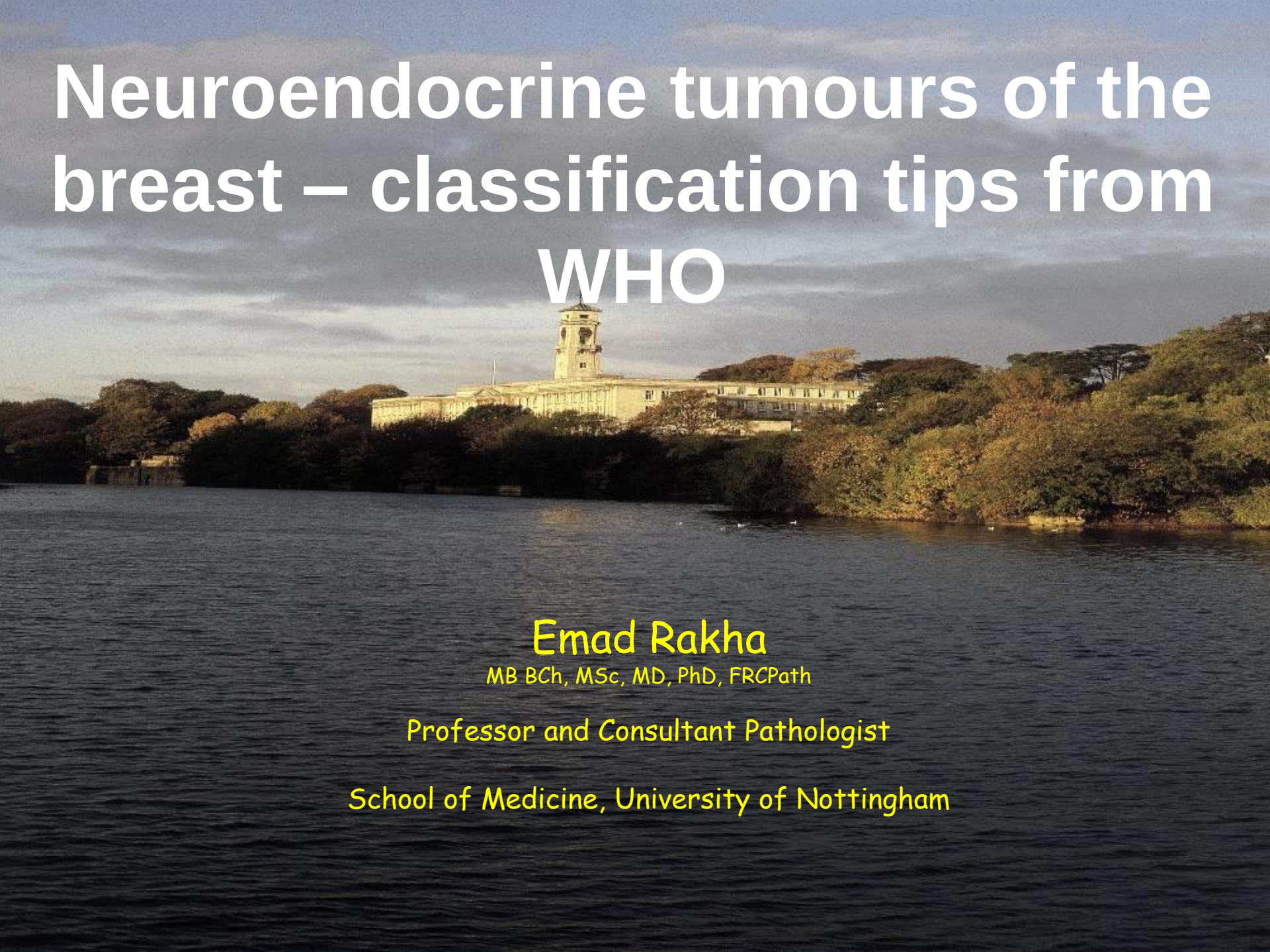
Neuroendocrine tumours of the breast – classification tips from WHO



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* BC with NE differentiation were first described in 1963 by Feyrter and Hartmann. In 1977, Cubilla and Woodruff described 8 other cases of BC with a carcinoid growth pattern

* Primary NE carcinoma of the breast has been recognized as a subtype of BC and included in the WHO classification in 2003.

* Since its description, definition and clinical significance (clinical behaviour and treatment options) remain controversial

* Based on IHC expression of NE markers, the frequency of NE tumours in the breast varied from 3% up to 30% with different cutoff of positivity

Classification of NE BC

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#

Apart from rare cases of small cell carcinoma, analogous to its pulmonary counterpart, the definition of NENs in the breast varies widely, resulting in variable incidence from less than 0.1% up to 20%.

* The incidence of NE carcinomas of the breast has been reported to range from 1-5% of BC (in WHO 2003) but <1% in WHO 2012

* Wang et al (2014) identified 142 NE carcinomas of the breast out of 381,644 cases of BC registered in the SEER database, which comprised <0.1% of total BCs.

* In fact only a limited number of studies on NE BC have been reported in the literature with isolated case reports and very few retrospective (mainly from SEER database)

Sapino et al 2001 (50 NE BC)
Shin et al (2000) 9 SCC
Bogina et al (2016) 55 NE BC

*** In 2003 WHO classification; NE tumour were defined as "*a group of neoplasms showing morphological features similar to those of NE tumours of the gastrointestinal tract and lung, with expression of NE markers in >50% of the tumour cell population*"**

*** *Large-cell NE carcinoma was included but NOT* NST with focal NE differentiation**

*** No comments on carcinoid in the breast or distinction of SPC or mucinous carcinoma with NE features from NE carcinoma**

* In 2012, the WHO Working Group used a terminology *"Carcinomas with neuroendocrine features"*

* Breast tumours with NE features were classified into three groups:

Neuroendocrine tumour, well differentiated (carcinoid-like)
Neuroendocrine carcinoma, poorly differentiated/ small-cell carcinoma
Invasive carcinoma with NE differentiation

- NST or special BC types with NE differentiation were included

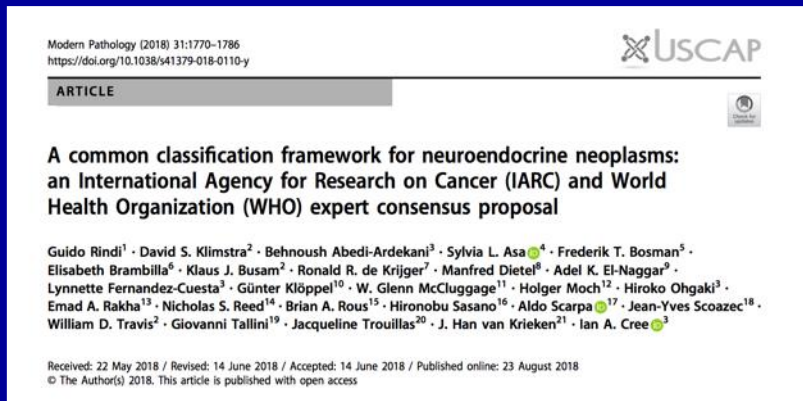
- No requirement for a specific threshold for NE IHC marker positivity (>50% cutoff was removed)

- Large cell NE carcinoma was removed

* 2018 meeting organised by IARC and WHO (Lyon) aimed at using a uniform classification framework for NE neoplasm (NEN) at all anatomical locations to reduce inconsistencies and contradictions among the various systems currently in use and an expert consensus statement was proposed and published

* It was proposed and agreed to adopt the term "NEN" to encompass all tumour classes with predominant neuroendocrine differentiation

* The key feature is a distinction between well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs), as both share common expression of neuroendocrine markers.



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USCAP

ARTICLE

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

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However, many challenges in the breast

* Marked overlap between NEN and other BCs showing NE differentiation including invasive and DCIS and some BC (SPC and the hypercellular variant of mucinous carcinoma) fulfil the criteria for designation as mammary NEN.

* Most studies failed to identified NE cells in the normal breast

* *Differentiation rather than histogenesis* theory

* Clinical syndromes related to hormone production are extremely rare in breast NENs

* The classic organoid features of carcinoid tumours of the lung and GI tract (i.e., ribbons, cords and rosettes) are not features of primary NENs of the breast.

* In 5th edition of the WHO book

* Introduction of NEN

• **Neuroendocrine tumour (NET): defined as: An invasive tumour characterised by morphology of low, intermediate grade NE tumour; supported by the presence of neurosecretory granules and a diffuse, uniform immunoreactivity with neuroendocrine markers.**

• Papillary and insular pattern and alveolar-like structures may be seen

• Applying the Nottingham grading system, NET should be *G1 or G2*.

• SPC and the mucinous carcinoma expressing NE markers should not be classified as NET, because they are distinct breast neoplasms.

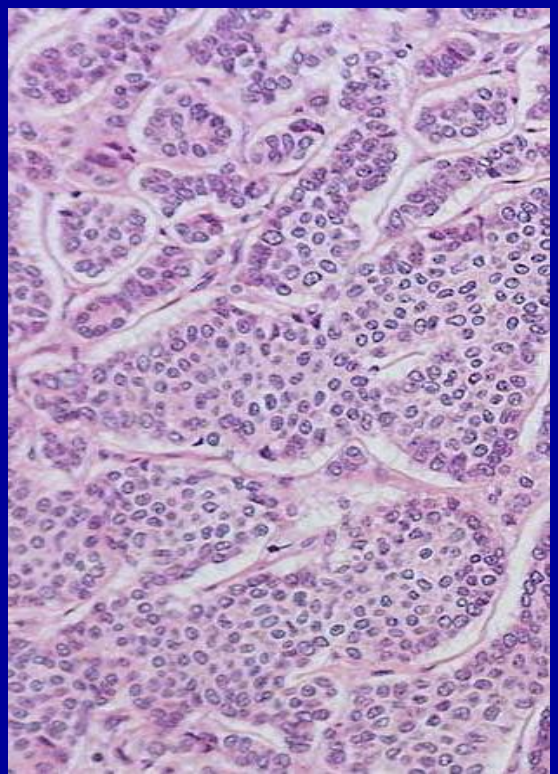
• Distinction from other mammary carcinoma should be based on the presence and extent of histological features characteristic of NE differentiation in the tumour.

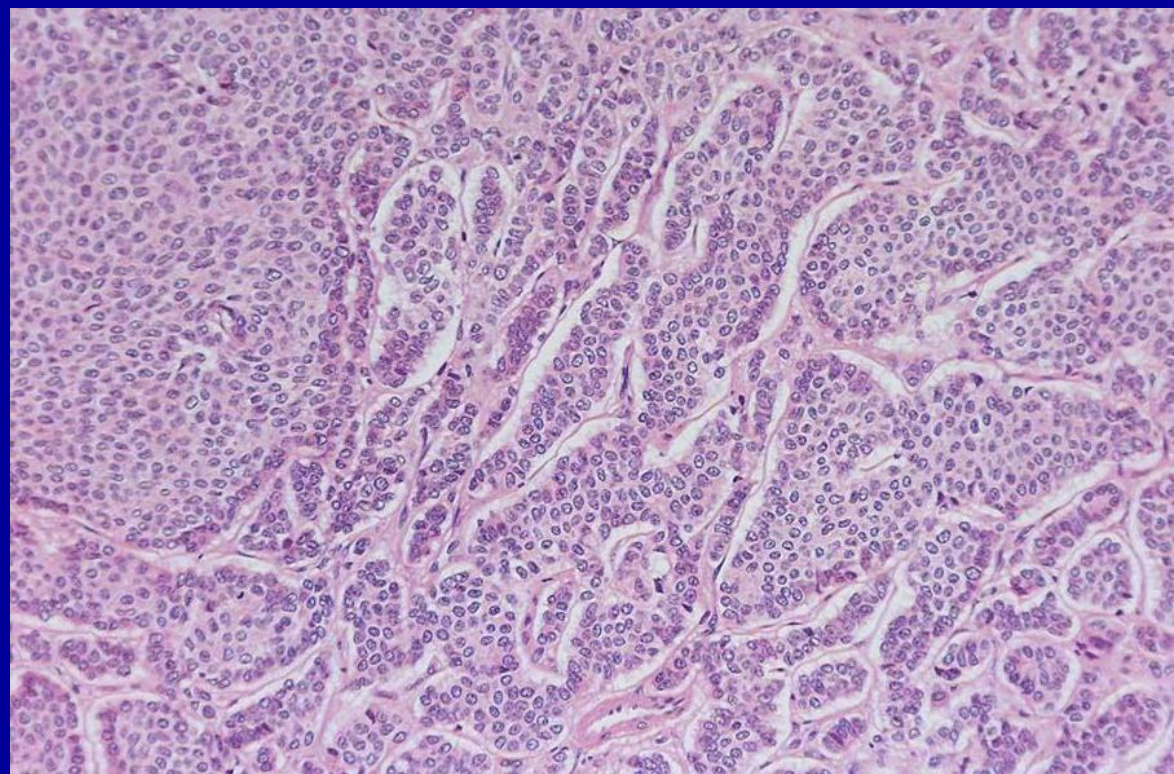
• DD from metastatic NET of lungs and GIT

