Classificazione anatomo-patologica WHO 2019

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The WHO Classification of Tumours

- It is an essential tool for **standardizing diagnostic practice** worldwide
- It is particularly important that **cancers** continue to be classified and **diagnosed according to the same standards internationally** so that patients can benefit from multicentre clinical trials, as well as from the results of local trials conducted on different continents
- It serves as a vehicle for **the translation of cancer research into practice**. The **diagnostic criteria** and standards that make up the classification are underpinned by **evidence evaluated and debated by experts in the field**

WHO Classification of tumours 5th edition: Breast tumours
2nd Editorial Board meeting: 9-11 December 2018

WHO classification of tumors of the breast 2019

- Organized in sequence from benign epithelial proliferations and precursors, through benign neoplasms, to in situ and invasive breast cancer, followed by mesenchymal and haematolymphoid neoplasms, tumours of the male breast, and genetic tumour syndromes

- General chapter of invasive carcinoma
  - Core biopsy notes
  - Stromal features
  - Characteristic after neoadjuvant treatement
  - Section of molecular pathology

- Non special type and Special histologic types:
  - ➢ Medullary carcinomas
  - ➢ NE tumors
  - ➢ New histologic types

Diagnosis on core biopsy

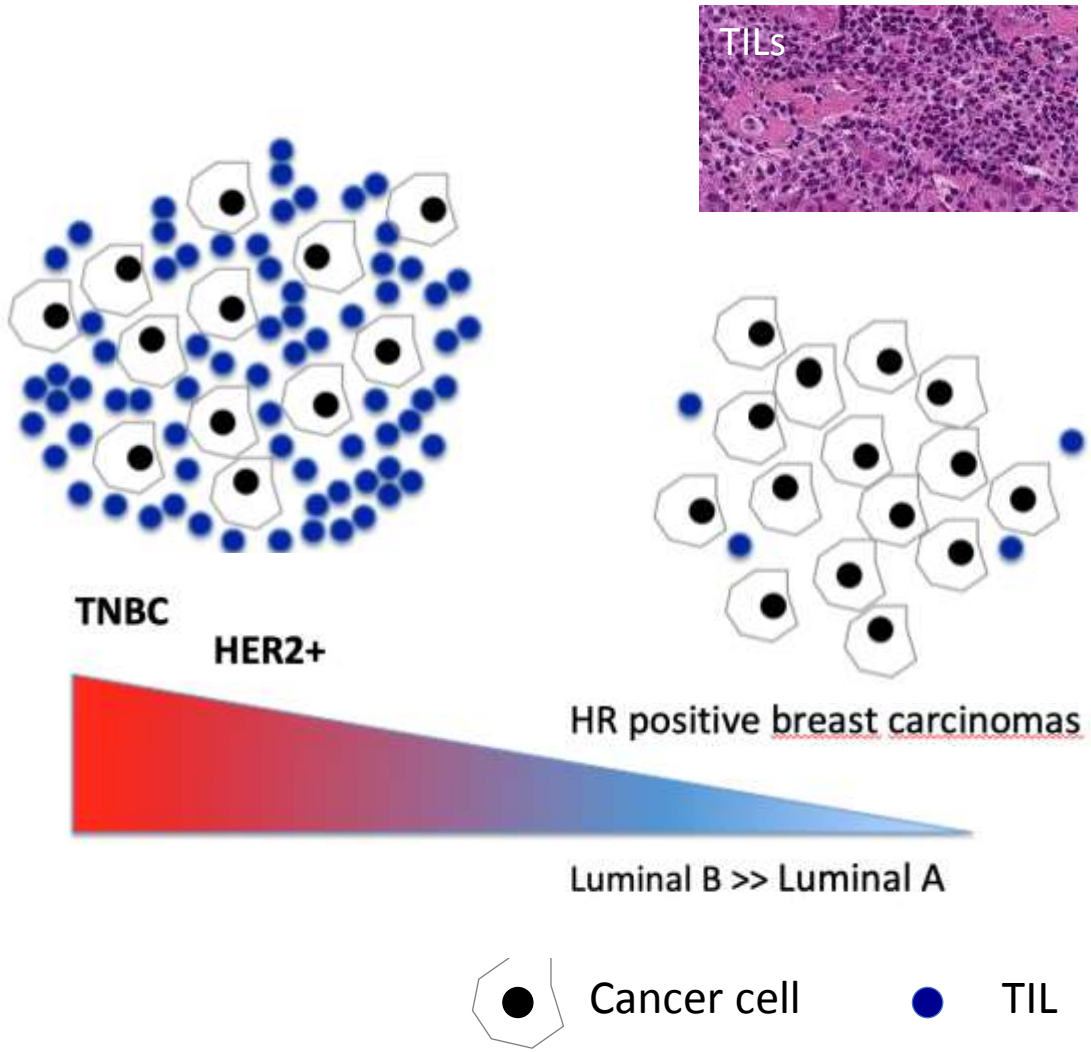
- If there is not 100% certainty in the diagnosis of invasion on CNB, an equivocal classification of a lesion as “suspicious”, “indeterminate”, “cannot rule out invasion”, or “uncertain malignant potential” may be most appropriate, with deferral to a surgical specimen for definitive classification.

- When the diagnosis of invasion is made on CNB, **a preliminary histological grade** should be reported, and **ER/PR and HER2 testing can be performed** if there is sufficient invasive cancer for testing

Invasive breast carcinoma - Stromal response patterns

- The immune infiltrate in tumours is referred to as TILs

- The extent of TILs in IBC is gaining importance as a prognostic marker, with high numbers of TILs associated with a better outcome and better response to neoadjuvant therapy in triple-negative and HER2-positive breast carcinomas



Stromal response patterns

- For quantifying TILs, it is recommended to follow the internal consensus scoring recommendations => International Immuno-Oncology Biomarker Working Group on Breast Cancer. Available from: https://www.tilsinbreastcancer.org/.

