1-associated breast carcinomas

Socorro Maria Rodriguez-Pinilla, David Sarrio, Emiliano Honrado, Gema Moreno-Bueno, David Hardisson, Francisco Calero, Javier Benitez and Jose Palacios

J. Clin. Pathol. published online 14 Nov 2006;
doi:10.1136/jcp.2006.042143



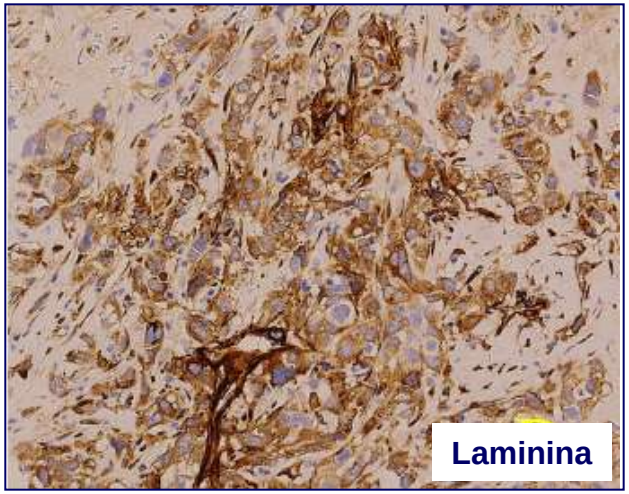
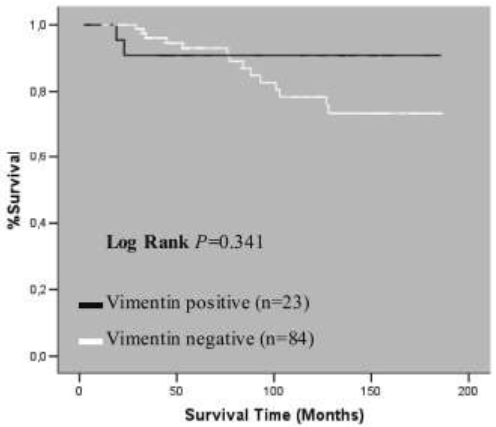


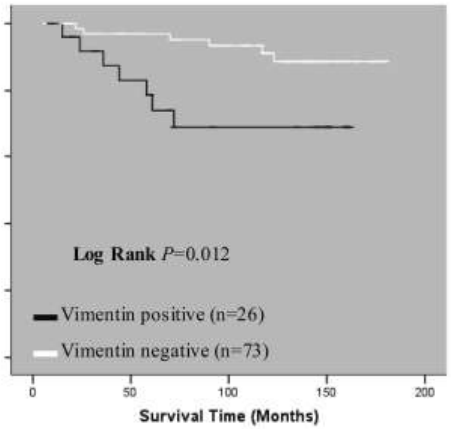
Table 1. Relationships between vimentin and laminin expressio clinicopathological and immunohistochemical characteristics.

	Vimentin-positive	P	Laminin-positive	P
Menopausal Status				
Premenopausal	17/99 (17.2%)		17/98 (17.3%)	
Postmenopausal	34/116 (29.3%)	0.037	22/115 (19.1%)	0.737
Size				
p T1	21/114 (18.4%)		18/114 (15.8%)	
p T2	23/70 (32.9%)	0.026	17/69 (24.6%)	0.141
Grade				
1	4/52 (7.7%)		1/52 (1.9%)	
2	9/57 (15.8%)		7/56 (12.5%)	
3	34/84 (40.5%)	<0.001	24/83 (28.9%)	<0.001
ER				
Positive	11/161 (6.8%)		12/160 (7.5%)	
Negative	40/60 (66.7%)	<0.001	27/59 (45.8%)	<0.001
PR				
Positive	14/149 (9.4%)		15/147 (10.2%)	
Negative	38/74 (51.4%)	<0.001	24/73 (32.9%)	<0.001
P53				
Positive	16/60 (26.7%)		17/59 (28.8%)	
Negative	35/157 (22.3%)	0.497	22/156 (14.1%)	0.012
HER2				
Positive	6/37 (16.2%)		8/35 (22.9%)	
Negative	46/187 (24.6%)	0.270	31/187 (16.6%)	0.370
CK5/6				
Positive	20/35 (57.1%)		12/35 (34.3%)	
Negative	32/186(17.2%)	<0.001	27/184 (14.7%)	0.005
EGFR				
Positive	13/21 (61.9%)		7/20 (35.0%)	
Negative	38/191 (19.9%)	<0.001	30/191 (15.7%)	0.031
Laminin				
Positive	22/39 (56.4%)			
Negative	30/181 (16.6%)	<0.001		
Basal-like*				
Positive	21/27 (77.8%)		11/26 (42.3%)	
Negative	30/194 (15.5%)	<0.001	28/193 (14.5%)	0.001

DSS chemotherapy-treated patients and vimentin expression



DSS chemotherapy non-treated patients and vimentin expression



Modern Pathology (2007) 20, 474–481
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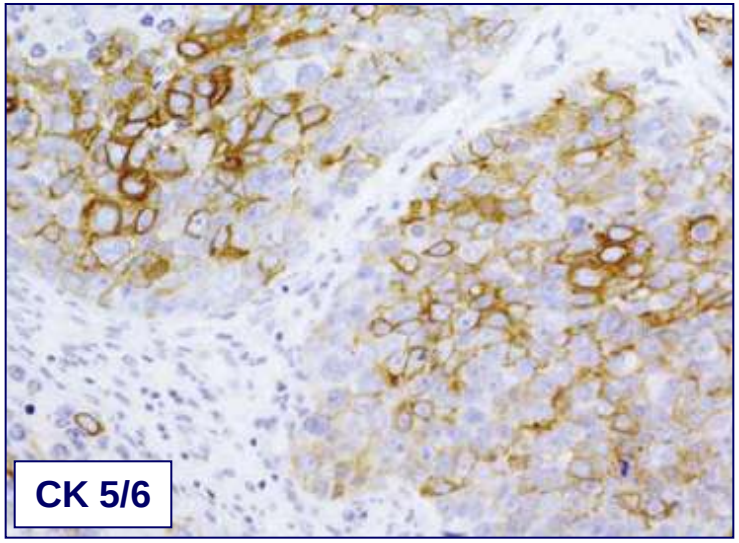
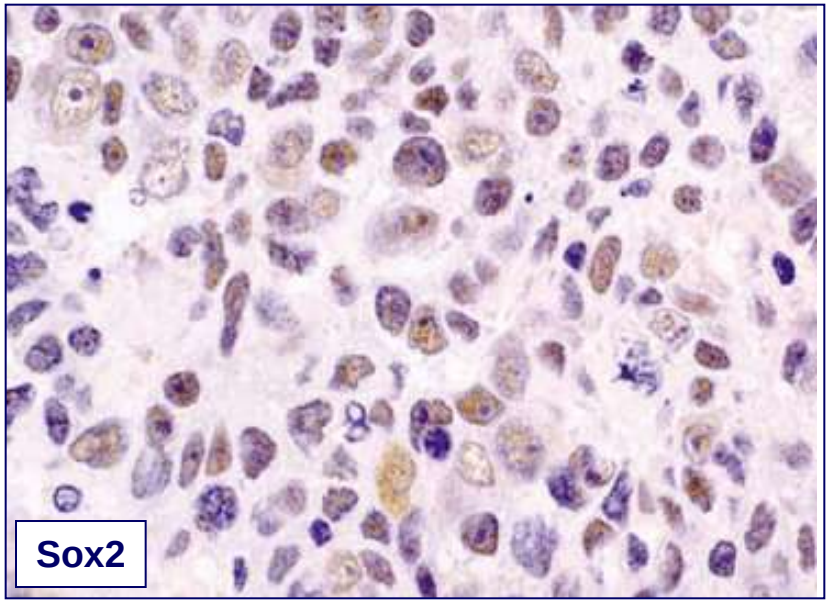
www.modernpathology.org

Sox2: a possible driver of the basal-like phenotype in sporadic breast cancer

Socorro M Rodriguez-Pinilla[1,2], David Sarrio[1], Gema Moreno-Bueno[1], Yolanda Rodriguez-Gil[3], Miguel A Martinez[3], Lucia Hernandez[3], David Hardisson[4], Jorge S Reis-Filho[2] and Jose Palacios[1]





- Sox2 es un factor de transcripción (3q).
- 226 carcinomas de mama esporádicos pN0.
- ER/HER2 (-) y CK 5/6 y/o EGFR (+).
- 13,7% de carcinomas con fenotipo basal.
- Expresión de Sox2 en 16,7%:
  - **43,3%** en fenotipo basal.
  - 10,6% en fenotipo luminal.
  - 13,3% en HER2+.
- Asociación de Sox2 con expresión de CK 5/6, EGFR y vimentina.