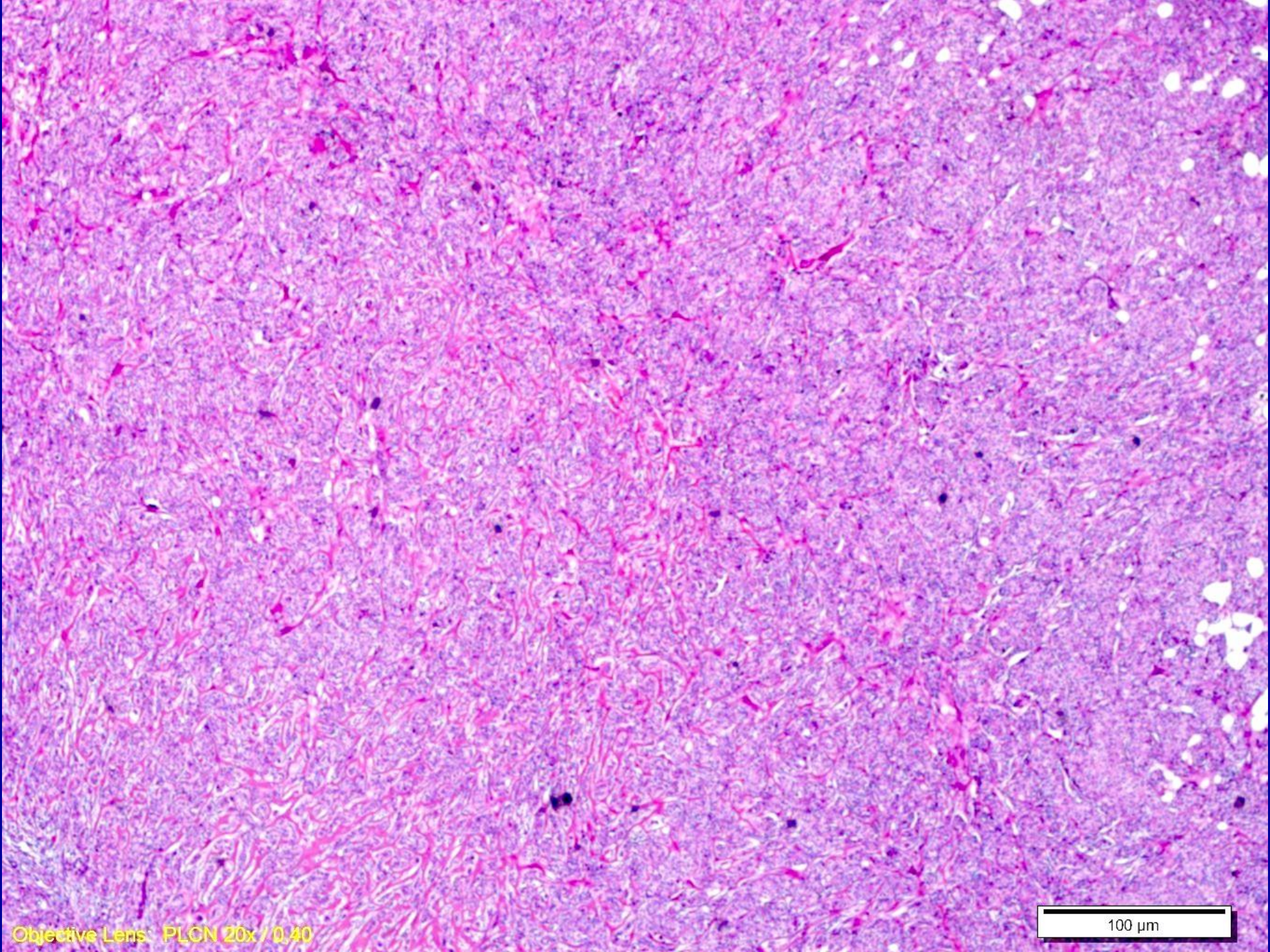
1-NE Tumour, Well Differentiated

*These tumours consist of densely cellular solid nest and trabeculae of cells that vary from spindle to plasmacytoid and large clear cells separated by delicate fibrovasular stroma

*Majority are low and intermediate nuclear grade



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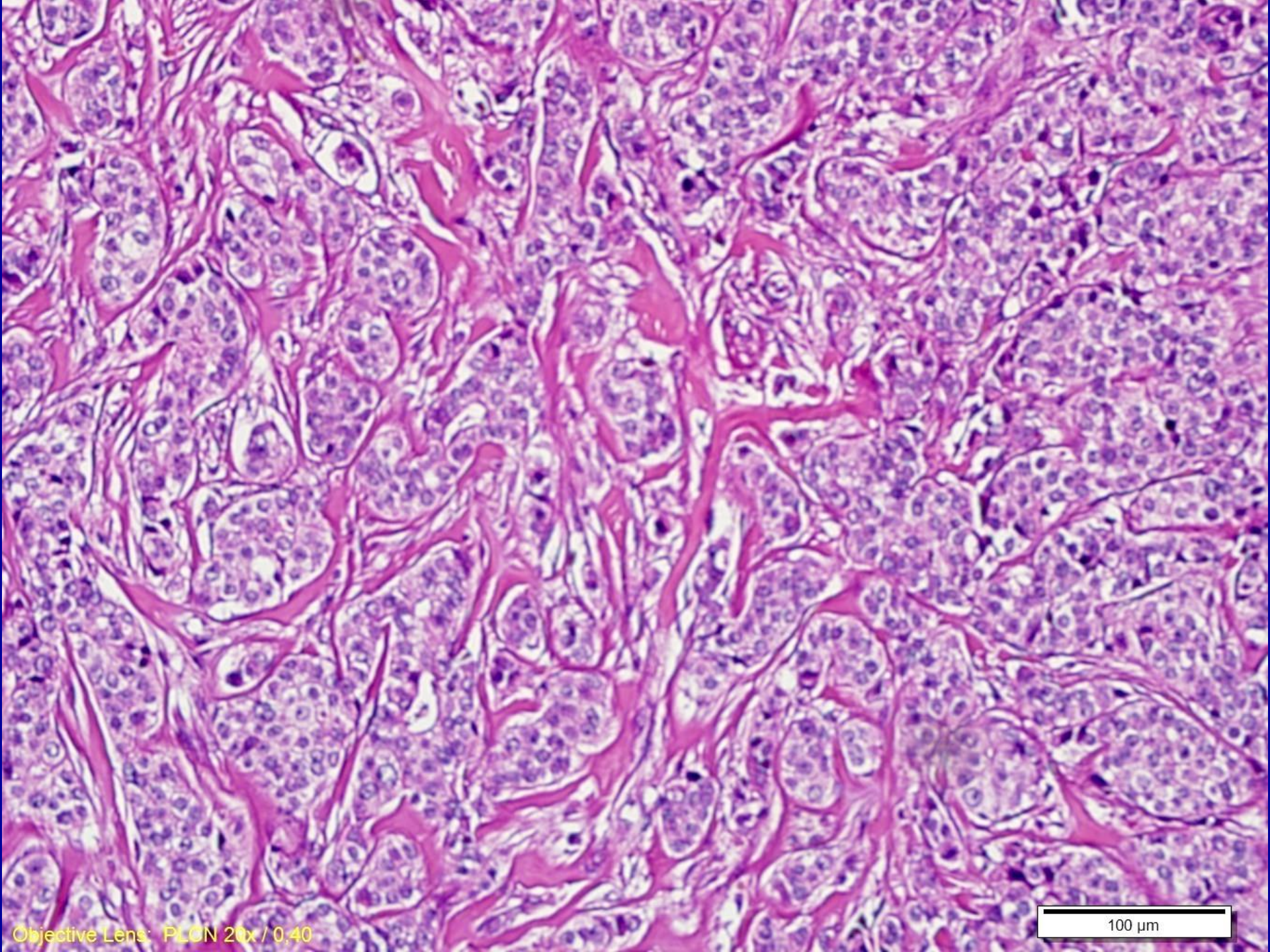