- It is recommended that quantification is done on H&E-stained tissue sections at a magnification of 20–40× with a 10× ocular in core biopsies or surgical specimens, on the most representative tumour block

NST – The inclusion of so called “Medullary” carcinomas

2012

- Carcinomas with medullary features
- medullary carcinoma
- atypical medullary carcinoma
- invasive carcinoma of no special type (NST) with medullary features

2019

- Invasive carcinoma NST with medullary pattern (or basal-like features)

Considered as part of a spectrum of tumour-infiltrating lymphocyte–rich breast cancers

Special types - Neuroendocrine tumors/carcinomas acc. to WHO 2019

NEUROENDOCRINE NEOPLASMS

- Neuroendocrine tumor
- Neuroendocrine carcinoma

Classifications of Neuroendocrine neoplasms in the breast

Papotti et al 1989	Maluf et al 1995	Sapino et al 2000 >50% of NE cells
Type A (cohesive)	Low grade “insular”	Solid cohesive
Type E (atypical carcinoid)		
Type F (ILC confluent)	Alveolar lobular	Alveolar
Type G (small cell)	Small cell undifferentiated	Merkel cell like/small cell
Type D (trabecular)		
Type C (mixed A+B)	Solid Papillary§	Solid Papillary§
Type B (mucoid)#	Cellular mucinous#	Cellular Mucinous#

§Tsang and Chang 1996 #Capella et al 1980

WHO Classifications of Neuroendocrine neoplasms in the breast

WHO 2003
A group of neoplasms showing morphological features similar to those of neuroendocrine tumours of the gastrointestinal tract and lung, **with expression of neuroendocrine markers in >50% of the tumour cell population.**
HISTOTYPES
Solid neuroendocrine carcinoma
Small-cell/oat cell carcinoma
Large-cell neuroendocrine carcinoma
Metastatic carcinoid

1232 consecutive cases of invasive BC.

We divided NEBC into **focal (10–49% positive cells**) and **diffuse (≥50% positive cells**) and compared the outcome of patients with NEBC with strictly matched non-NEBC.

No differences of prognosis between focal and diffuse NE differentiantion

Bogina G et al Histopathology 2016, 68, 422–432.

WHO Classifications of Neuroendocrine neoplasms in the breast

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HISTOTYPES	
Solid neuroendocrine carcinoma	Neuroendocrine tumour, well differentiated (carcinoid-like)
Small-cell/oat cell carcinoma	Neuroendocrine carcinoma, poorly differentiated/ small-cell carcinoma
Large-cell neuroendocrine carcinoma	Invasive carcinoma with neuroendocrine differentiation
Metastatic carcinoid	

A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal

Guido Rindi et al. Modern Pathology (2018) 31:1770–1786. https://doi.org/10.1038/s41379-018-0110-y

The classification of **neuroendocrine neoplasms** (NENs) **differs between organ systems** and currently **causes considerable confusion.**

A uniform classification framework for NENs at any anatomical location may reduce inconsistencies and contradictions among the various systems currently in use.

The classification suggested here is intended to allow pathologists and clinicians to manage their patients with NENs consistently, while acknowledging organ-specific differences in classification criteria, tumor biology, and prognostic factors.

Guido Rindi et al. Modern Pathology (2018) 31:1770–1786.

A framework for NEN classification is proposed in which the term

- Neuroendocrine Carcinoma (NEC) is clearly indicative of high-grade malignant histology and biologic behavior.
- Neuroendocrine tumor (NET), in contrast, is intended to designate a family of well differentiated neoplasms whose potential to metastasize or invade the adjacent tissues depends on tumor site and type, and grade [1 , 2].

WHO Classifications of Neuroendocrine neoplasms in the breast

WHO 2003	WHO 2012	WHO 2019
A group of neoplasms showing morphological features similar to those of neuroendocrine tumours of the gastrointestinal tract and lung, **with expression of neuroendocrine markers in >50% of the tumour cell population.**	Breast carcinomas with neuroendocrine features showed morphological features similar to neuroendocrine tumours of the gastrointestinal tract and lung.	A uniform classification framework for NENs at all anatomical locations was proposed in order to reduce inconsistencies and contradictions among the various systems currently in use.
HISTOTYPES		
Solid neuroendocrine carcinoma	Neuroendocrine tumour, well differentiated (carcinoid-like)	
Small-cell/oat cell carcinoma	Neuroendocrine carcinoma, poorly differentiated/ small-cell carcinoma	
Large-cell neuroendocrine carcinoma	Invasive carcinoma with neuroendocrine differentiation	
Metastatic carcinoid		

2019 WHO Classification of Neuroendocrine neoplasms in the breast

WHO 2003	WHO 2012	WHO 2019
A group of neoplasms showing morphological features similar to those of neuroendocrine tumours of the gastrointestinal tract and lung, **with expression of neuroendocrine markers in >50% of the tumour cell population.**	Breast carcinomas with neuroendocrine features showed morphological features similar to neuroendocrine tumours of the gastrointestinal tract and lung.	"**neuroendocrine neoplasm (NEN)**" as a term encompassing all tumour classes with predominant neuroendocrine differentiation, including both well-differentiated and poorly differentiated forms.
	HISTOTYPES	
Solid neuroendocrine carcinoma	Neuroendocrine tumour, well differentiated (carcinoid-like)	Neuroendocrine Tumour
Small-cell/oat cell carcinoma	Neuroendocrine carcinoma, poorly differentiated/ small-cell carcinoma	Neuroendocrine Carcinoma
Large-cell neuroendocrine carcinoma	Invasive carcinoma with neuroendocrine differentiation	
Metastatic carcinoid		

Neuroendocrine tumor

- Rare entity
- The distinction between well-differentiated NETs and grade 1 or 2 breast carcinomas of other histological types expressing neuroendocrine markers should be based on the presence and extent of histological features characteristic of neuroendocrine differentiation in the tumour
- => exclude metastasis