Breast Cancer Research and Treatment (2006)
DOI 10.1007/s10549-006-9184-1
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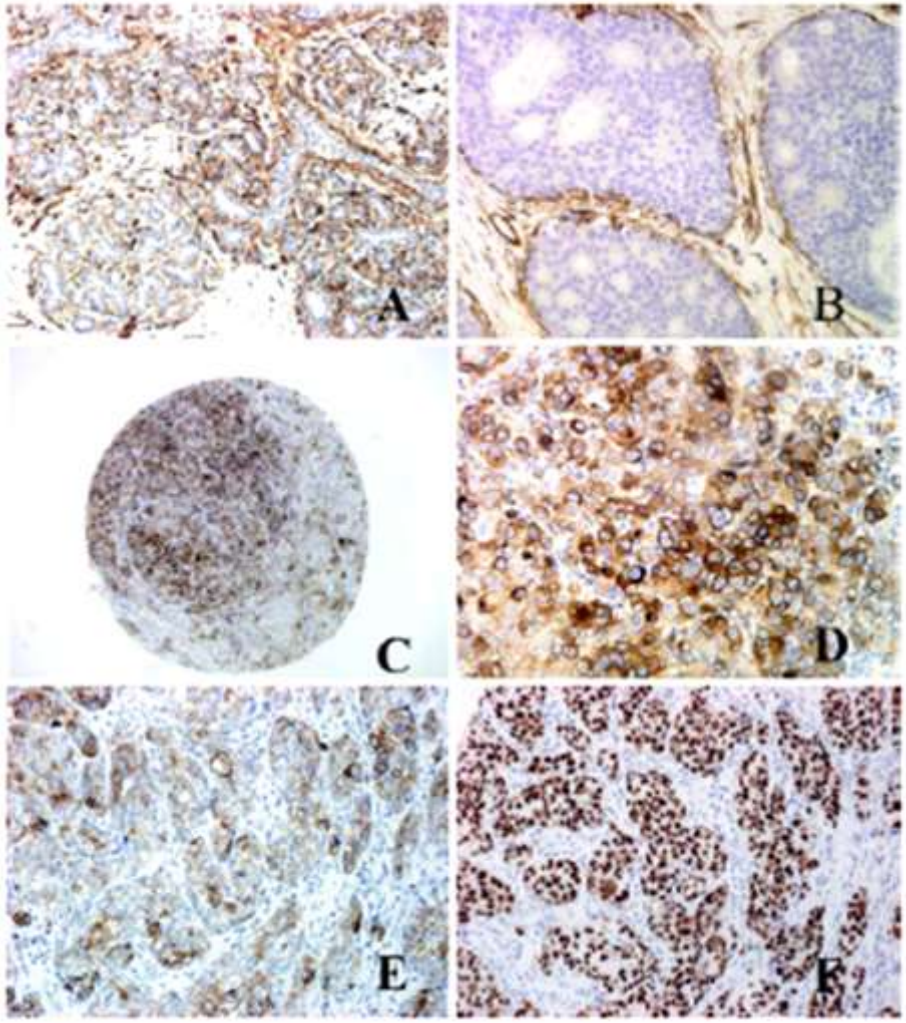
Clinical trial

Caveolin-1 expression is associated with a basal-like phenotype in sporadic and hereditary breast cancer

Socorro Maria Rodriguez Pinilla[1], Emiliano Honrado[2], David Hardisson[3], Javier Benitez[2], and José Palacios[1]

[1]*Breast and Gynaecological Cancer Group, Molecular Pathology Programme, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain;* [2]*Department of Human Genetics, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain;* [3]*Department of Pathology, La Paz Hospital, Madrid, Spain*



- 509 carcinomas de mama esporádicos.
- ER/HER2 (-) y CK 5/6 y/o EGFR (+).
- 10,6% de carcinomas con fenotipo basal.
- Expresión de CAV-1 en 4,2% de carcinomas.
- Asociación entre fenotipo basal-CAV-1:
  - ✓ **52% CAV-1 (+) tienen fenotipo basal.**
  - ✓ 9% CAV-1 (-) tienen fenotipo basal.

Patología

www.elsevier.es/patologia

Original

Expresión de p63 y citoqueratina 5/6 en los diferentes tipos moleculares del carcinoma de mama

Aldo Reigosa [a,b,c,*], Ángel Fernández [b], Daily Gutiérrez [b], Eduardo Caleiras [c], David Hardisson [d], Herbert Espig [e], Felipe Saldivia [c], Angeles Juarranz [f] y Francisco Sanz [f]

[a] Centro de Investigaciones Médicas y Biotecnológicas de la Universidad de Carabobo (CIMBUC), Valencia, Venezuela
[b] Departamento de Morfofisiopatología, Facultad de Ciencias de la Salud, Universidad de Carabobo, Venezuela
[c] Instituto de Oncología «Dr. Miguel Pérez Carreño» Valencia, Venezuela
[d] Departamento de Anatomía Patológica, Hospital Universitario La Paz, Facultad de Medicina, Universidad Autónoma de Madrid, España
[e] Escuela de Salud Pública, Facultad de Ciencias de la Salud, Universidad de Carabobo, Venezuela
[f] Departamento de Biología, Facultad de Ciencias, Universidad Autónoma de Madrid, España

RESUMEN

Antecedentes: El cáncer de mama es un grupo heterogéneo de tumores. Los estudios de *microarrays* de ADN han llevado a la clasificación del carcinoma invasor de mama en diferentes clases moleculares. El objetivo de este estudio fue determinar la expresión de p63 y citoqueratina 5/6 en carcinomas ductales invasores y su relación con las diferentes clases moleculares, en especial con el subgrupo de tipo basal.

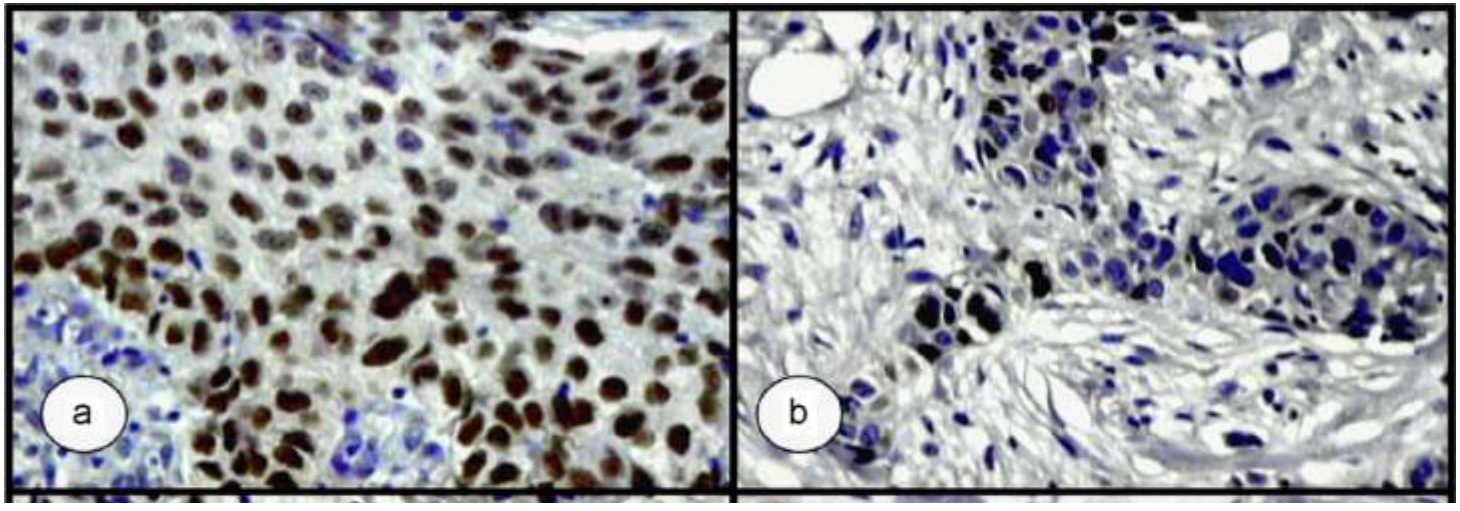
Métodos: Se realizó estudio inmunohistoquímico con los anticuerpos p63 y CK5/6 en 200 muestras de carcinoma ductal invasor sin otra especificación. En cada caso se había determinado previamente el estado de los receptores de estrógeno y progesterona (RE, RP), y de HER2. De acuerdo a estos datos, los tumores se clasificaron como luminal A, luminal B, HER2+ y tipo basal (triple negativo).