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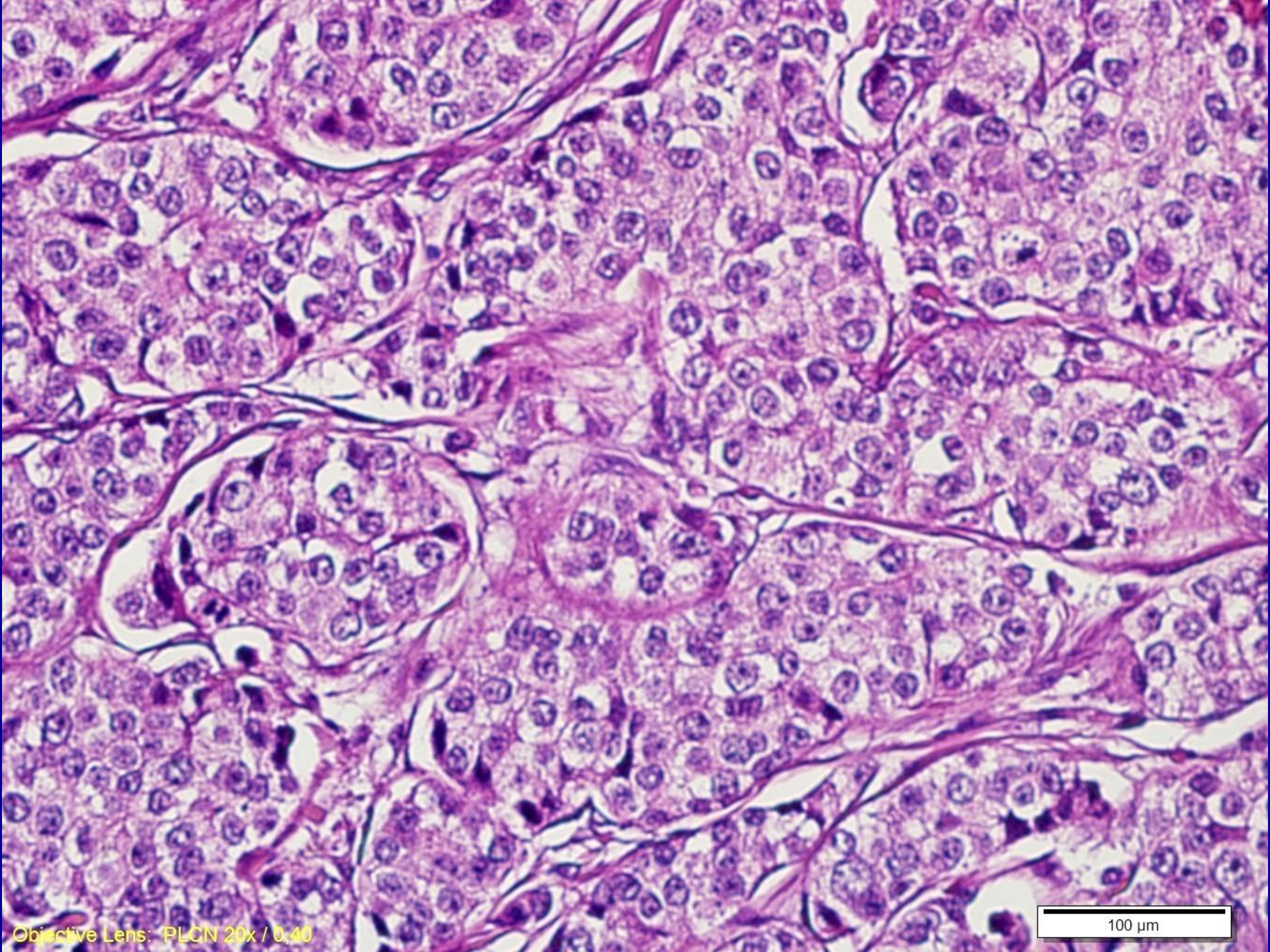
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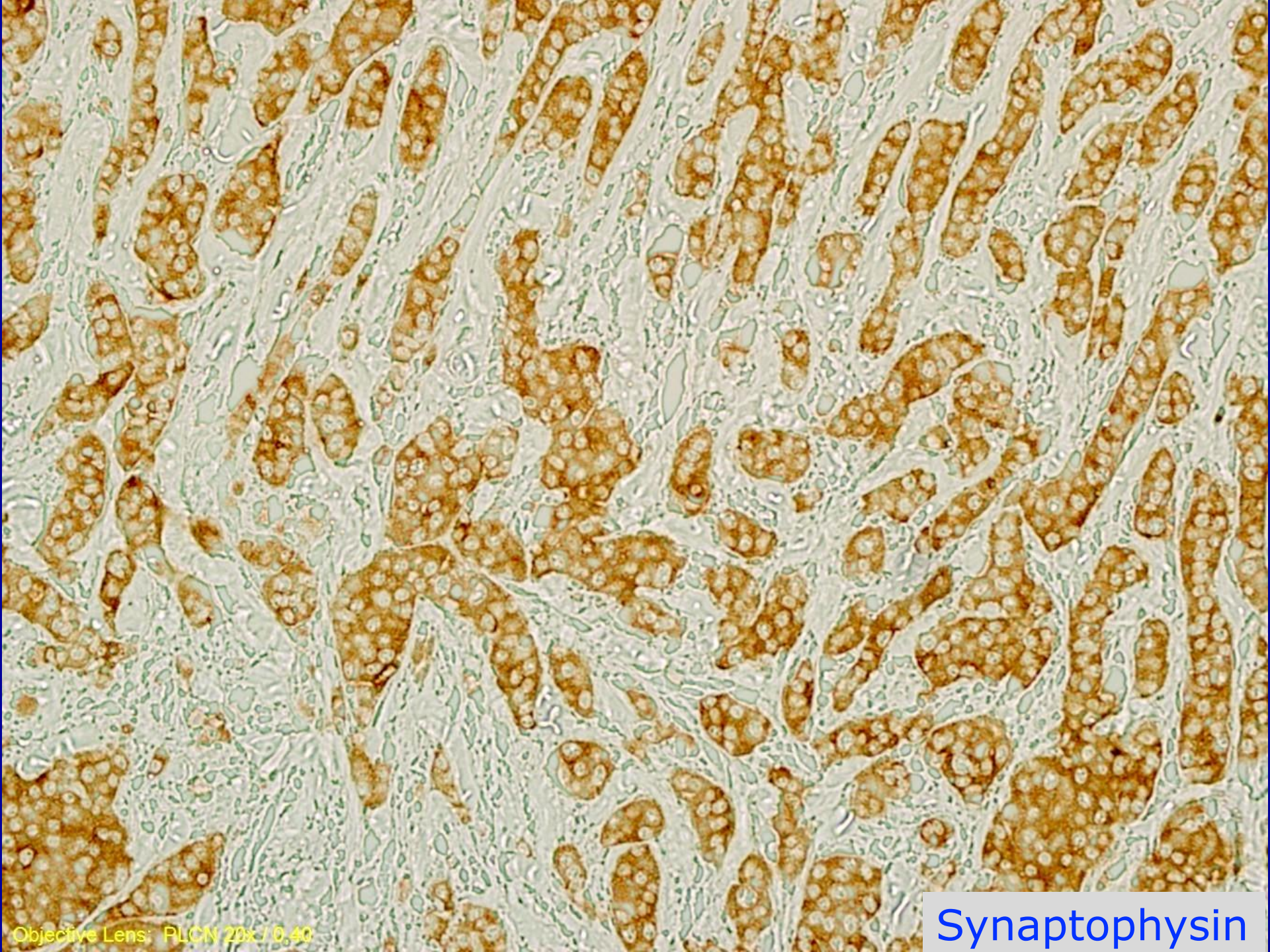
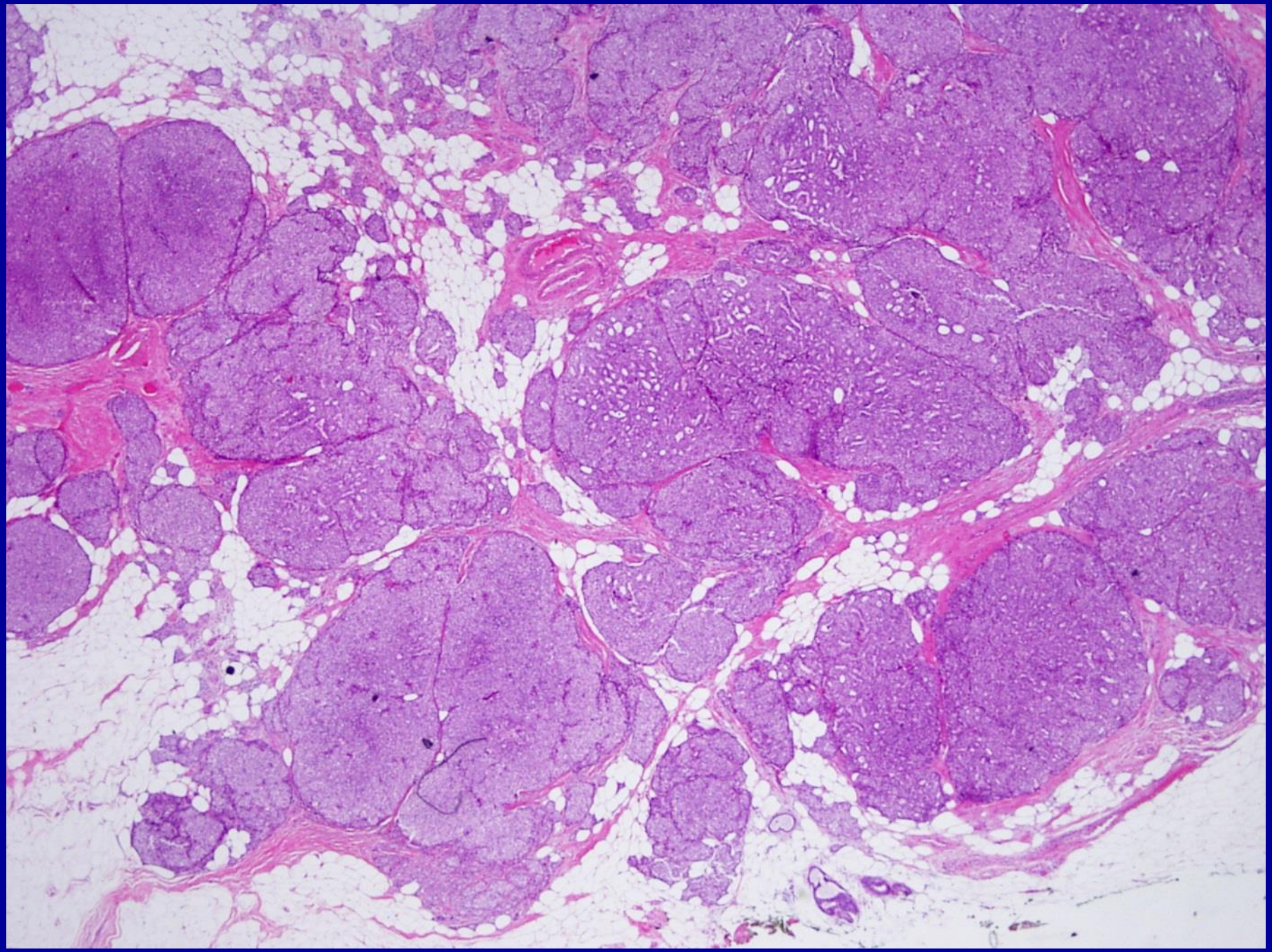
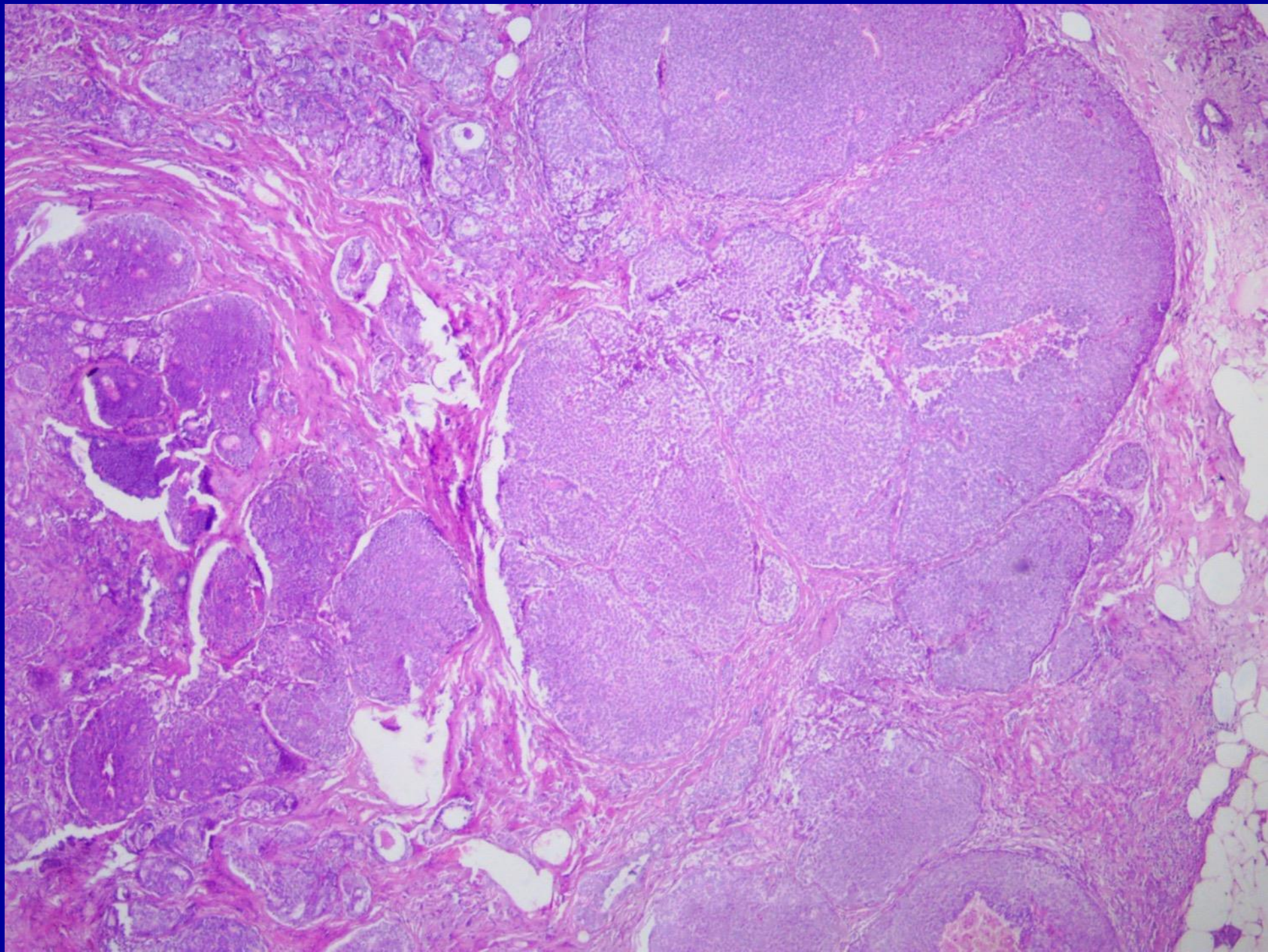
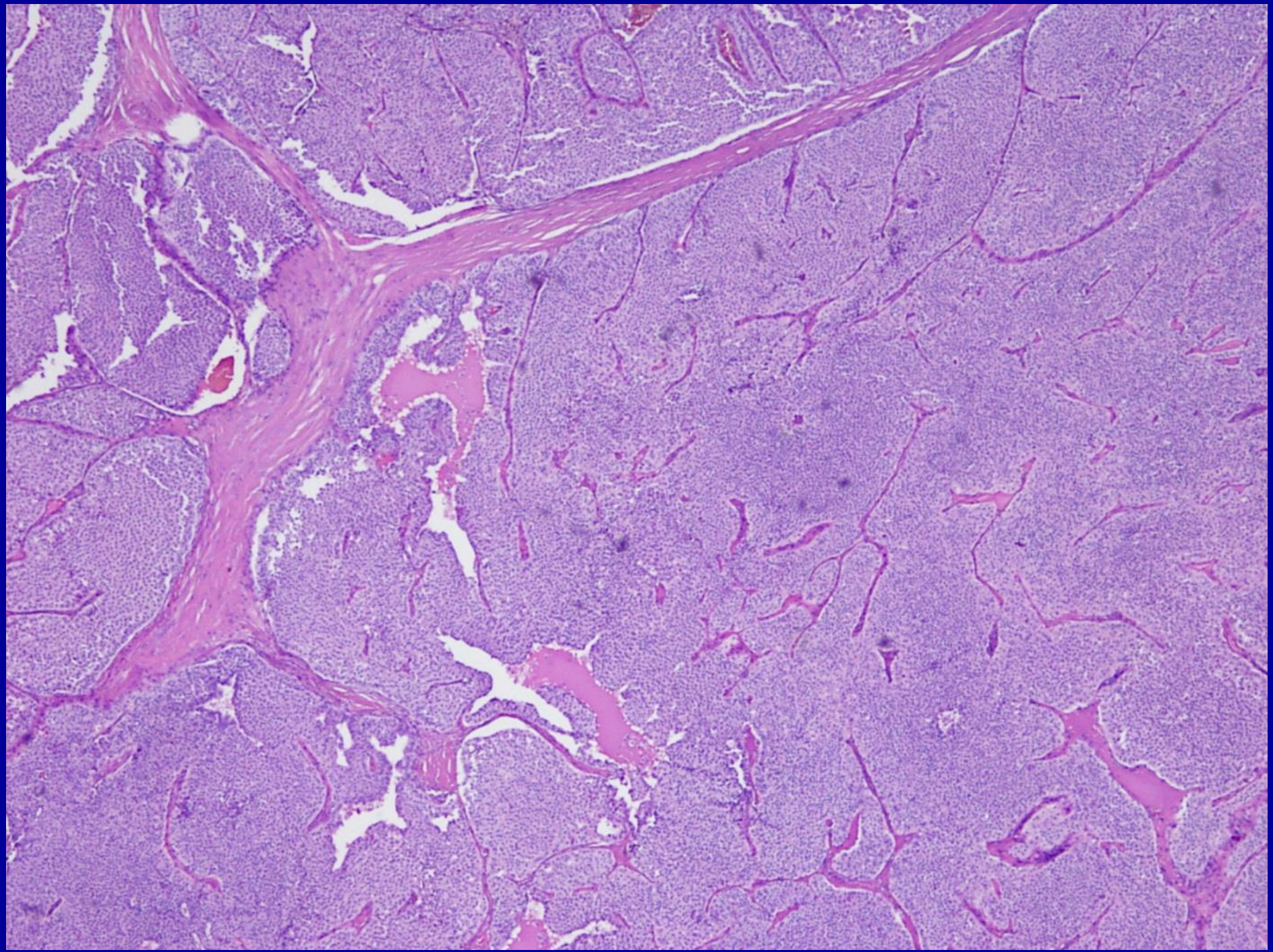