METASTASES *vs* PRIMARY NEUROENDOCRINE TUMOUR

Mohanty SK et al. Modern Pathology (2016) 29, 788–798

Primary tumour site

Lung
GI
Ovary
Cervix
Endometrium

Feature	metastases	primary
In situ NE	absent	present
ER	Rarely positive (lung-GI) weak and <50%	positive
Gata3	negative	positive
Mammaglobin	negative	positive
GCDFP-15	negative	(Positive)
CDX2; CK20	GI	negative
TTF-1	If +pulmonary origin	+/-
PAX8/PAX6	gastropancreatic and duodenal origin,	negative

Definition of NET – WHO 2019

Neuroendocrine tumour (NET) is an invasive tumour characterized by:

1. low/intermediate-grade
2. neuroendocrine morphology,
3. supported by the presence of neurosecretory granules and a diffuse, uniform immunoreactivity for neuroendocrine markers.

MARKERS OF NEUROENDOCRINE TUMOUR

Tan PH et al. Histopathology 2015, 66, 761–770

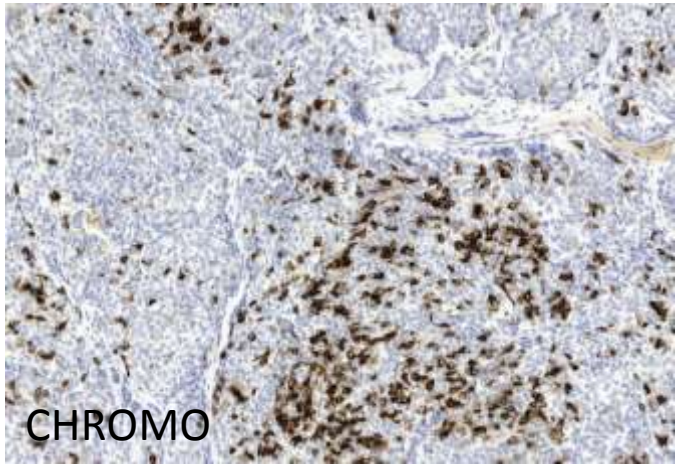
Markers of neuroendocrine differentiation

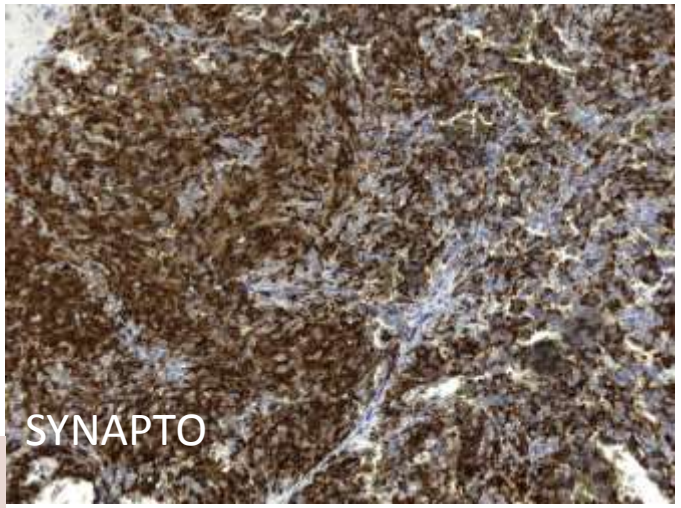
- CHROMOGRANIN A
- SYNAPTOPHYSIN

Markers highly sensitive low specific

- CD56

it can be used for screening only and not for confirmation. The interpretation of staining may be challenging.





Generally they are diffusely positive NE markers

Definition of NET – WHO 2019

Neuroendocrine tumour (NET) is an invasive tumour characterized by:

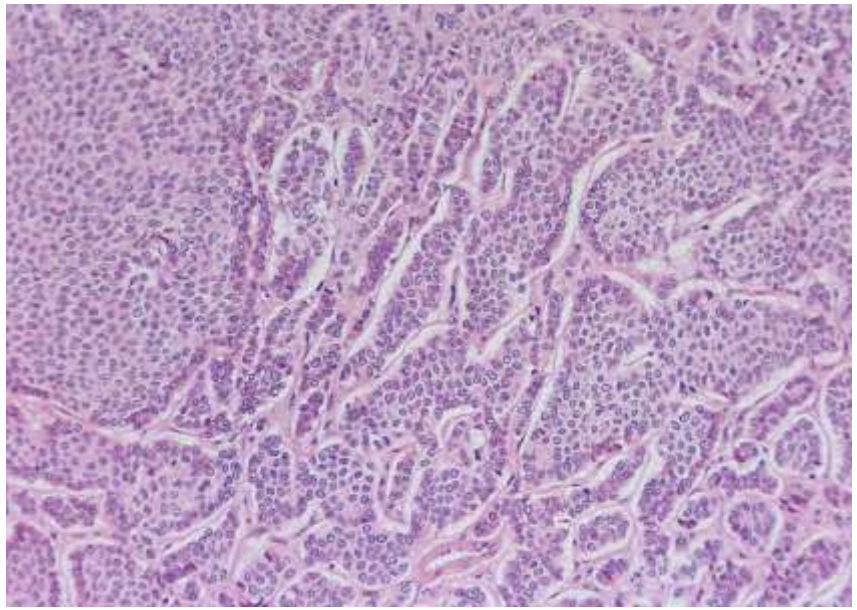
1. low/intermediate-grade
2. neuroendocrine morphology,
3. supported by the presence of neurosecretory granules and a diffuse, uniform immunoreactivity for neuroendocrine markers.