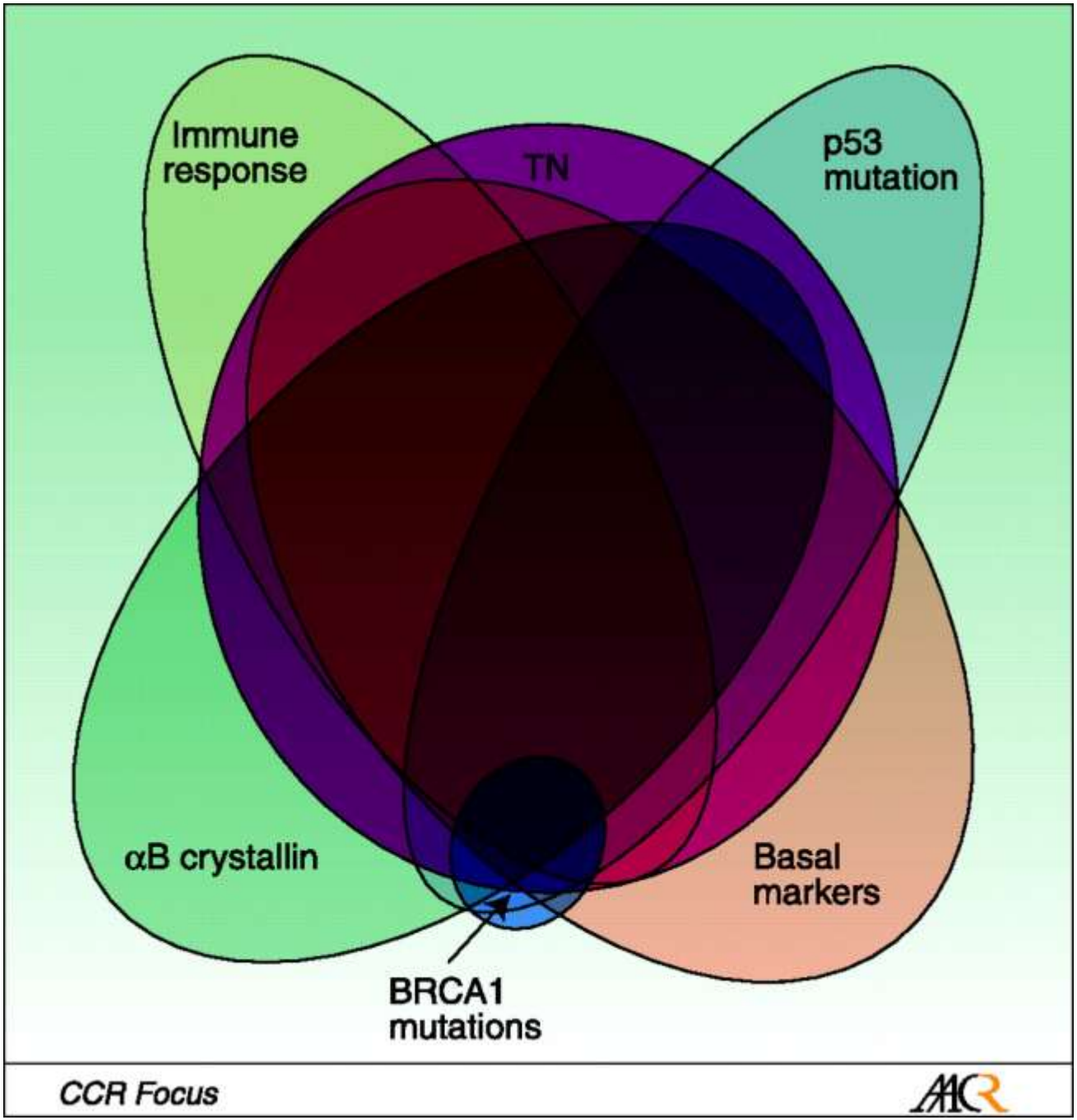
Resultados: Se observó expresión de p63 en 5 casos de HER2+ y 19 casos de tumores del tipo basal (23,2%), se demostró una fuerte relación entre la expresión de CK5/6 y los tumores de tipo basal (59,8%, $p < 0,0001$), pero también se expresó en un caso luminal A, 3 luminal B y 8 HER2+.

Conclusiones: No todos los casos triple negativo son de tipo basal. Es necesario estandarizar la clasificación molecular basada en inmunohistoquímica, así como el panel de anticuerpos a utilizar, en especial para la identificación del tipo basal.

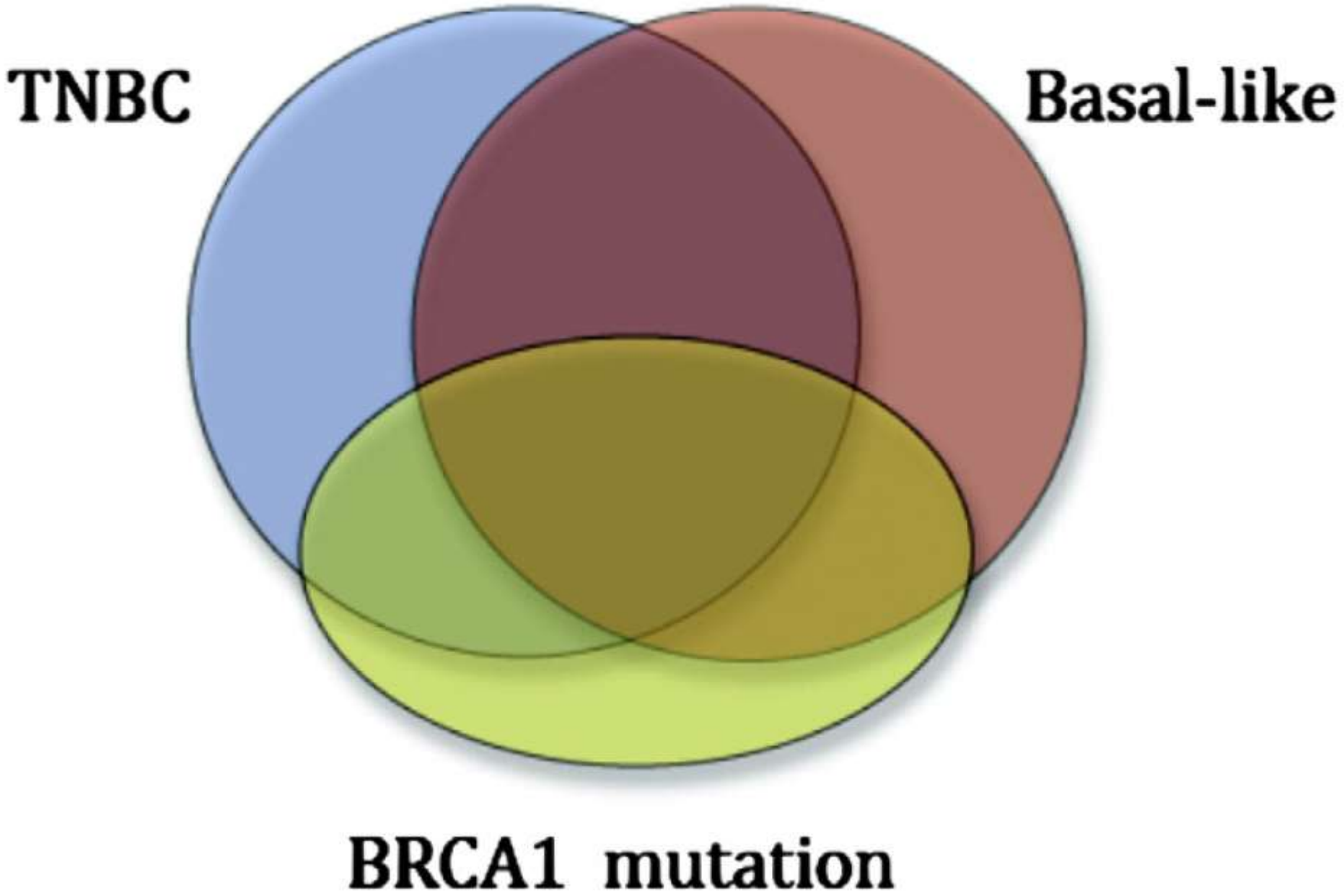
Tabla 3
Comparación de la expresión de diferentes marcadores de acuerdo al tipo molecular

Clase molecular	*RE (%)*	*RP (%)*	*HER2/neu (%)*	*p63 (%)*	*CK5/6 (%)*
Luminal A	40/40 (100)	40/40 (100)	0/40 (0)	0/40 (0)	1/40 (2,5)
Luminal B	27/40 (67,5)	24/40 (60)	8/40 (20)	0/40 (0)	3/40 (7,5)
HER2+	0/38 (0)	0/38 (0)	38/38 (100)	5/38 (13,2)	8/38 (21,1)
Basal	0/82 (0)	0/82 (0)	0/82 (0)	19/82 (23,2)	49/82 (59,8)