Synaptophysin

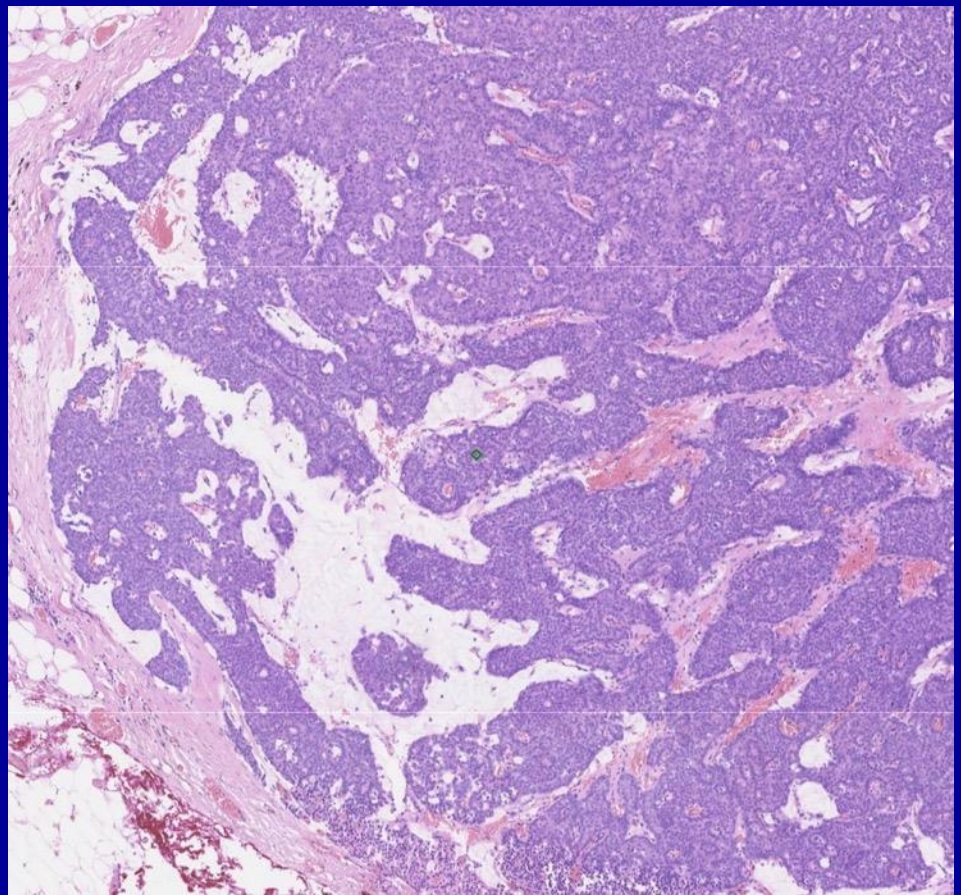




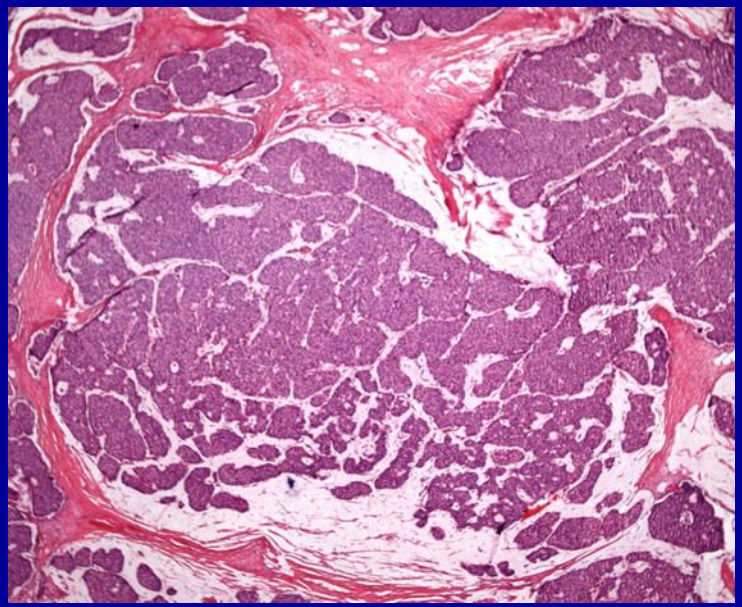


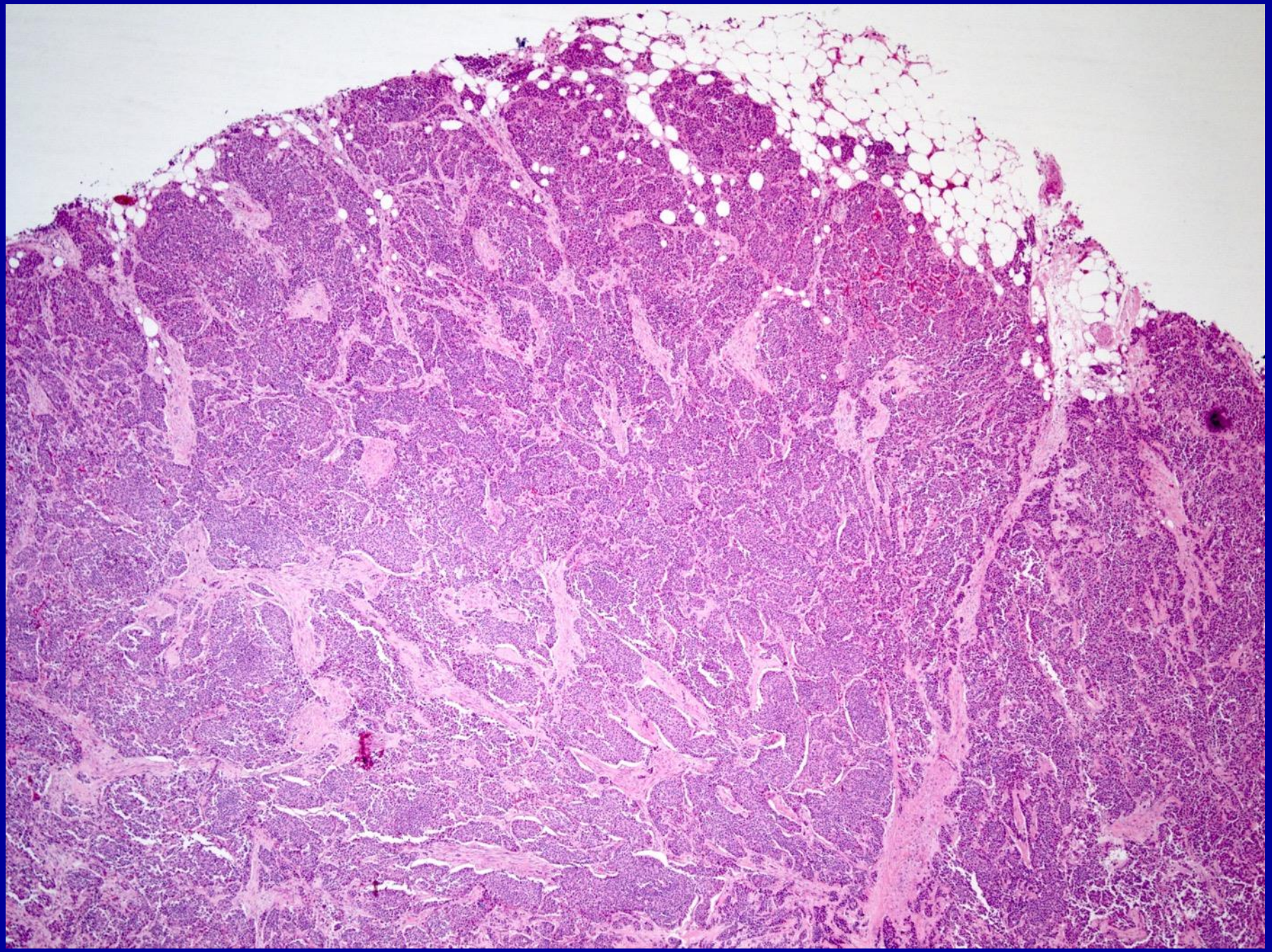
NE Tumour, Well Differentiated

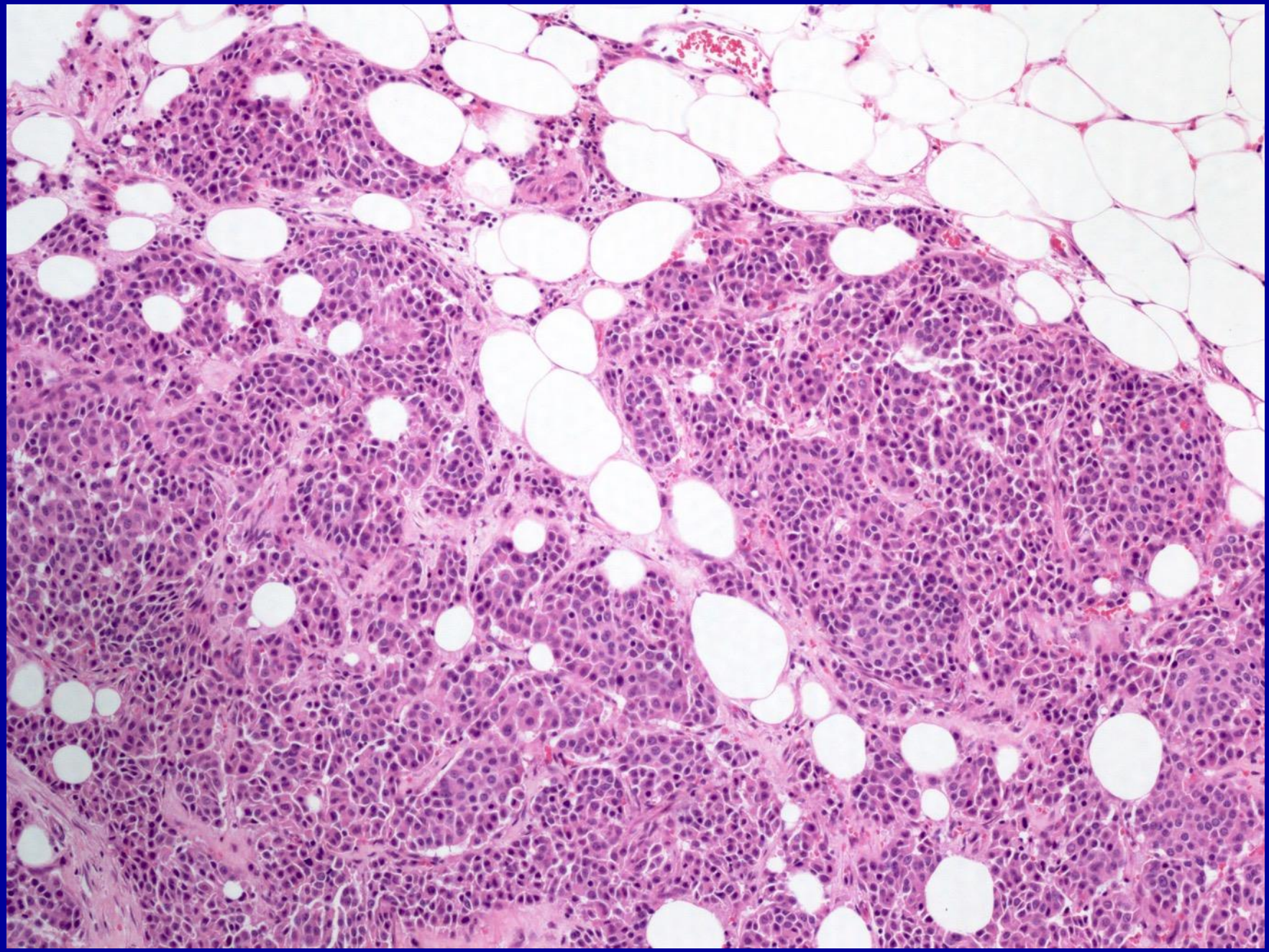
***If hypercellular type of mucinous carcinoma showing prominent NE differentiation and NE IHC marker expression, should it be diagnosed as mucinous or NE carcinoma in routine practice?**



A case of SPC with extracellular mucin and NE differentiation progressing to invasive carcinoma