Essential and desirable diagnostic criteria

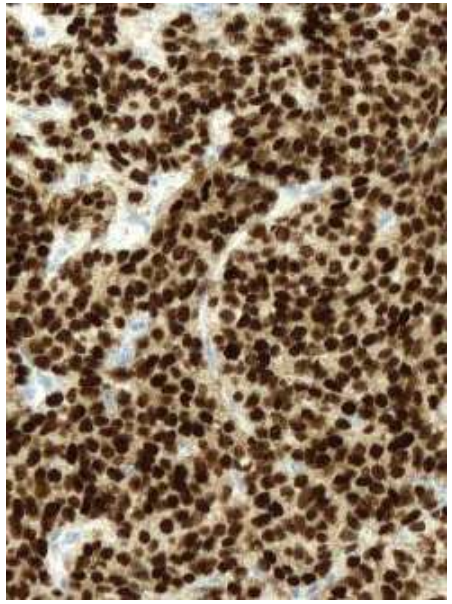
Essential:
histological features and immunoprofile characteristic of neuroendocrine differentiation;
NETs are not high-grade neoplasms.

Desirable: coexisting ductal carcinoma in situ.

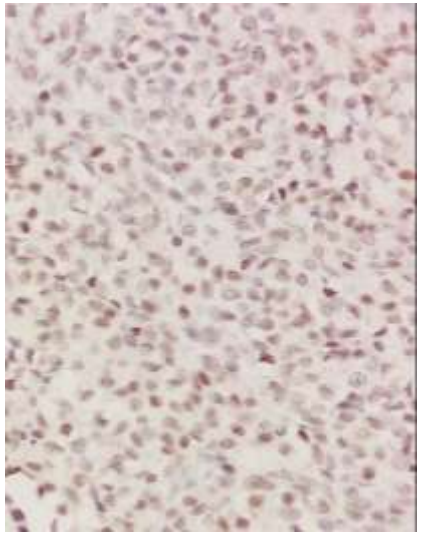
PROGNOSTIC MARKERS OF NET



ER



PR



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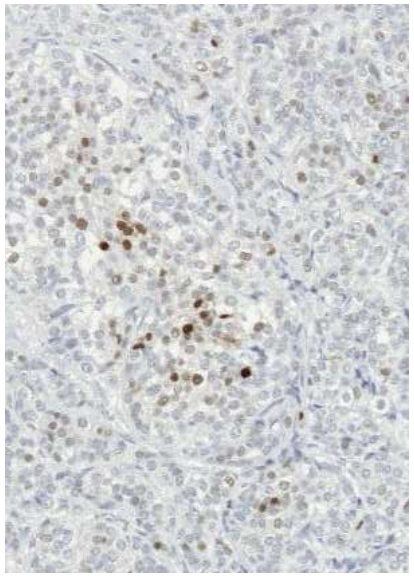
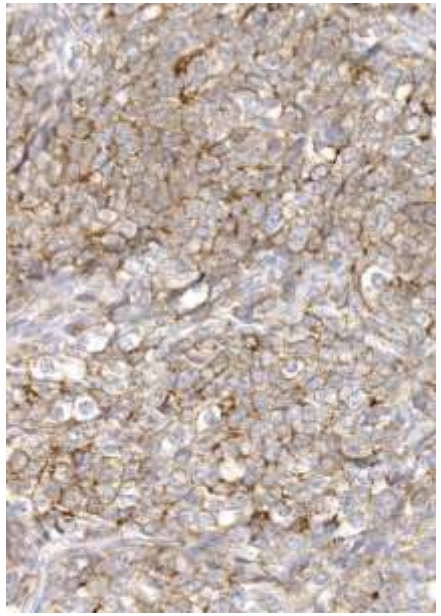


HER2- NA



AR+

Modern Pathology (2016) 29, 788–798

Prognosis and prediction of NET –WHO 2019

Tumour stage and histological grade, **which encompass mitotic counts**, are used as the main prognostic parameters.

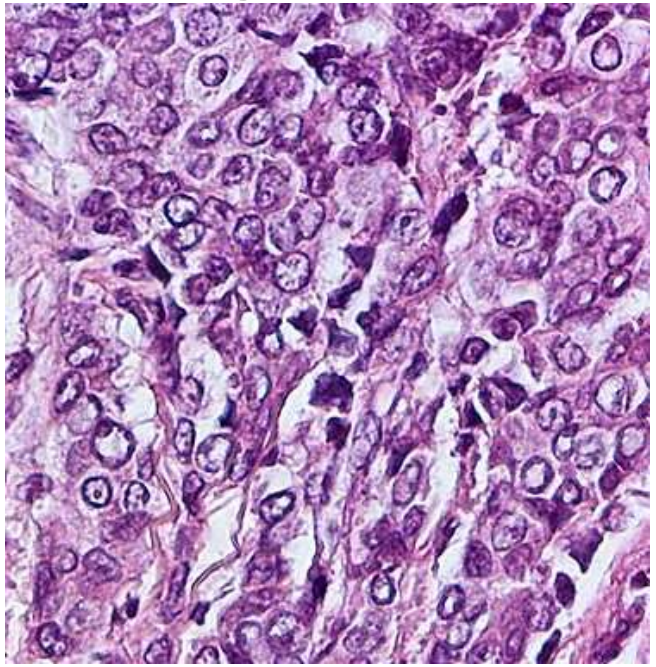
There are **no data from prospective clinical trials on the optimal management of NETs of the breast**, and these tumours are usually treated with the same strategy used for other types of invasive breast cancer.