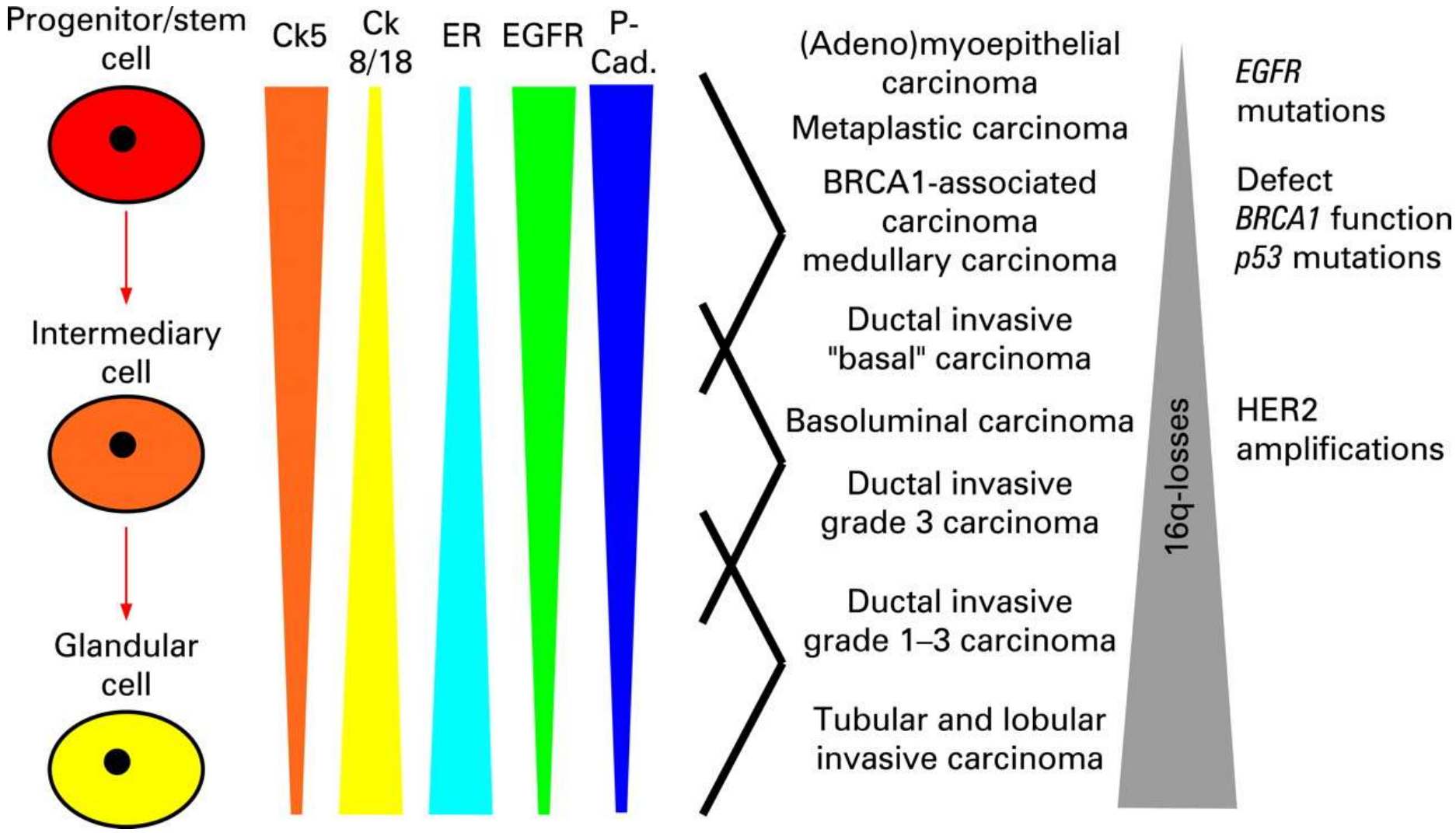


Schneider B P et al. Clin Cancer Res 2008;14:8010-8018



Oakman C et al. The Breast 2010

Associations of immunohistochemical expression patterns in physiological cellular subgroups within the normal breast and distinct subgroups of invasive breast cancer.



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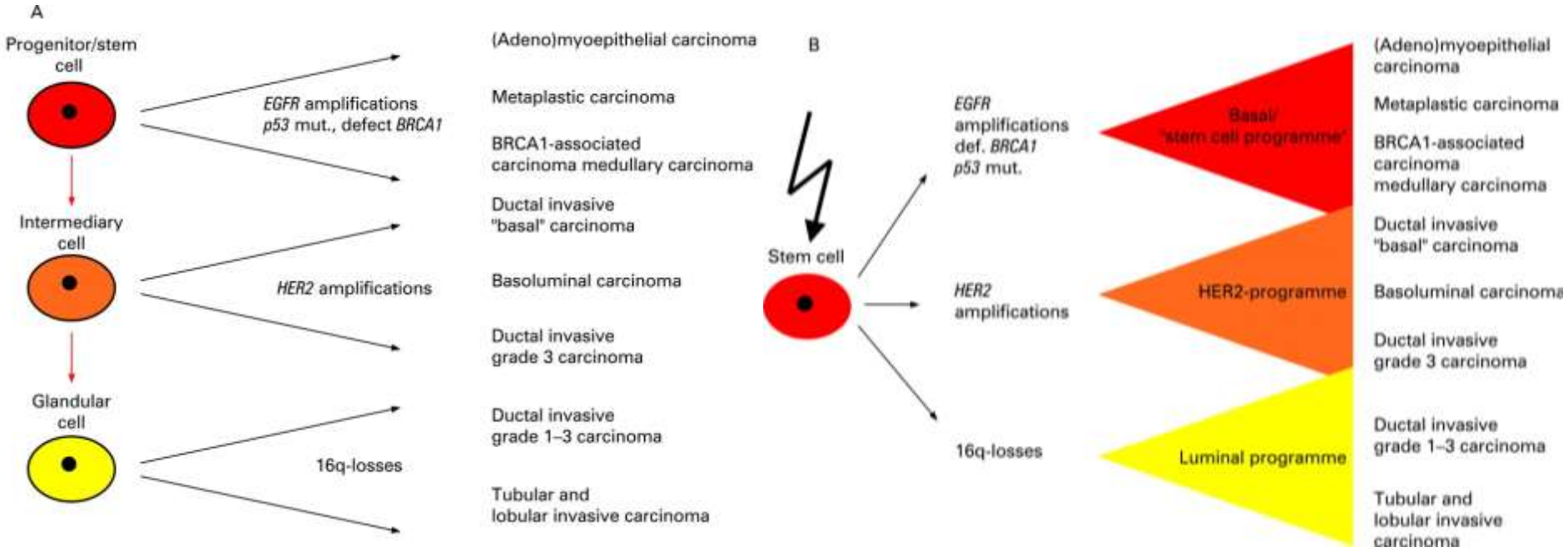
Korsching E et al. J Clin Pathol 2008;61:553-560

Different putative histogenetic models of the relationship between different subgroups of invasive breast cancer and progenitor cells/stem cells.

"Linear cell of origin theory"

"Stem cell hypothesis"