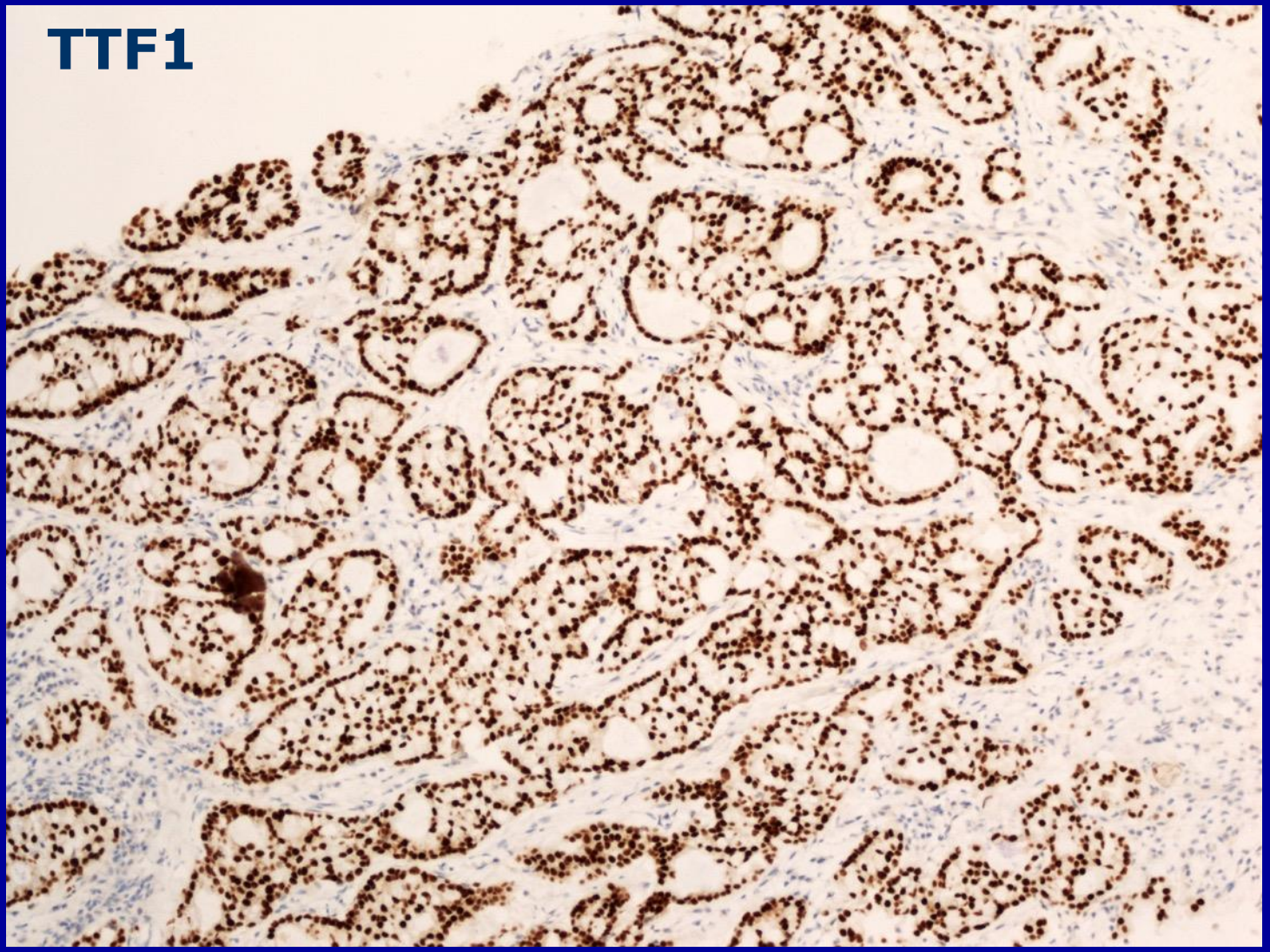


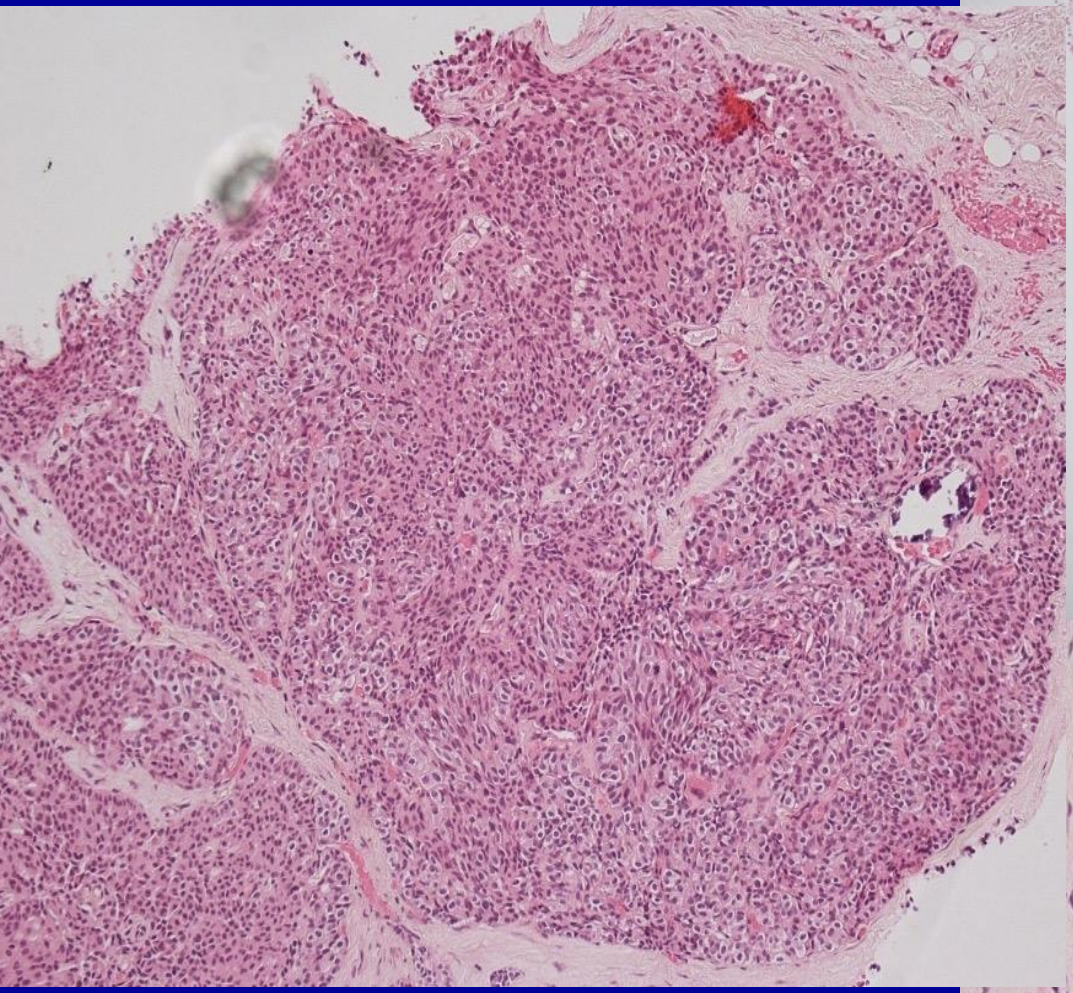
NE markers positive

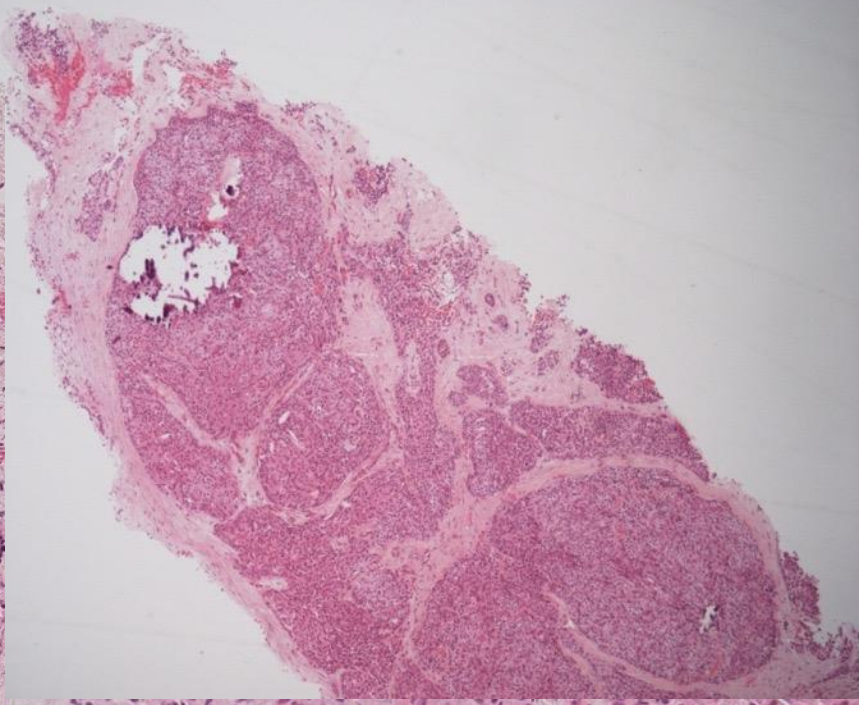
ER- negative
PR- negative

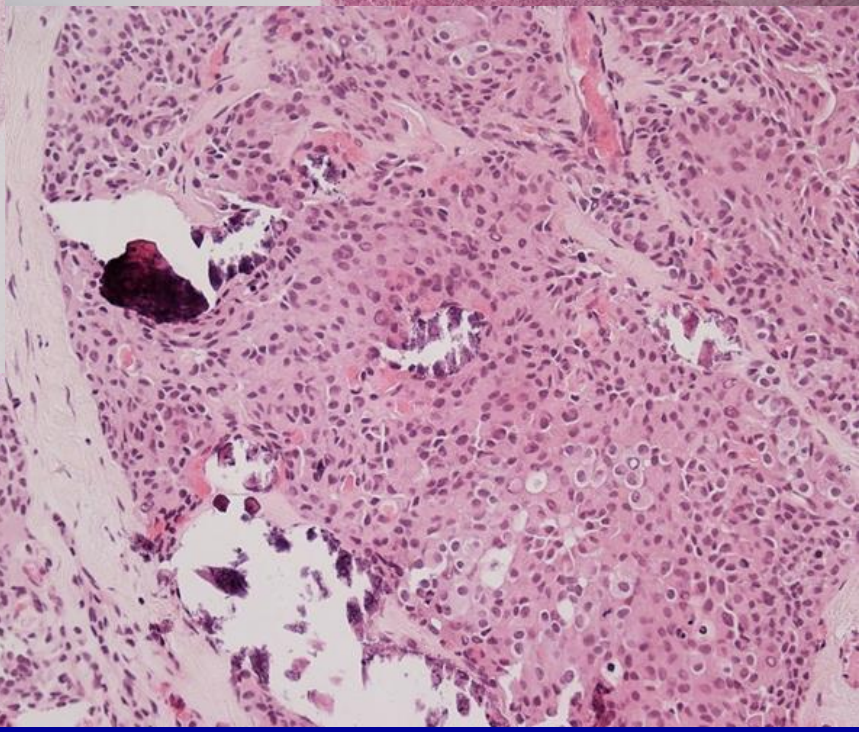
History of thyroid carcinoma

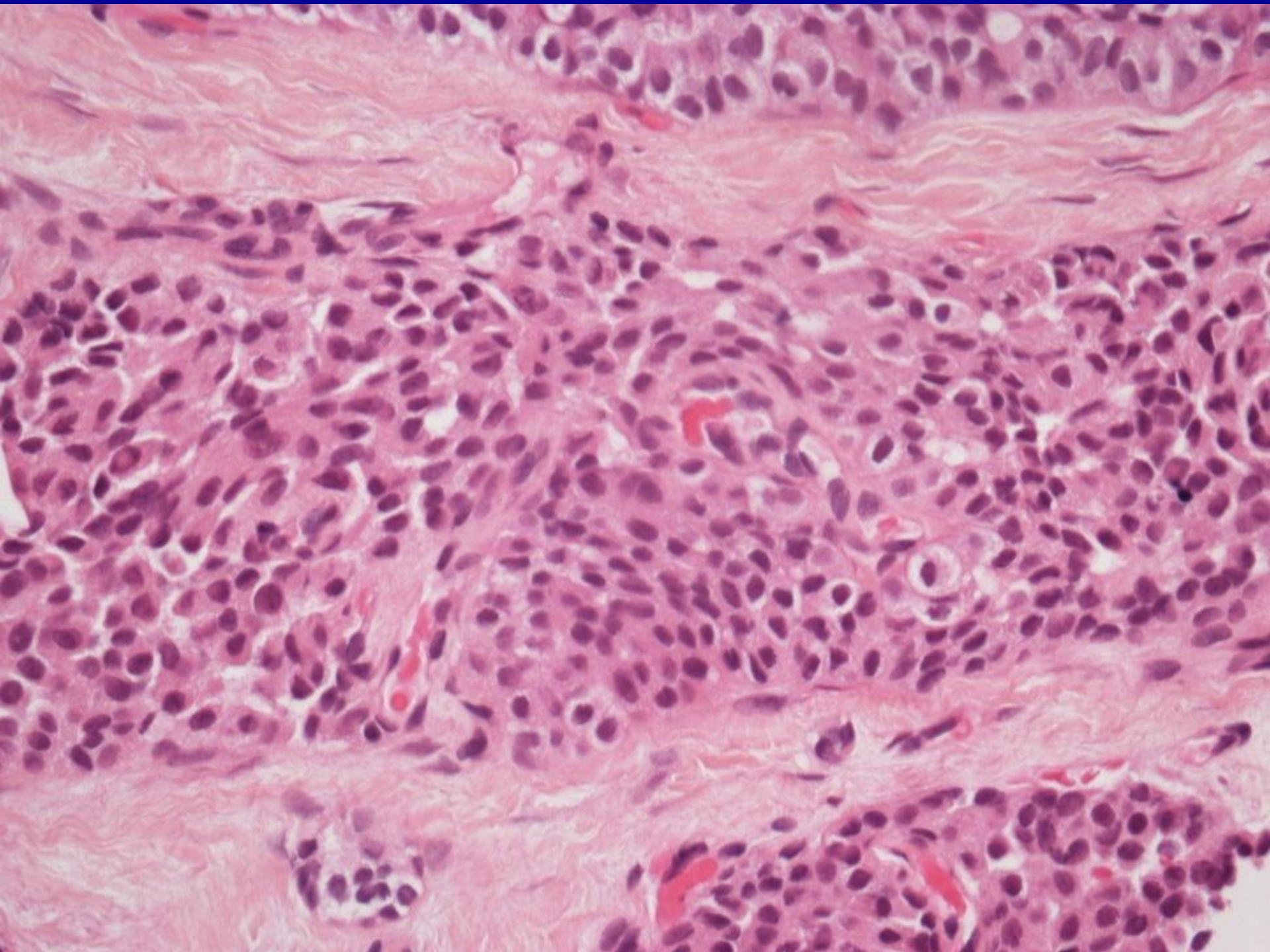
ER- negative
PR- negative

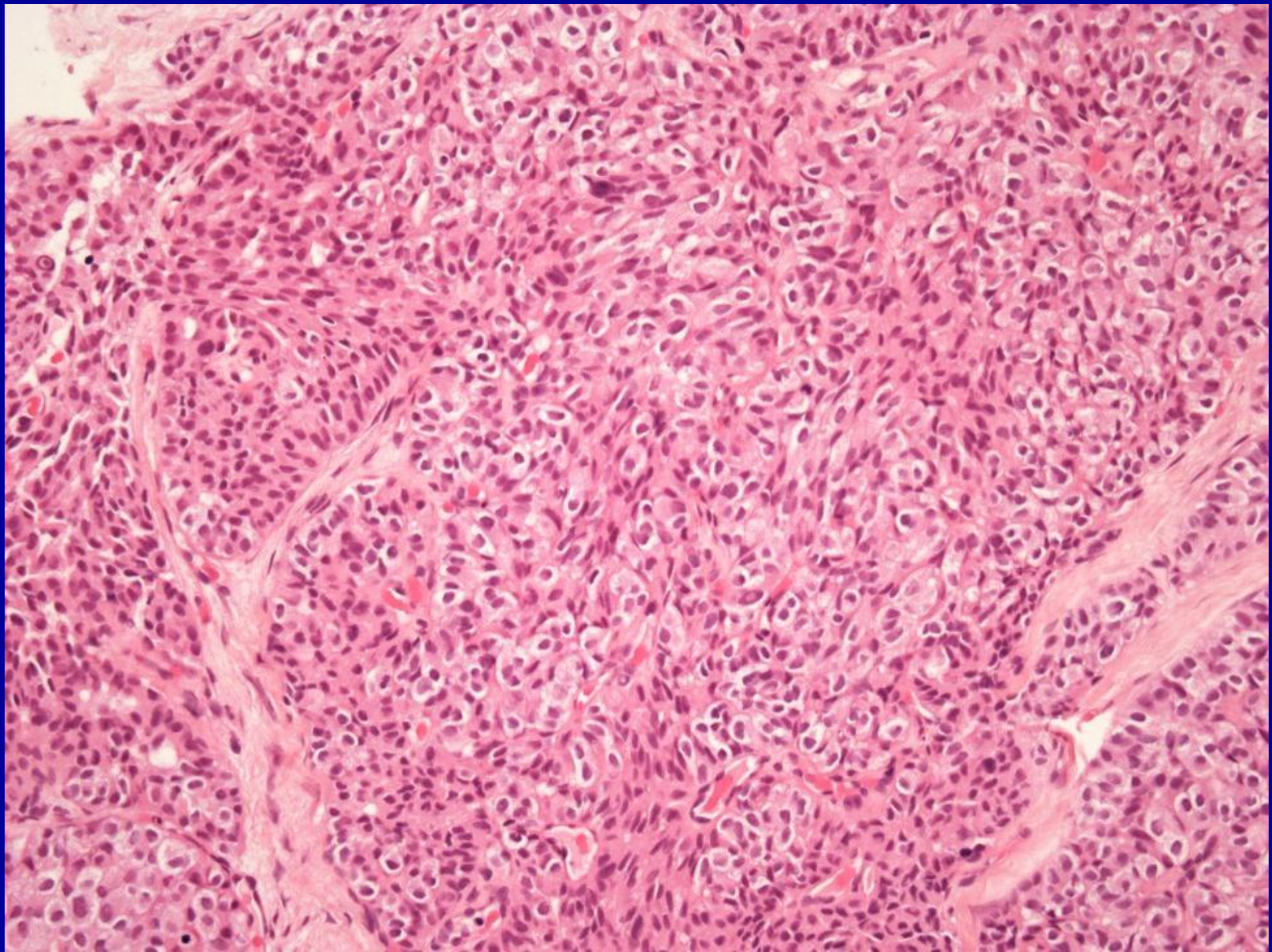


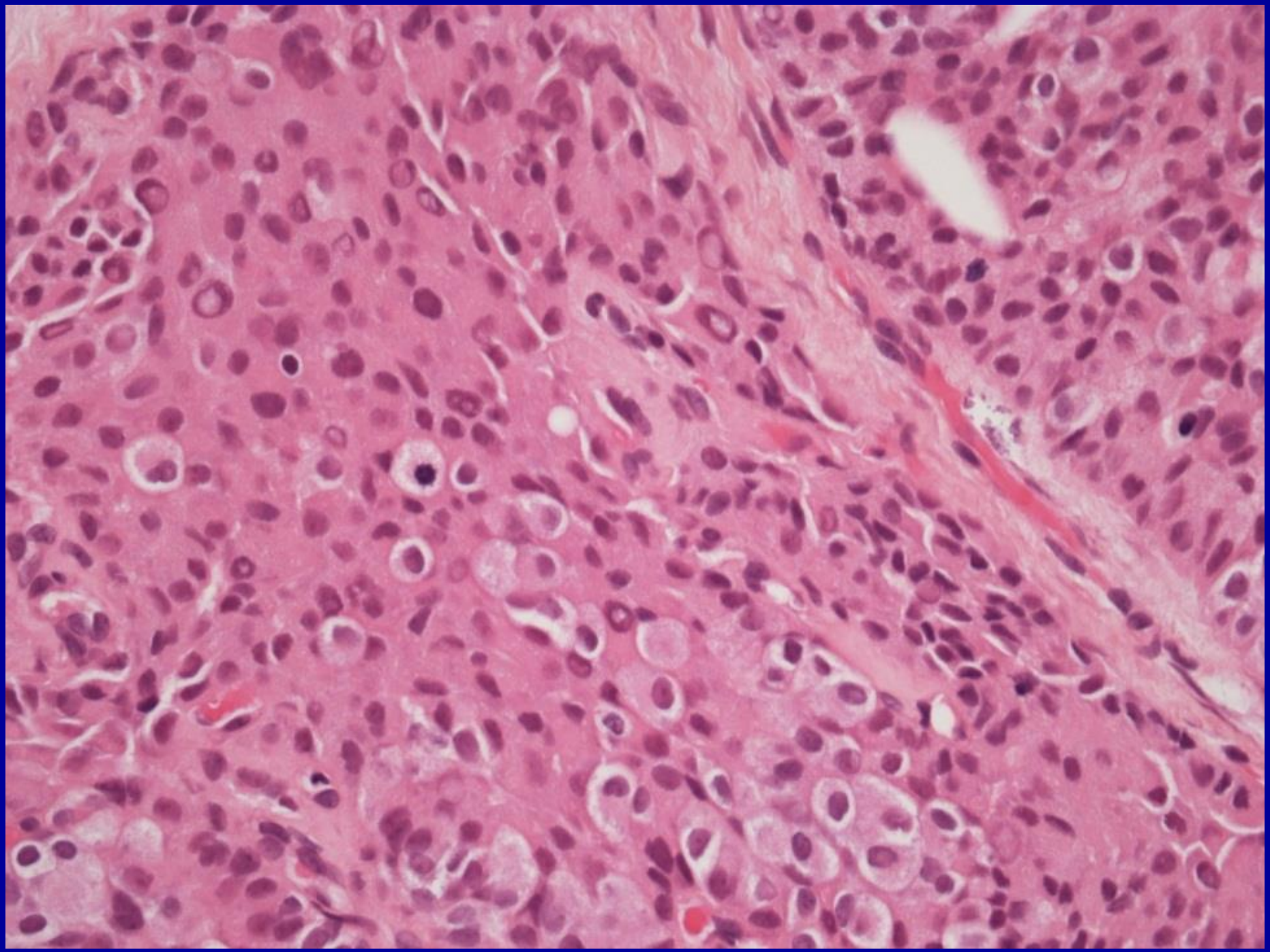