WHO Classifications of Neuroendocrine neoplasms in the breast

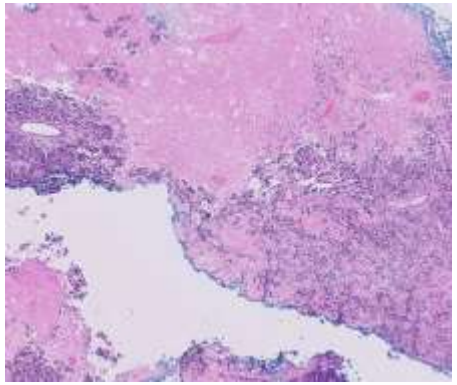
WHO 2003	WHO 2012	WHO 2019 *in press*
A group of neoplasms showing mor- phological features similar to those of neuroendocrine tumours of the gastrointestinal tract and lung, **with expression of neuroendocrine markers in >50% of the tumour cell population.**	Breast carcinomas with neuroendocrine features showed morphological features similar to neuroendocrine tumours of the gastrointestinal tract and lung.	A uniform classification framework for NENs at all anatomical locations was proposed in order to reduce inconsistencies and contradictions among the various systems currently in use.
HISTOTYPES		
Solid neuroendocrine carcinoma	Neuroendocrine tumour, well differentiated (carcinoid-like)	Neuroendocrine tumour (NET)
Small-cell/oat cell carcinoma	Neuroendocrine carcinoma, poorly differentiated/ small-cell carcinoma	Nuroendocrine carcinoma (NEC)
Large-cell neuroendocrine carcinoma	Invasive carcinoma with neuroendocrine differentiation	
Metastatic carcinoid		

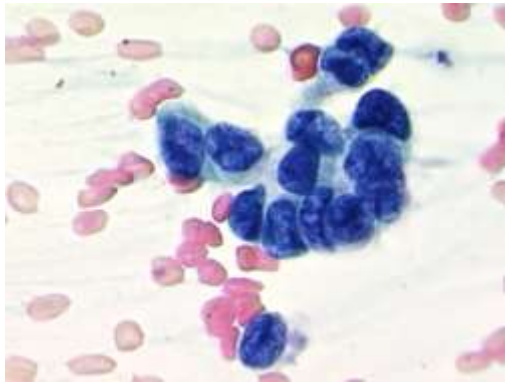
HISTOLOGY OF NEUROENDOCRINE CARCINOMA NEC

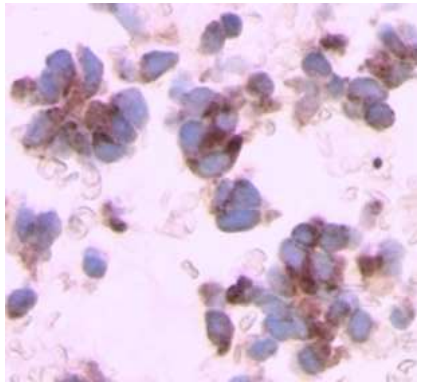
LARGE CELL NEC (grade 3)



PRIMARY SMALL CELL NEUROENDOCRINE CARCINOMA







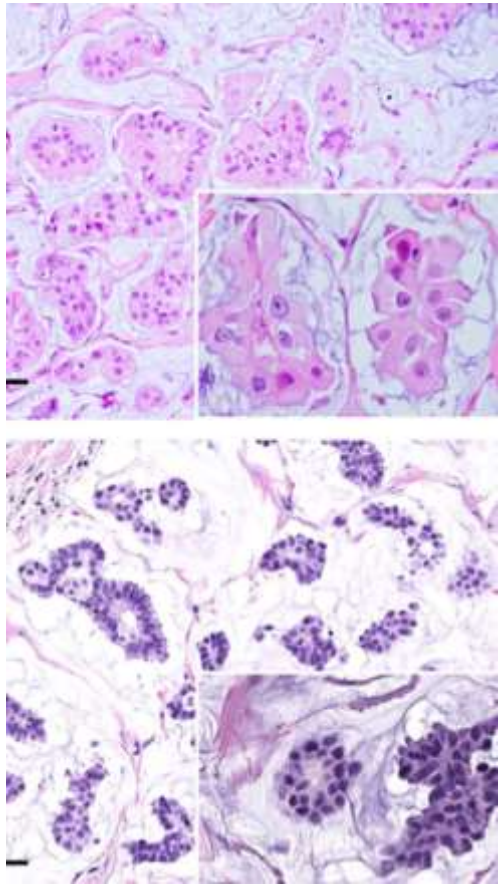
Others special types showing NE differentiation

- Classify acc. to special histologic type

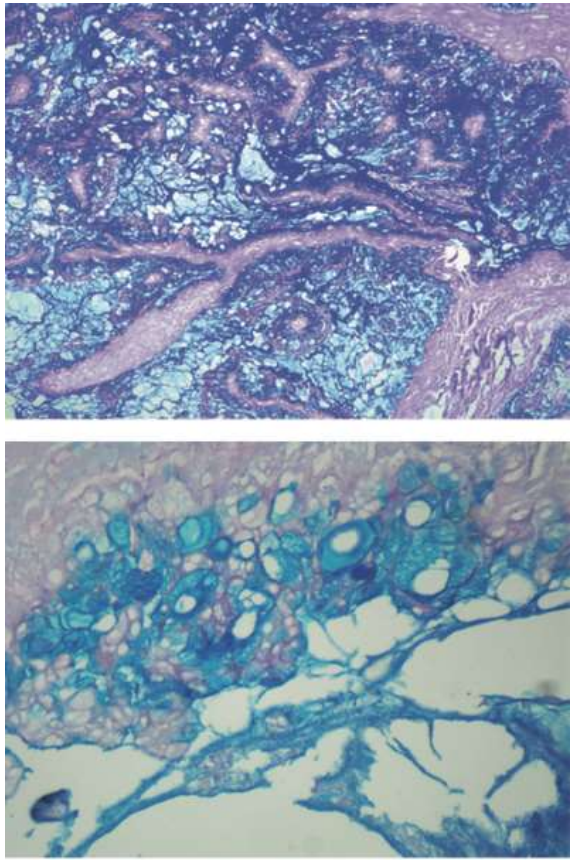
- Example**:**
  - **Solid papillary carcinomas** and
  - the **hypercellular subtype of mucinous carcinoma** expressing neuroendocrine markers **should not be classified** as NETs, because they are distinct breast neoplasms.