Korsching E et al. J Clin Pathol 2008;61:553-560

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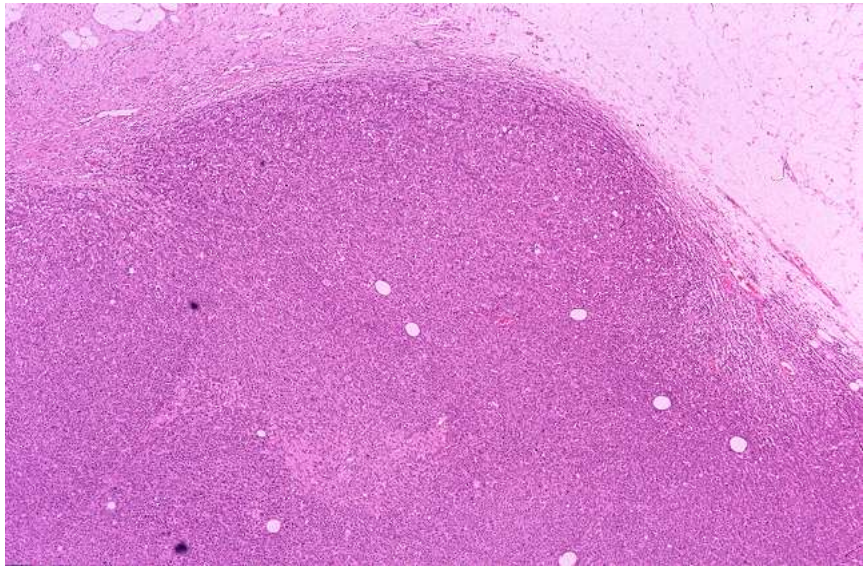
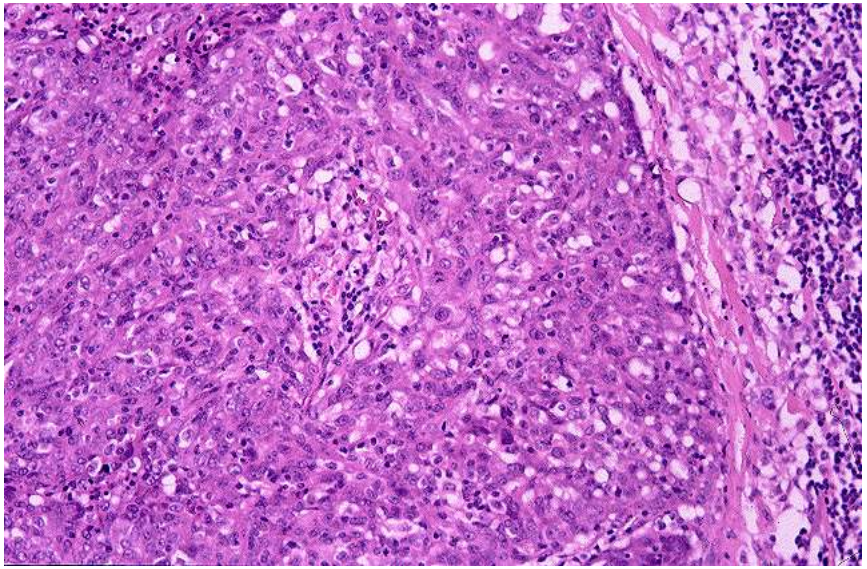
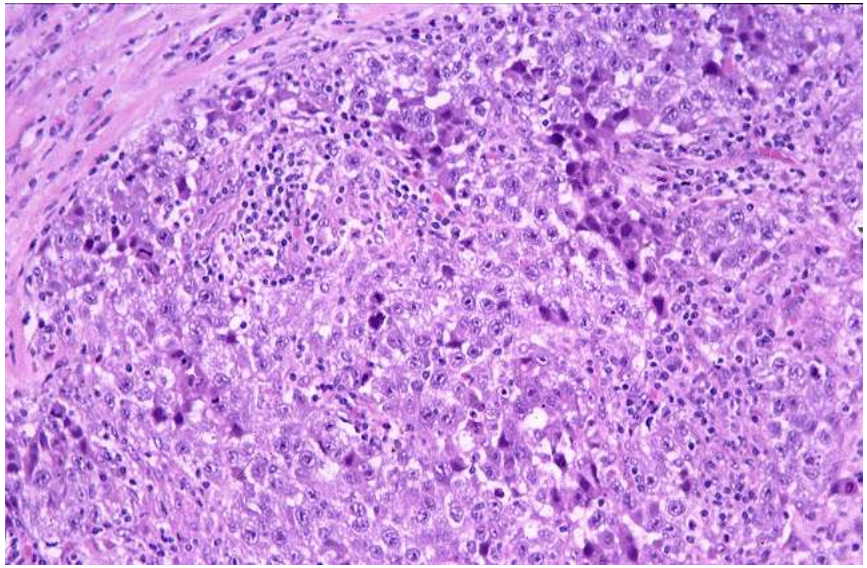
CÁNCER DE MAMA CON FENOTIPO BASAL

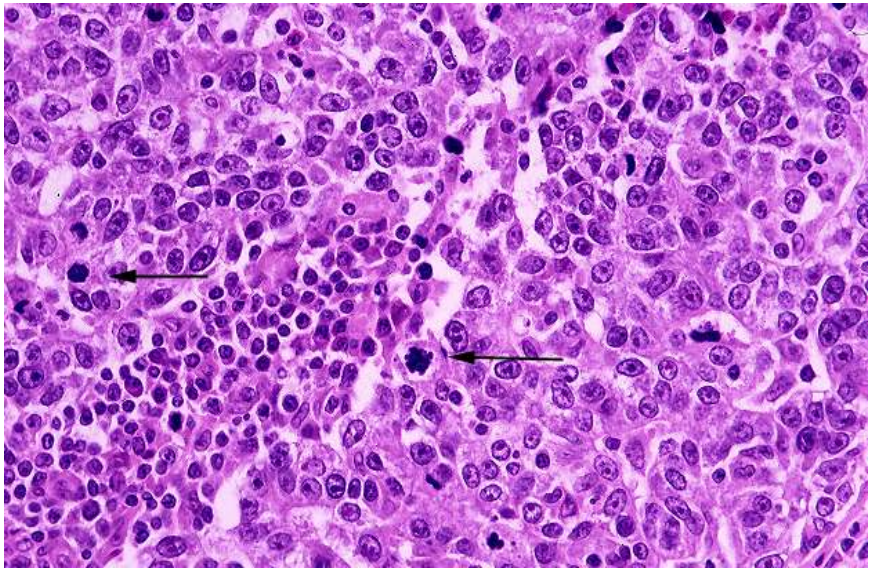
- **Definición, espectro morfológico.**
- **Marcadores, origen.**
- **Relación con *BRCA1*.**
- **Significado clínico.**

Carcinoma medular





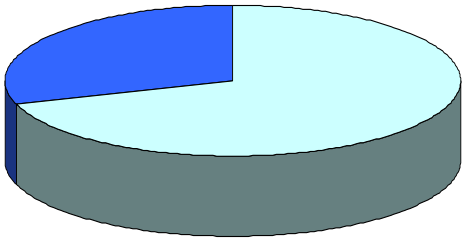




Cortesía Dr. J. Palacios, HU Virgen del Rocío, Sevilla

HEREDITARY BREAST CANCER

BRCA1/2: **30%**



BRCA (-): **70%**

PENETRANCE

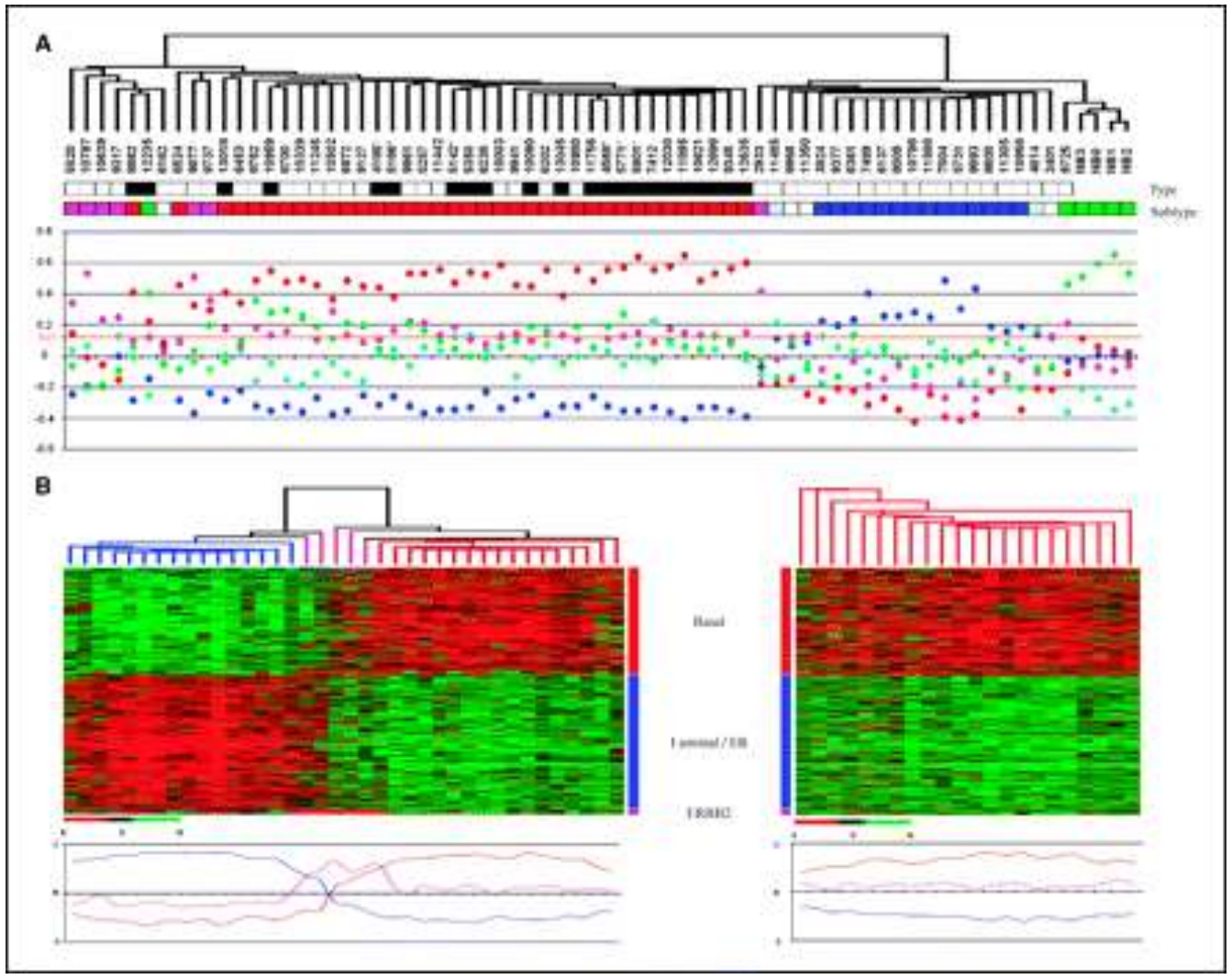
	Breast cancer	Ovarian cancer	Male BC
BRCA1	**65%**	**40%**	**-**
BRCA2	**45%**	**11%**	**8%**