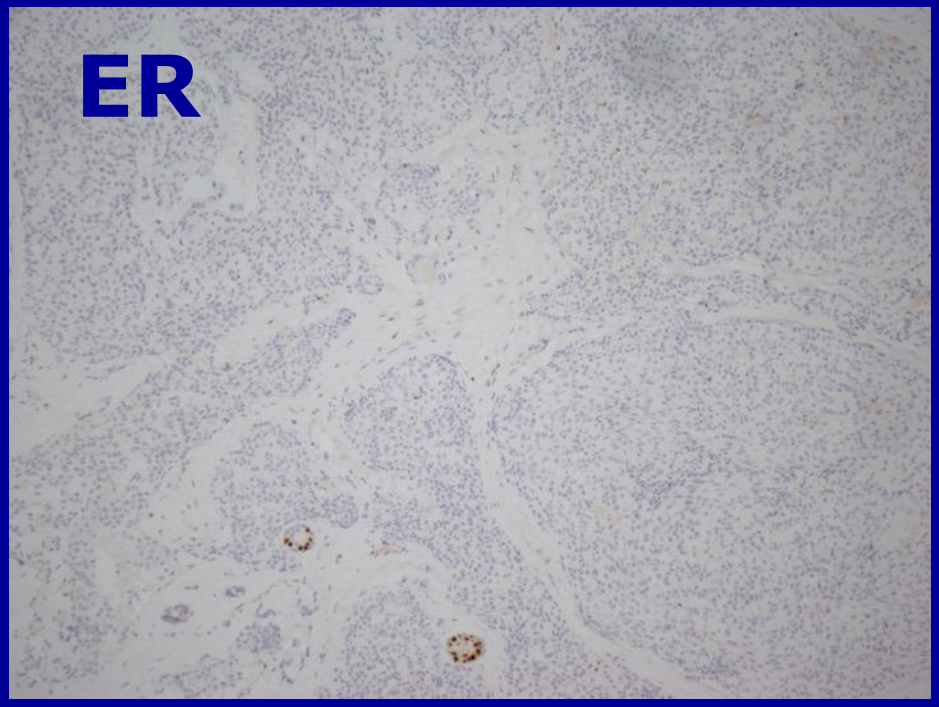






Differential

- Papillary breast carcinoma
- Neuroendocrine carcinoma breast
- Sclerosing lesion with UEH/DCIS
- Adenomyoepithelioma
- Invasive breast carcinoma
- Metastatic NEC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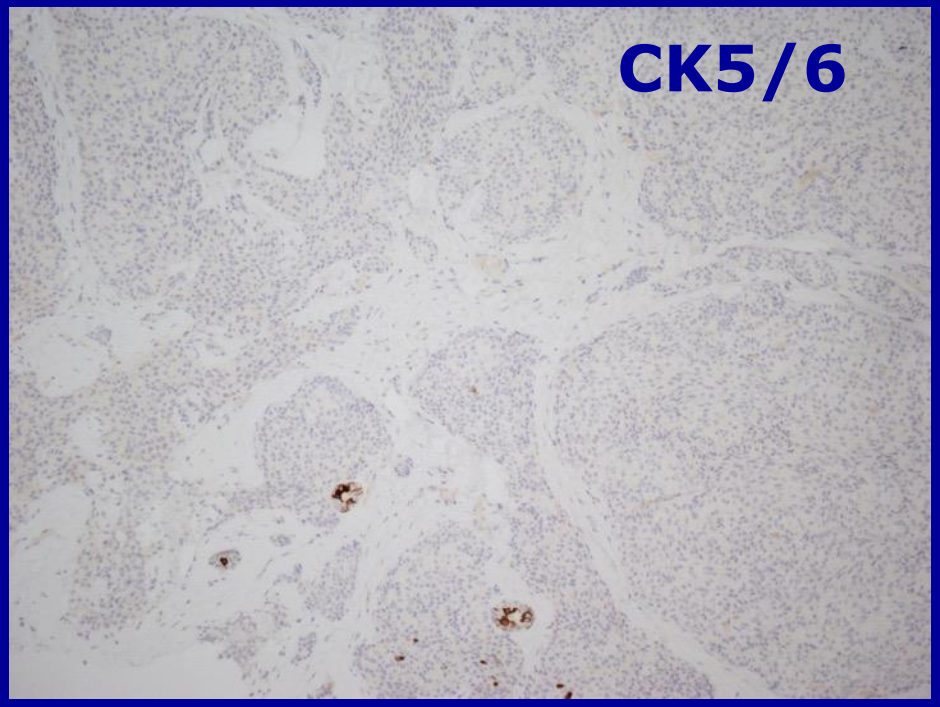
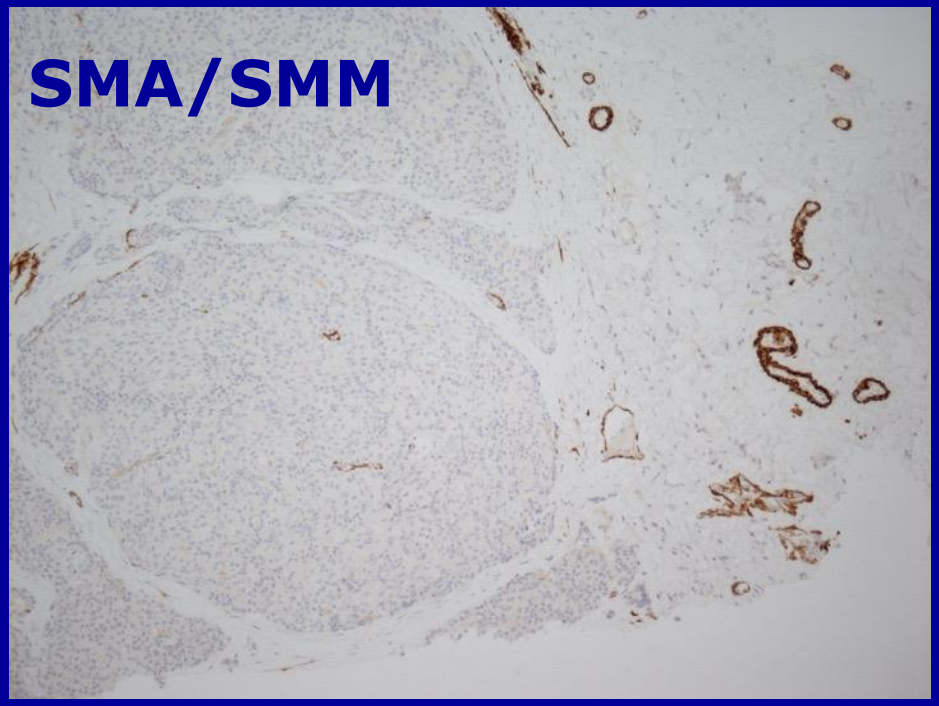
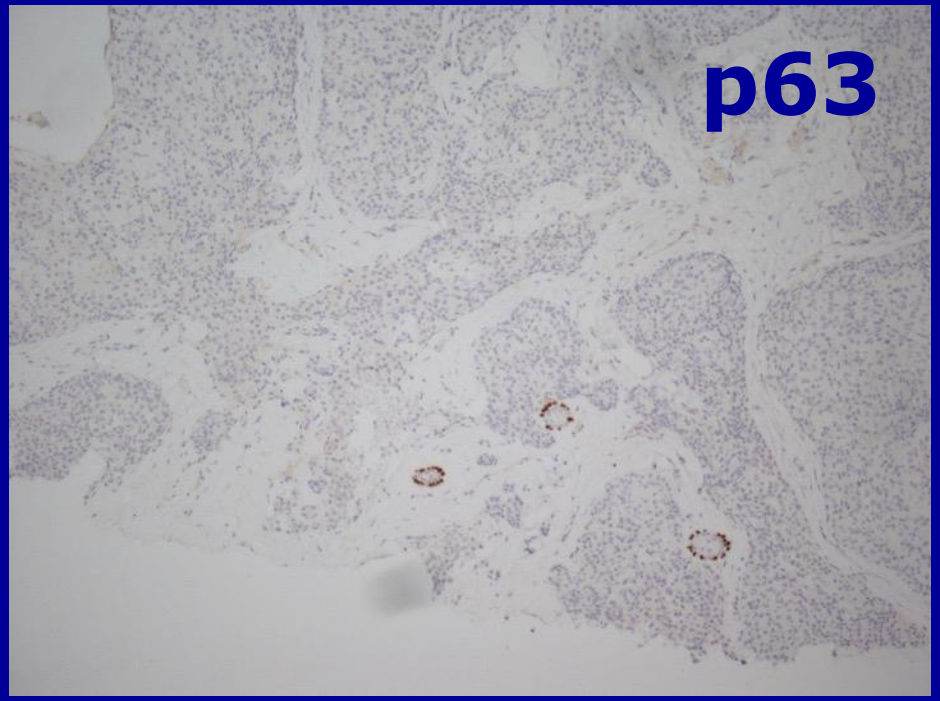