New entities

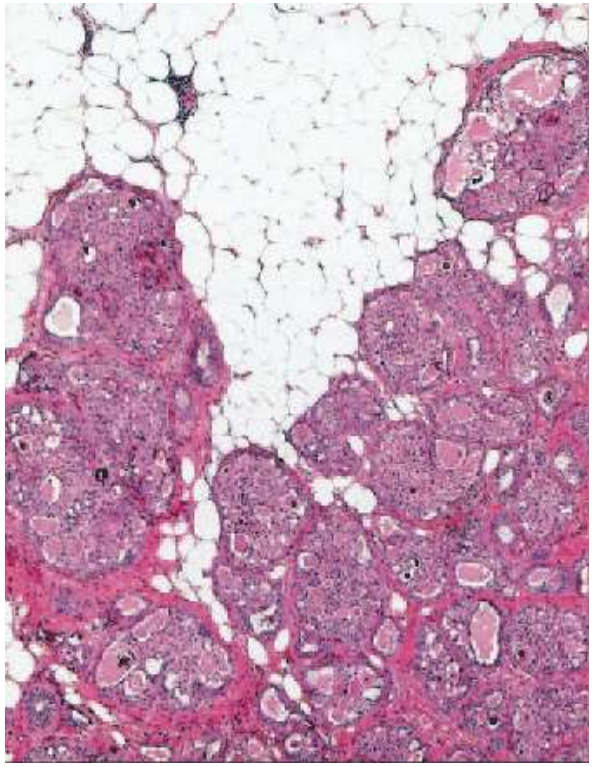
Micropapillary variant of mucinous carcinoma



Mucinous cystadenocarcinoma



Tall Cell Carcinoma with Reverse Polarity

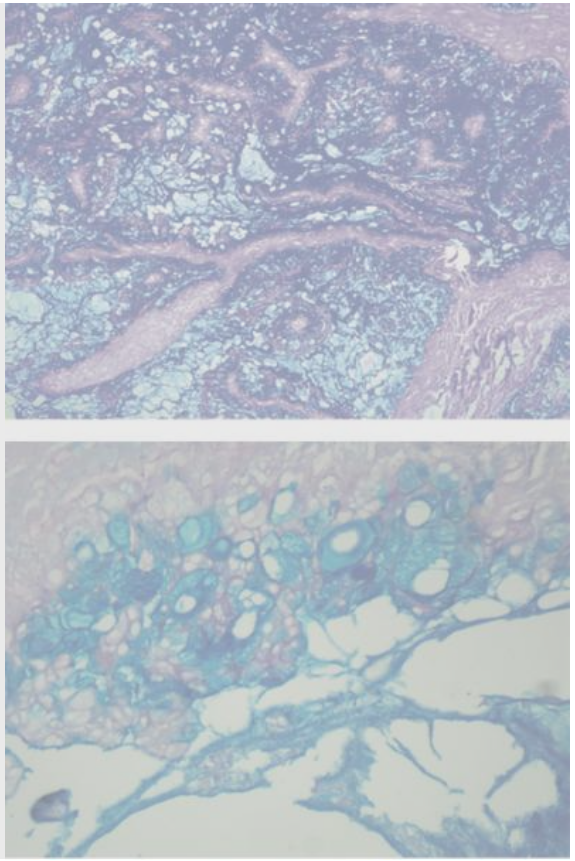


New entities

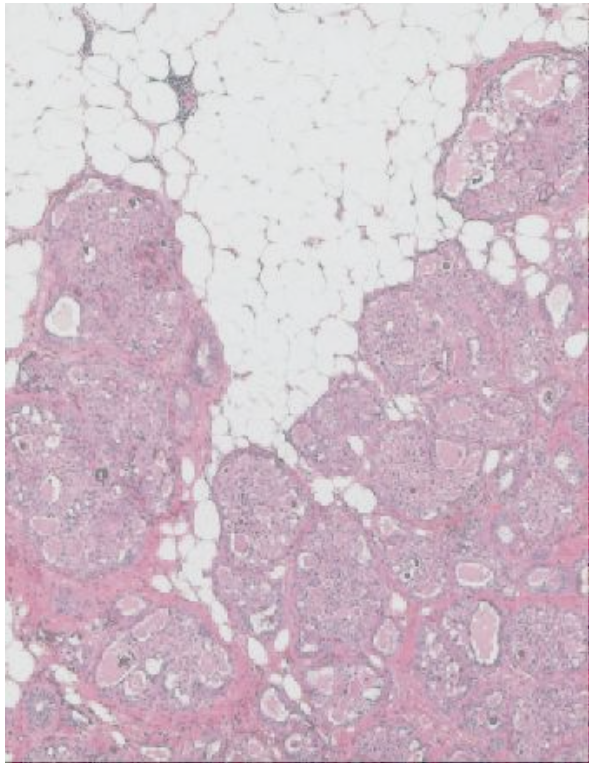
Micropapillary variant of mucinous carcinoma