BCLC Meeting. Madrid, June 2003

Research Article

Gene Expression Profiling Shows Medullary Breast Cancer Is a Subgroup of Basal Breast Cancers

François Bertucci,[1,2,5] Pascal Finetti,[1] Nathalie Cervera,[1] Emmanuelle Charafe-Jauffret,[1,3,5] Emilie Mamessier,[1] José Adélaïde,[1] Stéphane Debono,[6] Gilles Houvenaeghel,[4,5] Dominique Maraninchi,[2,5] Patrice Viens,[2,5] Colette Charpin,[5,7]



- Luminal A
- Luminal B
- Normal
- Basal
- HER2

Cancer Res, May 2006

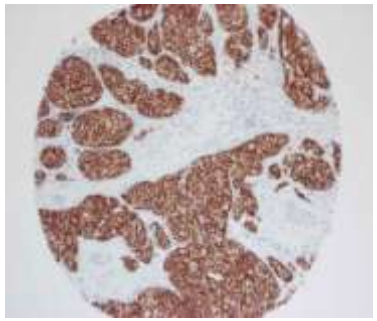
Differences between invasive breast carcinomas with medullary features (IBCMF) and grade 3 invasive ductal carcinoma of no special type (IDCG3).

	IBCMF	IDCG3	*P*
ER			
Positive	**2/35 (5.7%)**	**24/39 (61.5%)**	
Negative	**33/35 (94.3%)**	**15/39 (38.5%)**	**<0.001**
HER2			
Positive	**0/35 (0.0%)**	**9/38 (23.7%)**	
Negative	**35/35 (100.0%)**	**29/38 (76.3%)**	**0.002**
Ck5/6			
Positive	**21/35 (60.0%)**	**7/39 (17.9%)**	
Negative	**14/35 (40.0%)**	**32/39 (82.1%)**	**<0.001**
EGFR			
Positive	**9/35 (25.7%)**	**9/37 (24.3%)**	
Negative	**26/35 (74.3%)**	**28/37 (75.7%)**	**0.553**
Ck19			
Positive	**13/35 (37.1%)**	**26/38 (68.4%)**	
Negative	**22/35 (62.9%)**	**12/38 (31.6%)**	**0.007**
P-Cadherin			
Positive	**14/35 (40.0%)**	**3/38 (7.9%)**	
Negative	**21/35 (60.0%)**	**35/38 (92.1%)**	**0.001**
Basal-like phenotype			
Positive	**22/35 (62.9%)**	**7/37 (18.9%)**	
Negative	**13/35 (37.1%)**	**30/37 (81.1%)**	**<0.001**

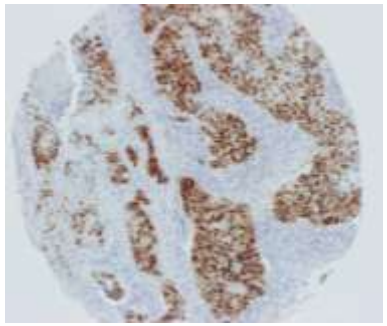
Rodríguez-Pinilla el al., Am J Surg Pathol 2006

BRCA1 AND BRCA2 BREAST CARCINOMAS

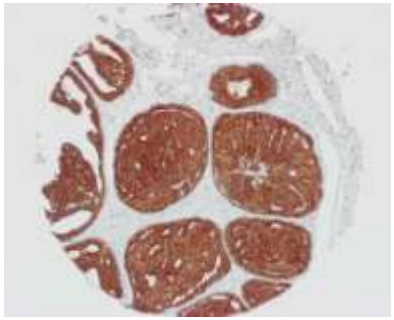
	GRADE	ER	PR	BCL2	Ki67	p53	HER2
BRCA1	**3**	**-**	**-**	**-**	**++**	**++**	**-**
BRCA2	**2/3**	**+**	**+**	**+**	**+**	**-**	**-**



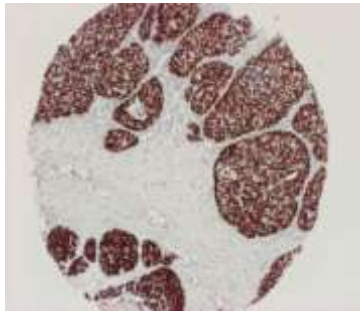
ER



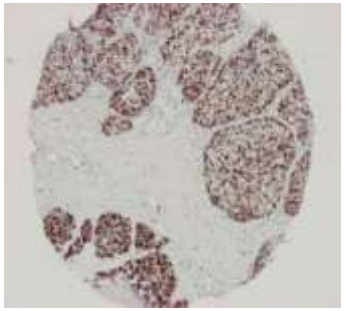
PR



BCL2



Ki67

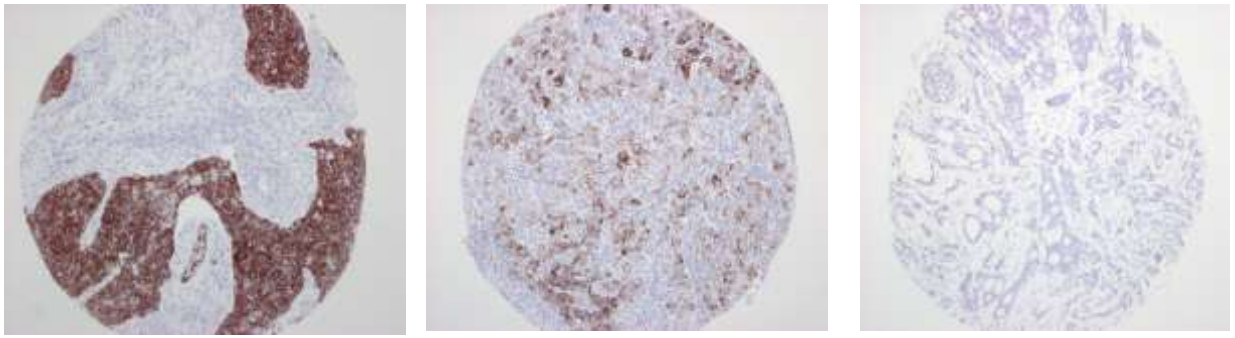


p53

(Palacios et al, Clin Cancer Res 2003).