CK5/6


SMA/SMM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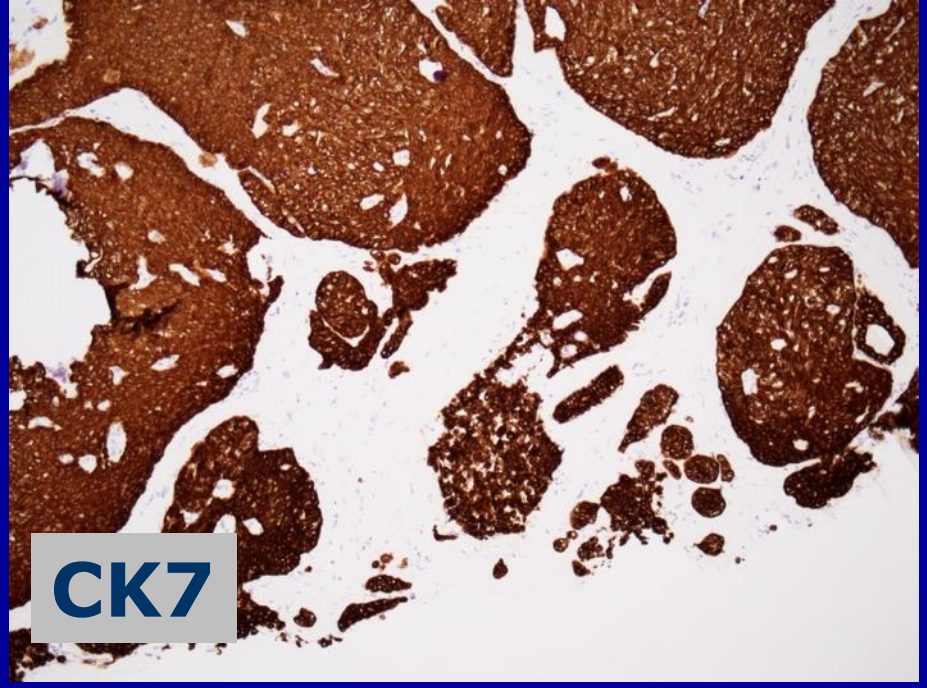
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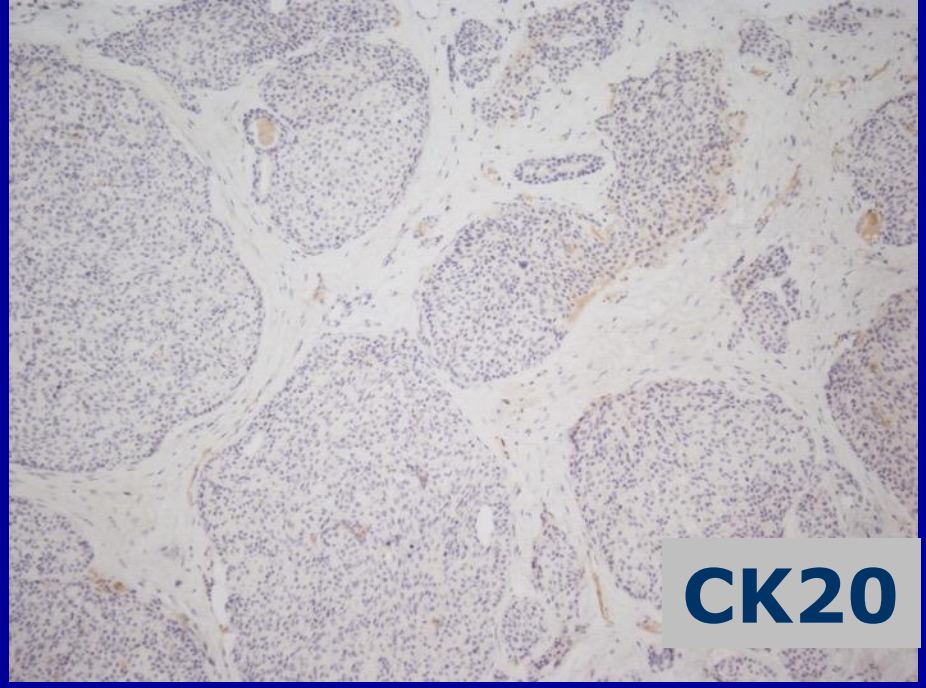
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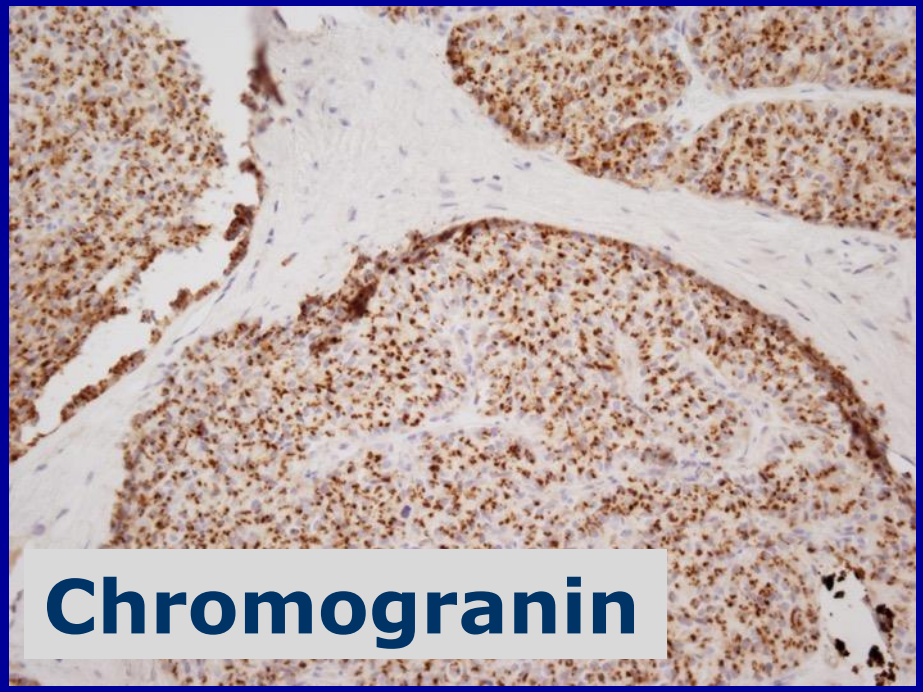
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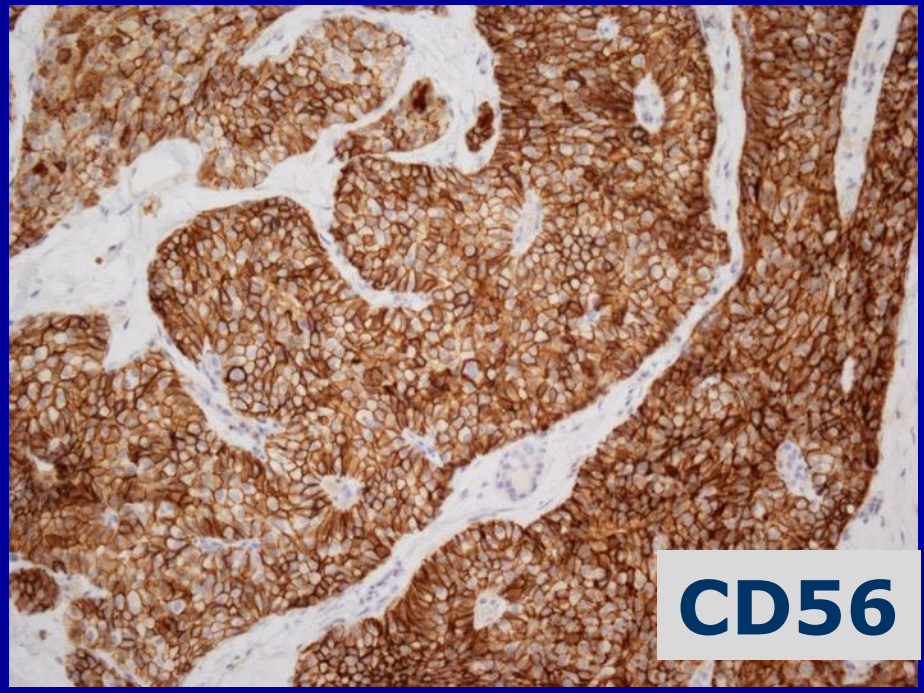
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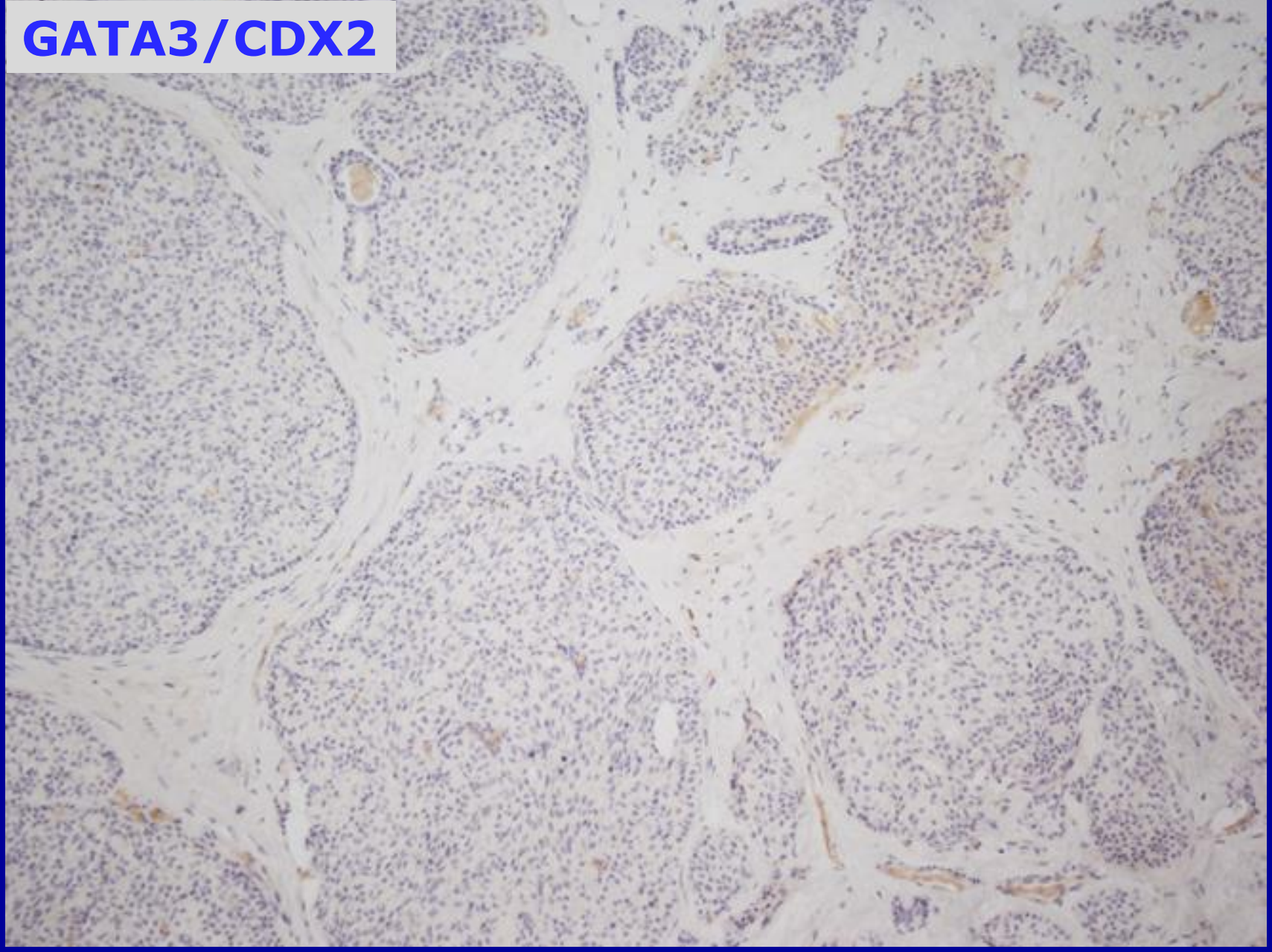
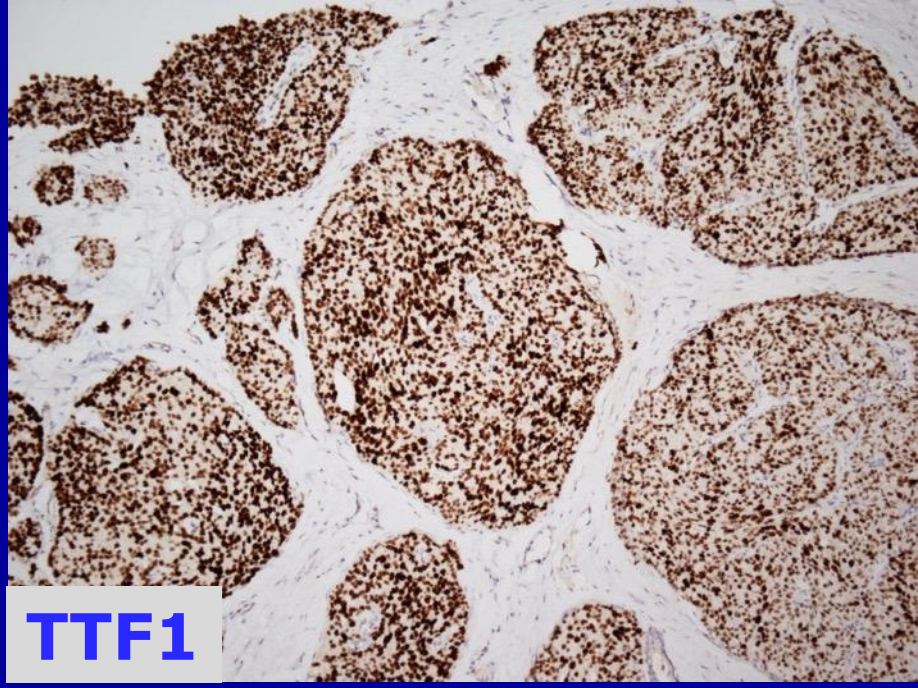


Diagnosis?

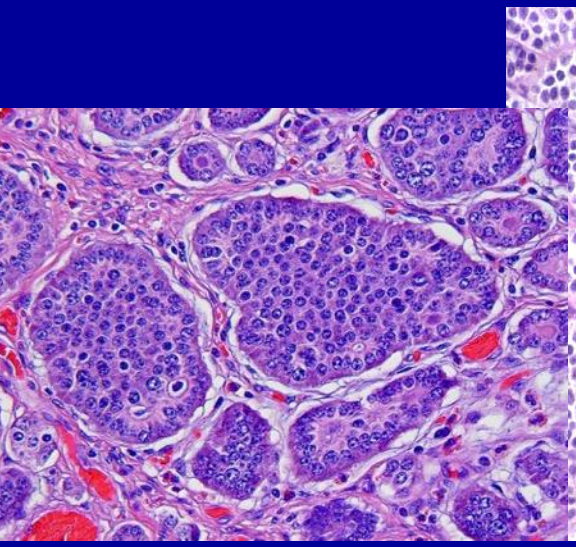


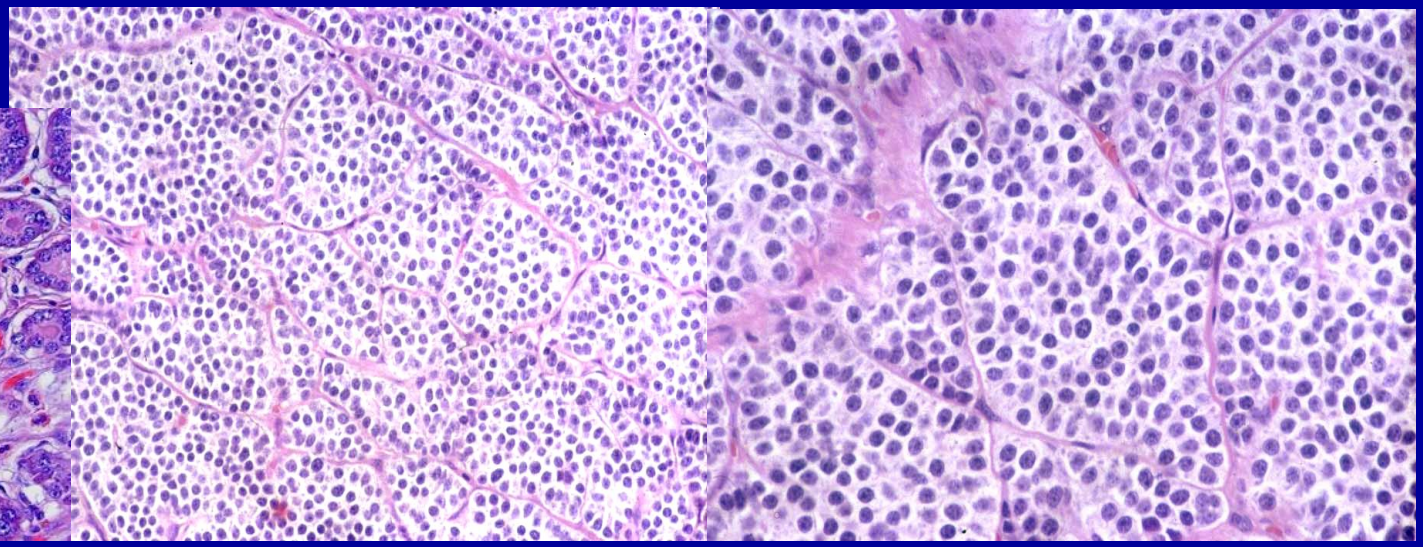
Metastatic Medullary Thyroid Carcinoma

Carcinoids

Unlike small cell carcinoma, primary carcinoid tumour of the breast was mainly reported as isolated case reports in 1970s and 1980s but current evidence indicate that almost all cases of typical carcinoid tumours in the breast are metastatic (Perry et al 2011).

This was not emphasised clearly in the WHO book





*** If in doubt and in cases with overlapping features between BC and carcinoid (metastatic):**

*** NET of the breast & SPC typically shows strong diffuse ER+ while carcinoid if positive it will be weak and focal.**

*** SPC may show focal ME cells (*in situ)* components**

*** Plus positivity of CK7, GCDFP-15 and GATA3 and negativity of CDX2 and TTF1 confirms SPC diagnosis**

** Site of origin*

Presence of DCIS, ER expression, axillary node metastasis, and lack of a history of an extramammary primary NE neoplasm can support that a breast NEN is primary in that location.