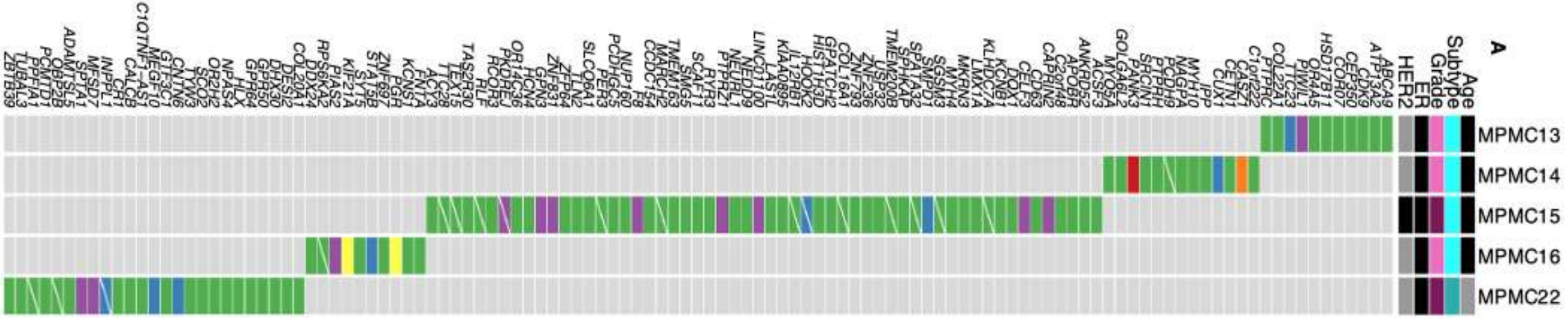
- They usually exhibit more nuclear atypia than conventional mucinous carcinomas
- They tend to occur at a younger age and has more-frequent lymphovascular invasion and lymph node metastasis

Mucinous cystadenocarcinoma



Tall Cell Carcinoma with Reverse Polarity





WES in 4 micropapillary variants of mucinous carcinomas

No recurrent somatic mutation in the MPMCs analysed
No mutations in genes that are significantly mutated in breast cancer, including *TP53, PIK3CA, GATA3, MAP3K1,* and *CDH1*

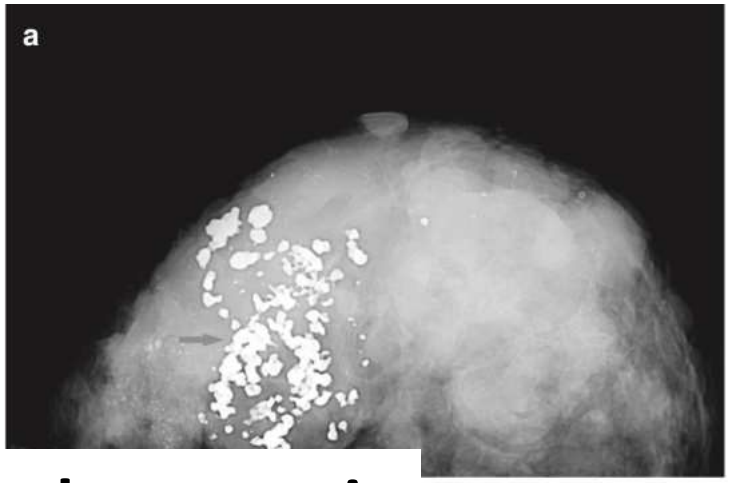
CNA analysis: some cases with CNA similar to mucinous, other cases with CNA similar to micropapillary carcinomas

Some MPMCs resemble breast mucinous carcinomasat the genetic level, others show genetic alterationssimilar to those of micropapillary carcinomas and other common forms of ER-positive breast cancer

Pareja F et al, Histopathology 2019, 75, 139–145.

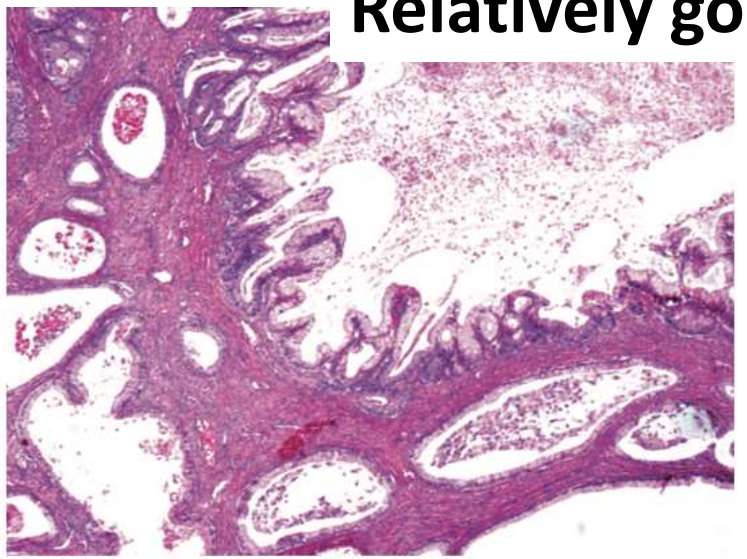
Mucinous cystadenocarcinoma of the breast

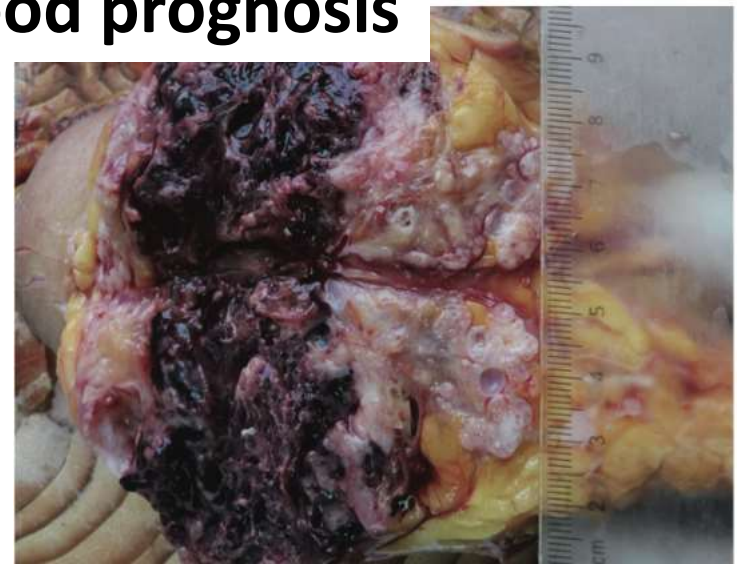
Invasive carcinoma featuring cystic structures lined by tall columunar cells with abundant intracytoplasmic mucin, resembling pancreatobiliary or ovarian mucinous cystadenocarcinoma