BASAL CELL MARKERS

	BRCA1	*BRCA2*	*Sporadic*
Cytokeratin 5/6	46%	9%	8.5%
Vimentin	80%	15%	23%
Fascin	84%	17%	25%
Laminin	75%	7%	39%
Caveolin 1	22%	0	4.2%



Cytokeratin 5/6

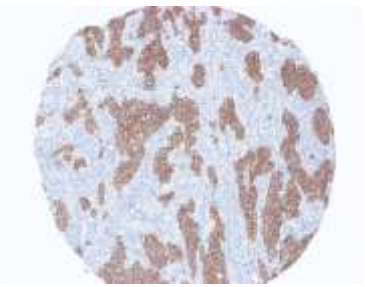
Palacios et al, J Nat Cancer Inst 2004

Rodríguez-Pinilla et al, Clin Cancer Res 206; Breat Cancer Res and Treat 2006; J Clin Pathol 2007

BASAL-LIKE PHENOTYPE IN FAMILIAL CANCER

The molecular pathology of hereditary breast cancer: genetic testing and therapeutic implications

Emiliano Honrado[1], Javier Benítez[1] and José Palacios[2]



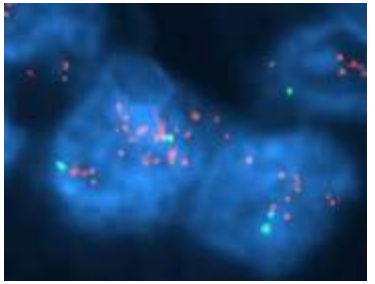


Table 2 Immunohistochemical characterization of familial and sporadic breast tumors

	BRCA1 (%)	*BRCA2 (%)*	*Non-BRCA1/2 (%)*	*Sporadic tumors (%)*	*References*
Estrogen receptor+	21	65	72	66	30,34,36–39 25,35,67
Progesterone receptor +	20	49	60	56	25,30,34–36,38,67
Ki-67+	56	21	7	22	34,38,67
p53+	45	27	12	27	25,30,34–36,38,67
HER2+	7	6	3	18	25,34–36,67
Cyclin D1+	30	56	—	79	67,38,69
Cyclin E+	47	35	—	27	69
p27+	40	85	—	60	69
Ck5/6+	65	7	—	8	91,92

Palacios et al, Clin Cancer Res 2003, J Nat Cancer Inst 2004, Breast Cancer Res Treat 2005
Honrado et al, Mod Pathol 2005
Rodríguez Pinilla et al, Breast Cancer Res Treat 2006

Prediction of *BRCA1* Status in Patients with Breast Cancer Using Estrogen Receptor and Basal Phenotype

Sunil R. Lakhani,[1,2] Jorge S. Reis-Filho,[1] Laura Fulford,[1] Frederique Penault-Llorca,[4] Marc van der Vijver,[5] Suzanne Parry,[1] Timothy Bishop,[6] Javier Benitez,[7] Carmen Rivas,[8] Yves-Jean Bignon,[4] Jenny Chang-Claude,[9] Ute Hamann,[9] Cees J. Cornelisse,[10] Peter Devilee,[10] Matthias W. Beckmann,[11] Carolin Nestle-Krämling,[11] Peter A. Daly,[12] Neva Haites,[13] Jenny Varley,[14] Fiona Lalloo,[15] Gareth Evans,[15] Christine Maugard,[16] Hanne Meijers-Heijboer,[17] Jan G.M. Klijn,[17] Edith Olah,[18] Barry A. Gusterson,[19] Silvana Pilotti,[21] Paolo Radice,[20] Siegfried Scherneck,[22] Hagay Sobol,[23] Jocelyne Jacquemier,[23] Teresa Wagner,[24] Julian Peto,[25,26] Michael R. Stratton,[25] Lesley McGuffog,[3] Douglas F. Easton,[3] and the Breast Cancer Linkage Consortium

Conclusion: The use of cytokeratin staining in combination with ER and morphology provides a more accurate predictor of *BRCA1* mutation status than previously available, that may be useful in selecting patients for *BRCA1* mutation testing. The high percentage of *BRCA1* cases positive for EGFR suggests that specific anti-tyrosine kinase therapy may be of potential benefit in these patients.

Research article

Open Access

Basal cytokeratins in breast tumours among *BRCA1*, *BRCA2* and mutation-negative breast cancer families

Hannaleena Eerola[1,2], Mira Heinonen[3,4], Päivi Heikkilä[5], Outi Kilpivaara[2], Anitta Tamminen[2], Kristiina Aittomäki[6], Carl Blomqvist[1], Ari Ristimäki[3,4] and Heli Nevanlinna[2]

Conclusion Although our study confirms that basal CKs can help to identify *BRCA1* mutation carriers, this effect was weaker than previously suggested and CKs did not independently predict *BRCA1* mutation either from sporadic or familial breast cancer cases. The most effective, independent predictors of *BRCA1* mutations were age at onset, HER2 status, and either ER or PR status, as compared with sporadic or non-*BRCA1*/*BRCA2* cancers.

CÁNCER DE MAMA CON FENOTIPO BASAL

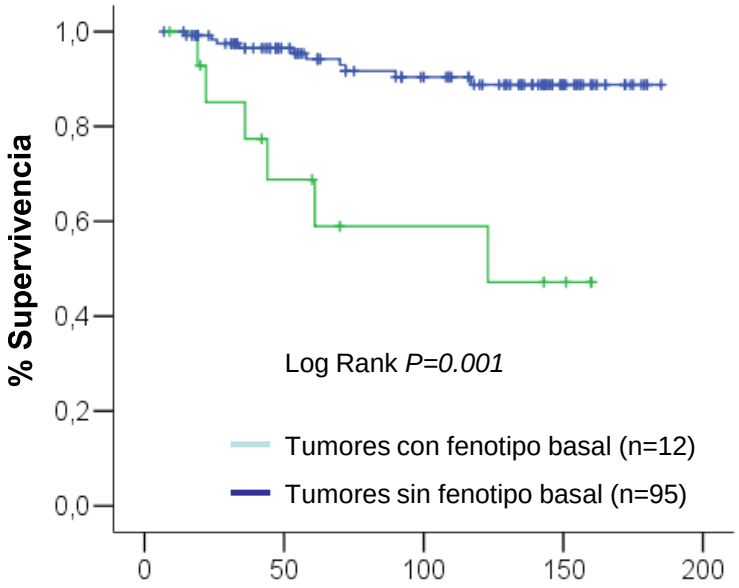
- **Definición, espectro morfológico.**
- **Marcadores, origen.**
- **Relación con *BRCA1*.**
- **Significado clínico.**

Prognostic Significance of Basal-Like Phenotype and Fascin Expression in Node-Negative Invasive Breast Carcinomas

Socorro María Rodríguez-Pinilla,[1] David Sarrió,[1] Emiliano Honrado,[2] David Hardisson,[3] Francisco Calero,[4] Javier Benitez,[2] and José Palacios[1]

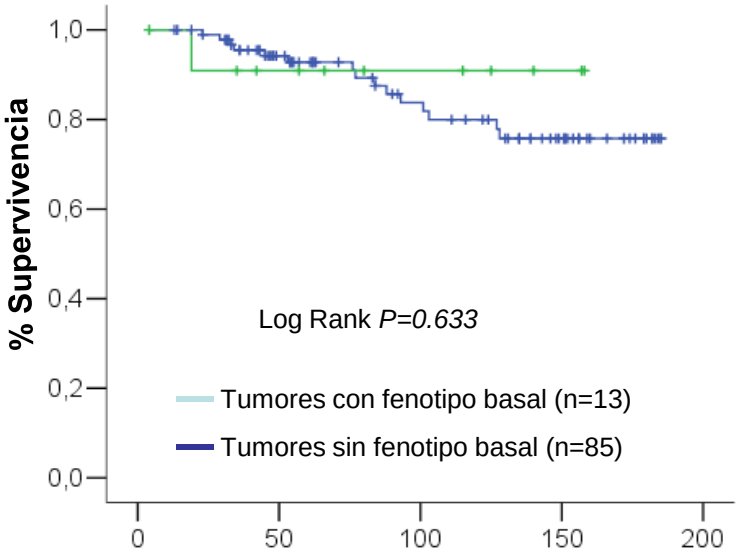
Clin Cancer Res 2006;12(5) March 1, 2006

TLE en pacientes no tratadas con CMF



Tiempo de supervivencia (meses)

TLE en pacientes tratadas con CMF



Tiempo de supervivencia (meses)

Breast Cancer Molecular Subtypes Respond Differently to Preoperative Chemotherapy

Roman Rouzier,[1,4] Charles M. Perou,[5] W. Fraser Symmans,[2] Nuhad Ibrahim,[1] Massimo Cristofanilli,[1] Keith Anderson,[3] Kenneth R. Hess,[3] James Stec,[6,7] Mark Ayers,[6] Peter Wagner,[1] Paolo Morandi,[1] Chang Fan,[5] Islam Rabiul,[1] Jeffrey S. Ross,[6] Gabriel N. Hortobagyi,[1] and Lajos Pusztai[1]

Table 2. Correlation between molecular classification and pathologic complete response

	Pathologic complete response		
	No	Yes	
Molecular classification	*n* [% (95% CI)]	*n* [% (95% CI)]	
Luminal A/B subtype	28 [93% (78-99)]	2 [7% (1-22)]	
Normal breast like	10 [100% (29-100)]	0 [0% (0-31)]	
erbB2+	11 [55% (32-77)]	9 [45% (23-68)]	
Basal subtype	12 [55% (32-76)]	10 [45% (24-68)]	$P < 0.001$

Clin Cancer Res 2005;11:5678-85.

Neoadjuvant chemotherapy: pCR rates for TNBC with comparison to non-TNBC.