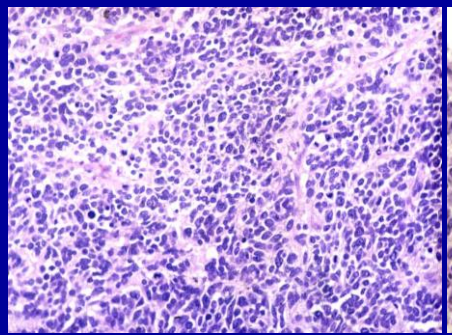
* In 5th edition of the WHO book

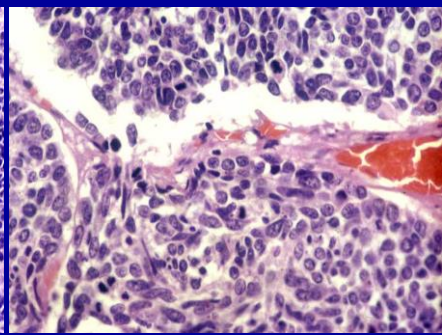
• **Neuroendocrine carcinoma (NEC): defined as: An invasive carcinoma characterized by high grade neuroendocrine morphology (small cell or large cell) supported by the presence of neurosecretory granules and a diffuse, uniform immunoreactivity with neuroendocrine markers.**

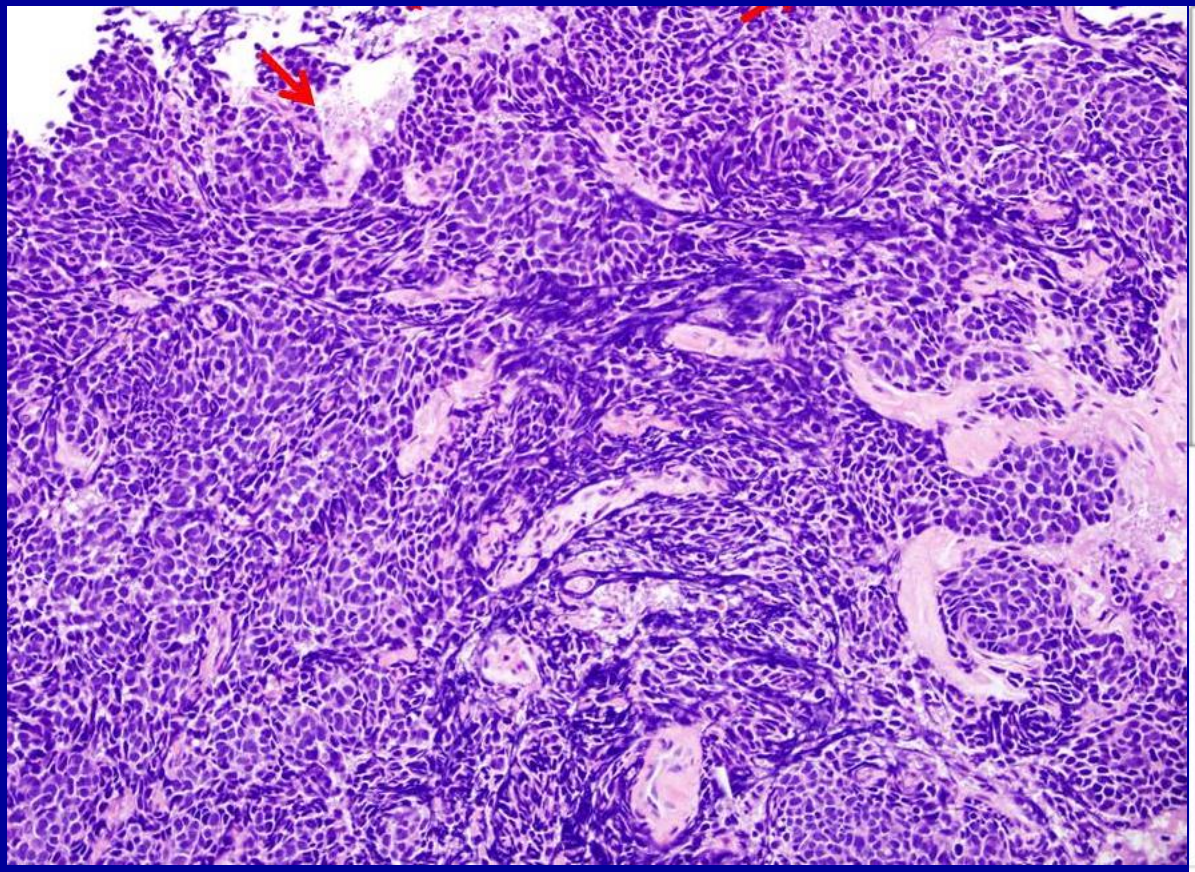
• NECs are morphologically indistinguishable from their counterpart in the lung on the basis of histological and immunohistochemical features

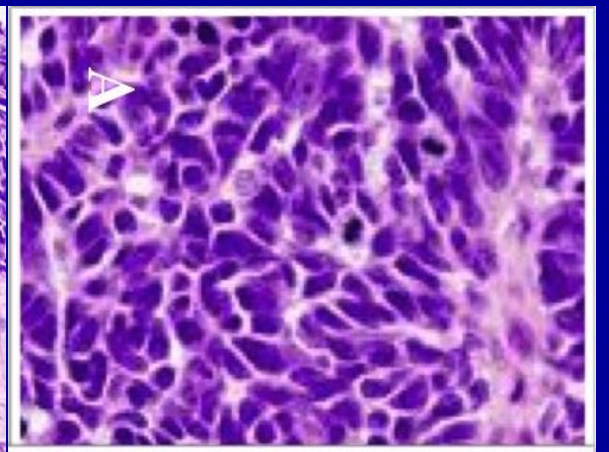
• Breast SCC may show DCIS, NST component ~(70%), ER expression

• DD from other breast high grade basaloid tumors such as solid high grade ACC, and basal-like carcinoma





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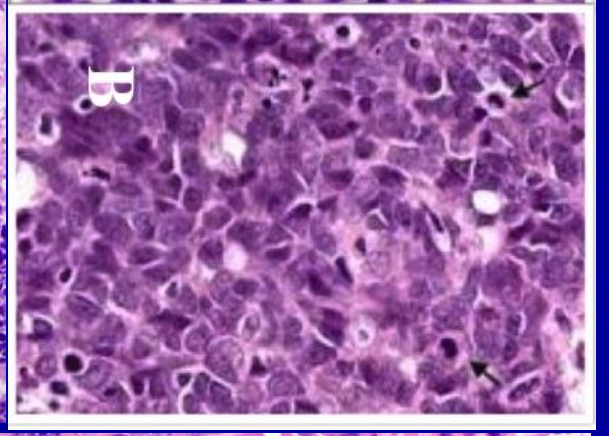
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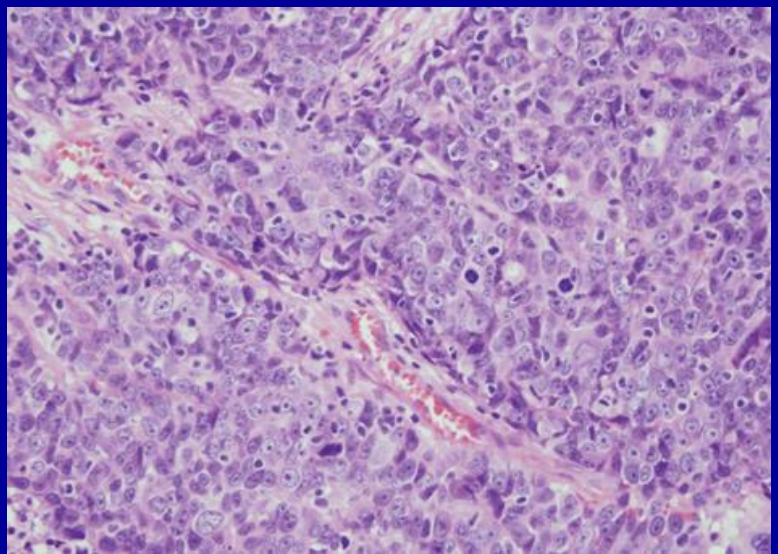

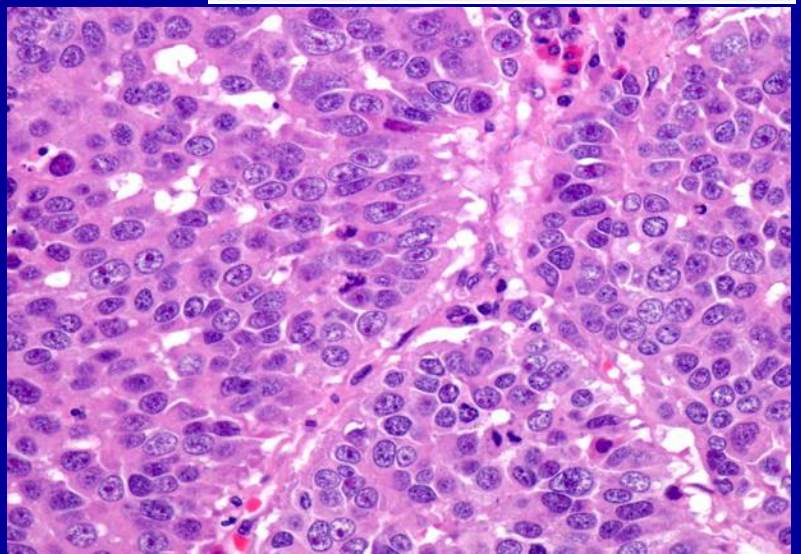

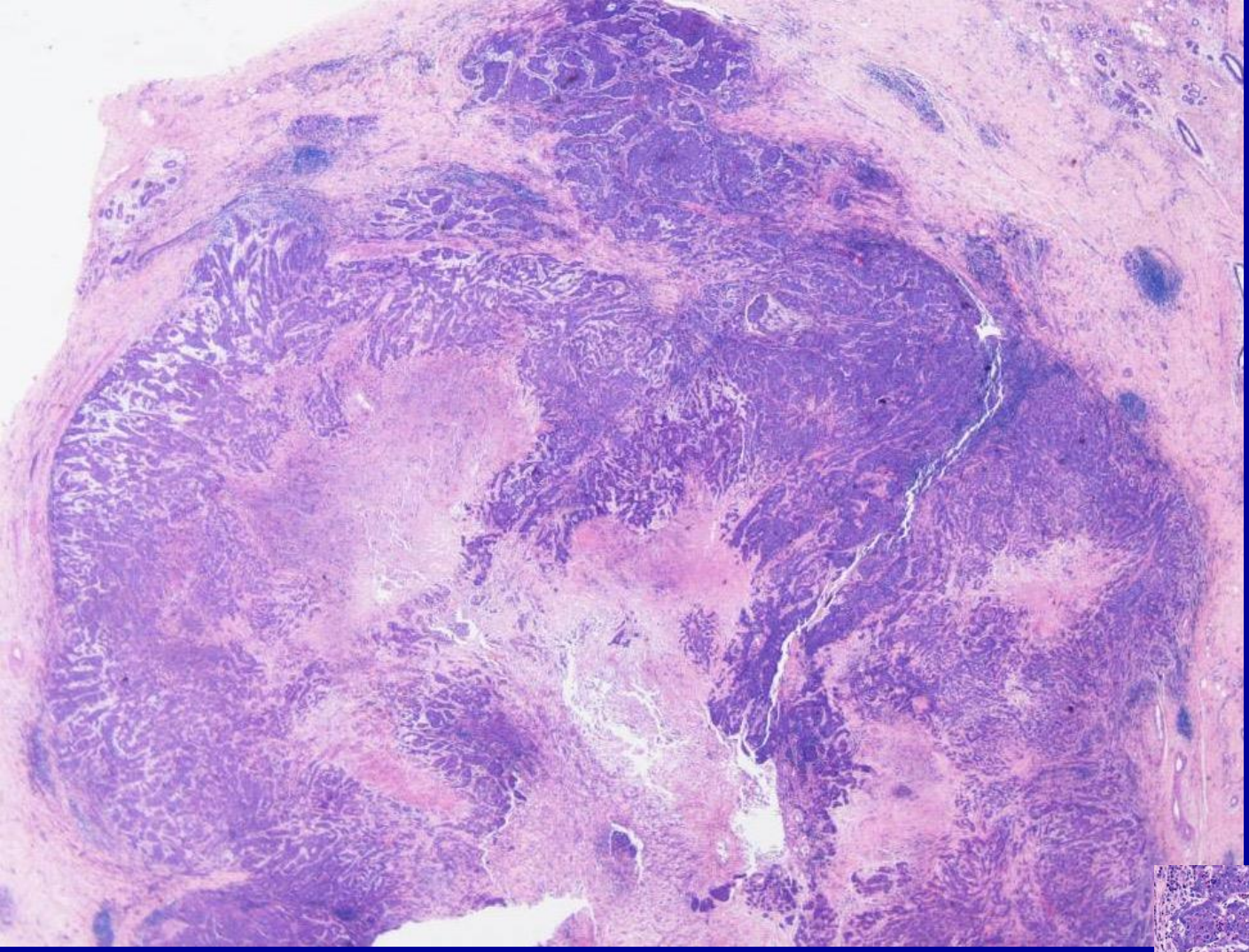

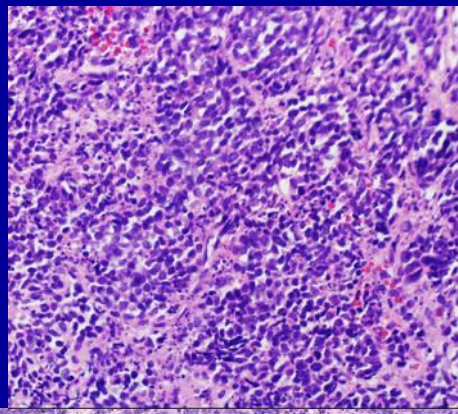

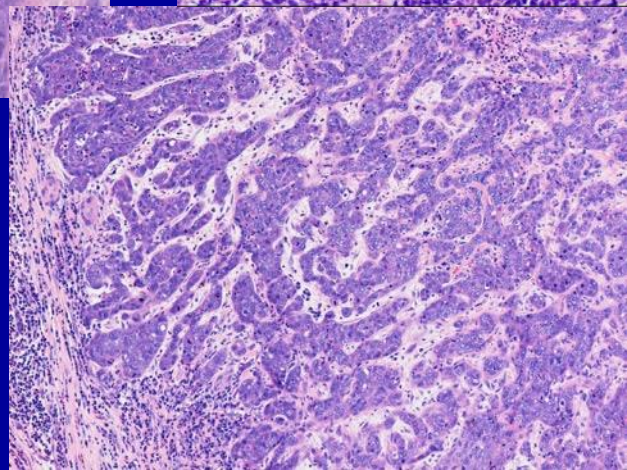

Basal-like carcinoma

In the large population-based study from SEER, patients with NE BC showed a shorter overall survival and disease-specific survival compared with BC not otherwise specified at the same stage

In another SEER study of 199 SCC of the breast, 42% were localised and only 19% had DM. SCC of the breast showed a more favourable prognosis by stage than SCC of the lung

No standard treatment options for low and intermediate grade NET although there is weak evidence of response of SCC to platinum salts (data from retrospective series and isolated case reports).

- **Most studies of primary NE BC showed no clinical or imaging features distinct from other types of BC.**

- **GEP analysis indicates that NE BC belongs to the luminal B subtype**

- **Morphological and IHC overlap between NE BC and other primary breast carcinomas (invasive SPC Vs NE BC, and SCC Vs basal-like BC** (Ersahin et al 2009).

*** Most important DD is to excluded metastasis.**

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