- Vanishingly rare entity (< 30 cases reported)
- **Mostly TNBC** (occasionally HER2+)
- Exclude metastasis

Relatively good prognosis





Images from Pathology International 2012; 62: 429–432

IDH2 Mutations Define a Unique Subtype of Breast Cancer with Altered Nuclear Polarity

Sarah Chiang[1], Britta Weigelt[1], Huei-Chi Wen[1], Fresia Pareja[1], Ashwini Raghavendra[1], Luciano G. Martelotto[1], Kathleen A. Burke[1], Thais Basili[1], Anqi Li[1], Felipe C. Geyer[1], Salvatore Piscuoglio[1], Charlotte K.Y. Ng[1], Achim A. Jungbluth[1], Jörg Balss[2], Stefan Pusch[2], Gabrielle M. Baker[3], Kimberly S. Cole[4], Andreas von Deimling[2,5], Julie M. Batten[6], Jonathan D. Marotti[7], Hwei-Choo Soh[8], Benjamin L. McCalip[9], Jonathan Serrano[10], Raymond S. Lim[1], Kalliopi P. Siziopikou[11], Song Lu[12], Xiaolong Liu[13], Tarek Hammour[14], Edi Brogi[1], Matija Snuderl[10], A. John Iafrate[6,15], Jorge S. Reis-Filho[1], and Stuart J. Schnitt[15,16]

Chiang et al, Cancer Res; 76(24), 2016

Alsadoun et al , Mod Pathol 2017
WHO 2019

Tall Cell Carcinoma with Reverse Polarity

A rare entity, a discrete subtype of invasive breast carcinoma
(a tumor with unique histologic and genetic properties)

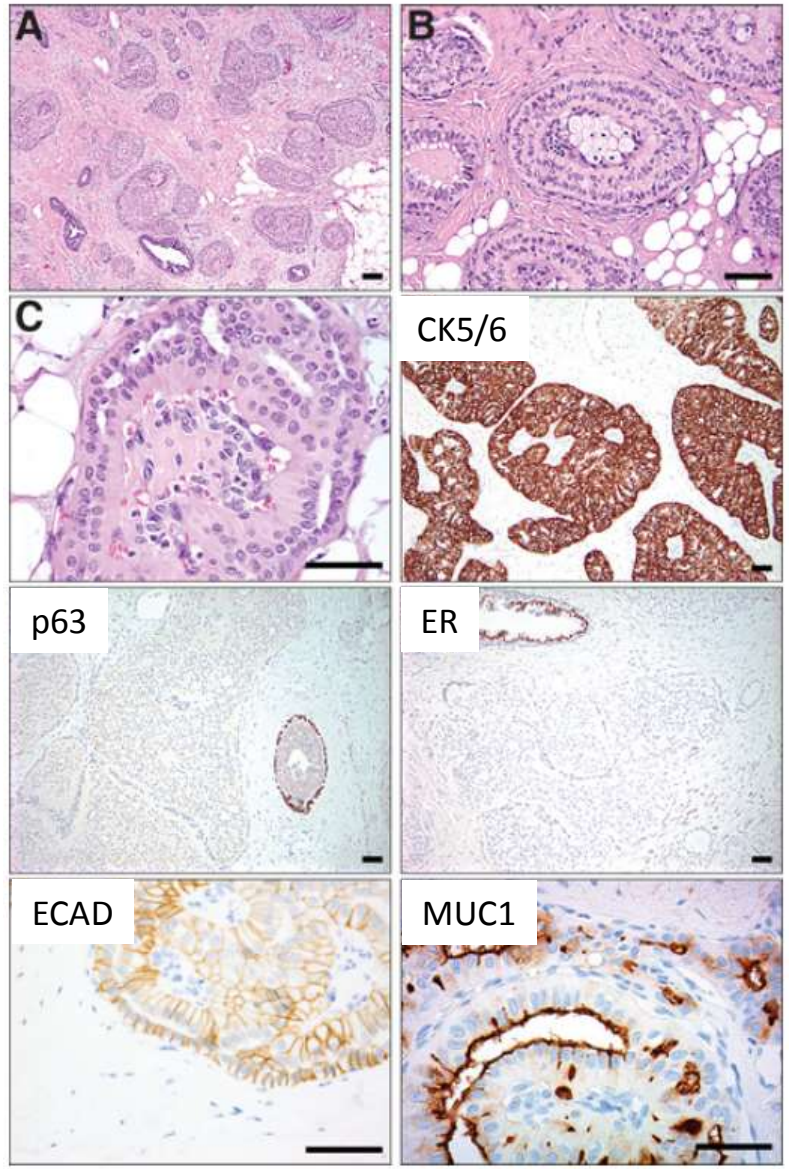
13 cases, WES
10/ 13 (**77%**): **R172 *IDH2* mutations**
Co-occurrence of *PIK3CA* or *PIK3R1* mutations in 8/10

PRUNE2 mutations: 67% de mutations (6/9 cases)

⇒**Indolent clinical course**, with a **favourable prognosis**.

⇒The majority of patients have been disease-free during the follow-up period (range: 3–132 months)

⇒Only one case with aggressive clinical behaviour (bone metastases) has been reported



2019 WHO Classification of Breast Tumors

- Not many changes
- Inclusion of stromal features
- Reclassification of Medullary Carcinomas
- Radical change in the classification of Neuroendocrine tumors/ carcinomas to create a common way of classification across sites
- Introduction of new special histologic types with unique histologic and genetic properties

=> Cancers have to be classified and diagnosed according to the same standards internationally, for patients and to help translate cancer research into practice

WHO Classification of Tumours ONLINE

Now available at: tumourclassification.iarc.who.int

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Breast Tumours

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