	Year	Detection method	Regimen	No. of TNBC pts	TNBC pCR (%)	Non-TNBC pCR (%)
Anthracycline						
Le Tourneau et al.[21]	2007	IHC	Overall	96	29	13
			- Intensified FAC	-56	- 47	
			- FEC	-40	- 13	
Bidard et al.[22]	2008	IHC	FAC or FEC	120	17	4
Anthracycline/taxane						
Rouzier et al.[23]	2005	Molecular	T-FAC	22	45	18
Fernandez-Morales et al.[24]	2006	IHC	Anthracycline + taxane	23	39	12
Carey et al.[20]	2007	IHC	AC +/− taxane	34	27	11
Keam et al.[25]	2007	IHC	Docetaxel + Doxorubicin	47	17	3
Liedtke et al.[3]	2008	IHC	Overall	255	22	11
			- FAC/FEC/AC	-70	- 20	
			- T-FAC/T-FEC	-125	- 28	
			- Single agent taxane	-17	- 12	
			- Other	-43	- 14	
Esserman et al.[26]	2009	Molecular	AC → Paclitaxel	45	34	21
Wang et al.[27]	2009	IHC	Anthracycline + taxane	21	38	12
Straver et al.[28]	2009	Molecular	AC, or AT, or T/Capecitabine	38	34	12
Platinum						
Garber et al.[29]	2006	IHC	Cisplatin	22	23	n/ap
Sikov et al.[30]	2007	IHC	Carboplatin + paclitaxel	12	67	39
Torrisi et al.[a,31]	2008	IHC	E/Cis/F → Paclitaxel	30	40	n/ap
Sirohi et al.[32]	2008	IHC	E/Cis/F	28	88[b]	51[b]
Leone et al.[33]	2009	IHC	Platinum + docetaxel +/− AC	125	34	n/av
Byrski et al.[a,c34]	2009	IHC	Cisplatin	10	90	n/ap
Other						
Roche et al.[35]	2006	IHC	Ixabepilone	42	19	8%

[a] Prospective study.
[b] Clinical complete response, not pathological complete response.
[c] Of 10 patients, all had BRCA1 mutation and 9 of 9 with known IHC status had TNBC. AC: doxorubicin/cyclophosphamide; AT: doxorubicin/docetaxel; E/Cis/F: epirubicin/cisplatin/5-fluorouracil; FAC: 5-fluorouracil/doxorubicin/cyclophosphamide; FEC: 5-fluorouracil/epirubicin/cyclophosphamide; IHC: immunohistochemistry; n/ap not applicable; n/av not available; pCR: pathological complete response; T: paclitaxel; TNBC: triple negative breast cancer.

Oakman C et al. The Breast 2010

FENOTIPO BASAL (RE/HER2-negativo, CK5- y/o EGFR-positivo)

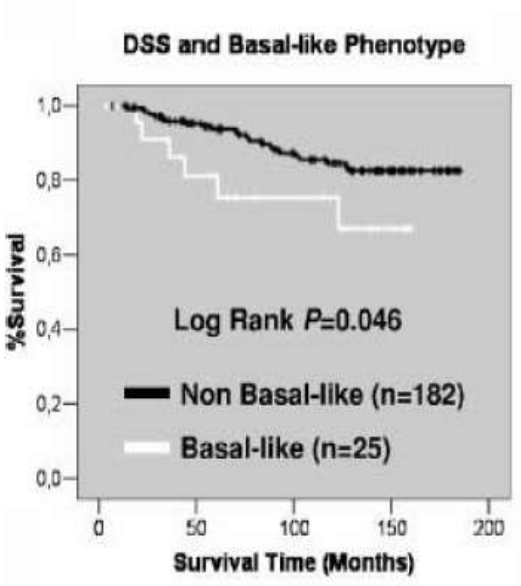


Table 3. Relationship between the basal-like phenotype and fascin expression and recurrence localization

	Recurrence				*P*
	Nonrecurrence	Local	Visceral	Bone	
Basal-like phenotype					
Negative	150 of 182 (82.4%)	10 of 182 (5.5%)	7 of 182 (3.8%)	15 of 182 (8.2%)	0.001
Positive	16 of 23 (69.6%)	4 of 23 (17.4%)	3 of 23 (13.0%)	0 of 23 (0.0%)	

Rodríguez-Pinilla el al., Clin Cancer Res 2006

Table 3 Therapeutic Strategies, Confirmed and in Development, for Triple-Negative Breast Cancer

Therapeutic Strategy or Target	Status of Development
Anthracycline-/taxane-based chemotherapy	Proven efficacy, phase II/III clinical trials[30-32,51]
Platinum agents	Active agents, phase II clinical trials[36-38]
EGFR inhibition	Modest activity, phase II clinical trials[36,38]
Antiangiogenesis	Efficacy in subset analysis, phase III trials[45,46]
PARP1 inhibition	Safety illustrated, efficacy results anticipated, phase I/II trials[39,47,48]
Src inhibition	Modest activity, phase II trials[49]
HDAC inhibition	Activity in preclinical studies, early clinical development[44,50]
MEK inhibition	Activity in preclinical studies[42]

Abbreviations: EGFR = epidermal growth factor receptor; HDAC = histone deacetylase; PARP1 = poly(adenosine diphosphate-ribose) polymerase–1

Anders CK & Carey LA. Clin Breast Cancer 2009

Ensayos clínicos en TNC

Summary of clinical trials with novel therapeutic agents clinically relevant in TNBC treatment.

Trial	Phase	Study compound	Regimen	*N*	Efficacy					
					pCR (*n*)	RR (*n*)	SD (*n*)	CB (*n*)	PFS (mo)	HR (95% CI)
Gronwald[63] (BRCA1)	II	CDDP	Neoadjuvant CDDPBSI 75 mg/m^2 q3w × four cycles	25	72% (18)	NA	NA	NA	NA	NA
Garber[64] (TNBC patients)	II	CDDP	Neoadjuvant CDDP 75 mg/m^2 q3w × four cycles	28	22% (6)	NA	NA	NA	NA	NA
Ryan[65] (TNBC patients)	II	CDDP, bevacizumab	Neoadjuvant CDDP 75 mg/m^2 q3w × 4 + bevacizumab 15 mg/kg q3w × 3	51	16% (8)	NA	NA	NA	NA	NA
O'Shaugnessy[68]	II	Cetuximab	ICb ± cetuximab	103	NA	49% vs 30%	NA	NA	NA	NA
TBCRC 001[69]	II	Cetuximab; Cb	Cetuximab ± Cb	102	NA	18% vs 6%	9% vs 4%	27% vs 10%[e]		
E2100[73]	III	Bevacizumab	Paclitaxel ± bevacizumab	722 (233)[b]	NA	36.9% vs 21.2% $p < 0.001$	NA	NA	11.8 vs 5.9 $p < 0.001$ 8.8 vs 4,6[b]	0.6 (0.51–0.7) 0.53 (0.4–0.7)[b]
AVADO[74]	III	Bevacizumab	Docetaxel ± bevacizumab	736	NA	63.1% vs 44.4%[c] $p = 0.0001$			8 vs 8.7 vs 8.8[d]	0.69 (0.54–0.89)[f] 0.61 (0.48–0.78)[e]
Fong[77]	I	Olaparib (AZD 2281)	Olaparib	60 (19 BRCA)	NA	47% (9)[g]	10% (2)[g]	63% (12)[g,h]		
O'Shaugnessy[78]	II	BSI-201	Cb-Gem ± BSI-201	120	NA	48% vs 16% $p = 0.002$		62% vs 21% $p = 0.0002$[a]	6.9 vs 3.3 $p < 0.0001$	0.34 (0.2–0.58)

CDDP, cisplatin; ICb, irinotecan + carboplatin; Cb, carboplatin; Gem, gemcitabine.
pCR, pathologic complete response rate; RR, response rate (complete response + partial response); SD, stable disease; CB, clinical benefit; NA, not applicable; PFS (mo), progression-free survival (months); HR, hazard ratio.
BRCA1, BRCA1 germline mutation carriers.

Bosch A et al. Cancer Treat Rev 2010

CÁNCER DE MAMA CON FENOTIPO BASAL

- **Grupo morfológicamente heterogéneo.**
- **RE/HER2-negativos CK5 y/o EGFR-positivos.**
- **15% Carc. esporádicos, > 70% Carc. *BRCA1*+.**
- **Biología agresiva, mejor respuesta a quimioterapia.**
- **Tendencia a metástasis viscerales (óseas infrecuentes).**

Hospital Universitario La Paz

SaludMadrid

Comunidad de Madrid

David Hardisson

dhardisson.hulp@salud.madrid.org

david.hardisson@uam.es

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