Papillary Breast Lesions Insights from WHO

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Review of **240 cases** identified over- and under-diagnosis in **13 cases** (5% of all cases); of these **9 were papillary lesions.**

Histopathology

Histopathology 2017, 70, 632–642. DOI: 10.1111/his.13117

Diagnostic concordance of breast pathologists: lessons from the National Health Service Breast Screening Programme Pathology External Quality Assurance Scheme

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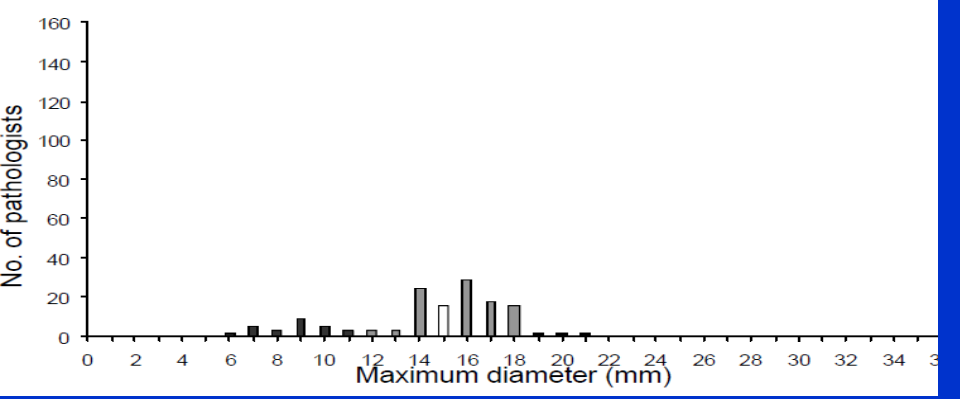
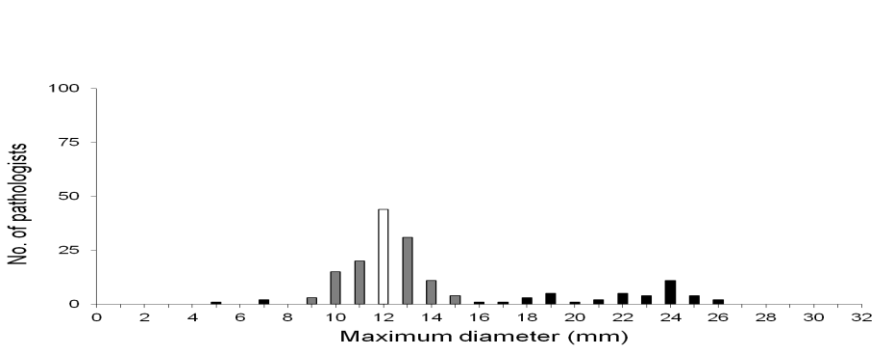
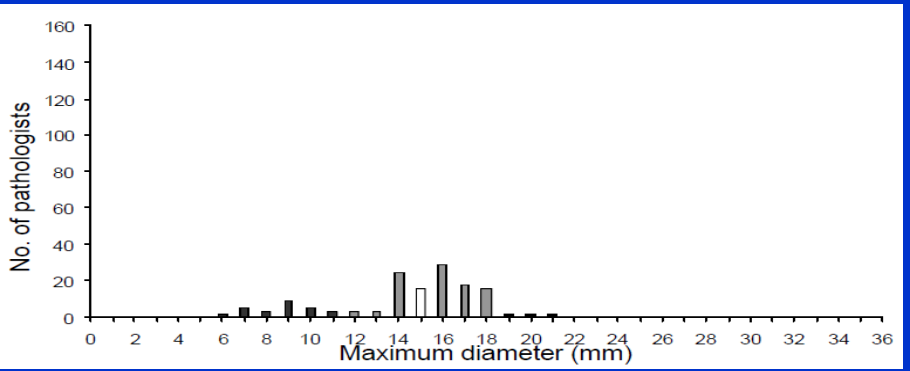
The diagnostic category distribution and number of papillary carcinomas

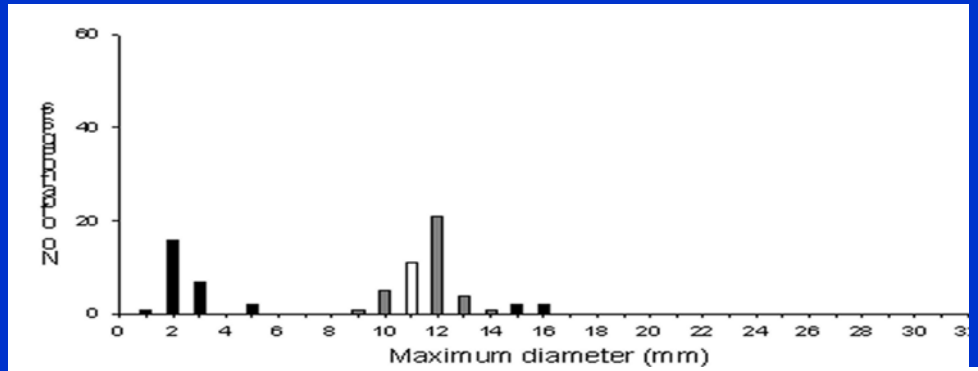
	Year	Final diagnosis (Size in mm)	Benign / atypical	Malignant			Total No of readers
				In-situ	Invasive	Total	
1	2007	Encapsulated PC	45 (8%)	355 (65%)	147 (27%)	502 (92)	547
2	2010	Encapsulated PC	54 (8%)	452 (70%)	145 (22%)	597 (92%)	651
3	2008	Solid PC with features of invasion	32 (6%)	107 (19%)	425 (75%)	532 (94%)	564
4	2009	Solid PC with some features of invasion	30 (5%)	107 (18%)	466 (77%)	573 (95%)	603
5	2011	Papillary DCIS	59 (12%)	384 (77%)	56 (11%)	440 (88%)	499
6	2011	Pure Invasive PC	7 (1%)	186 (28%)	478 (71%)	664 (99%)	671

Rakha et al Histopathology. 2016, 69(5):862-870









Histopathology

Histopathology 2016, **69**, 862–870. DOI: 10.1111/his.13009

Papillary carcinoma of the breast: diagnostic agreement and management implications

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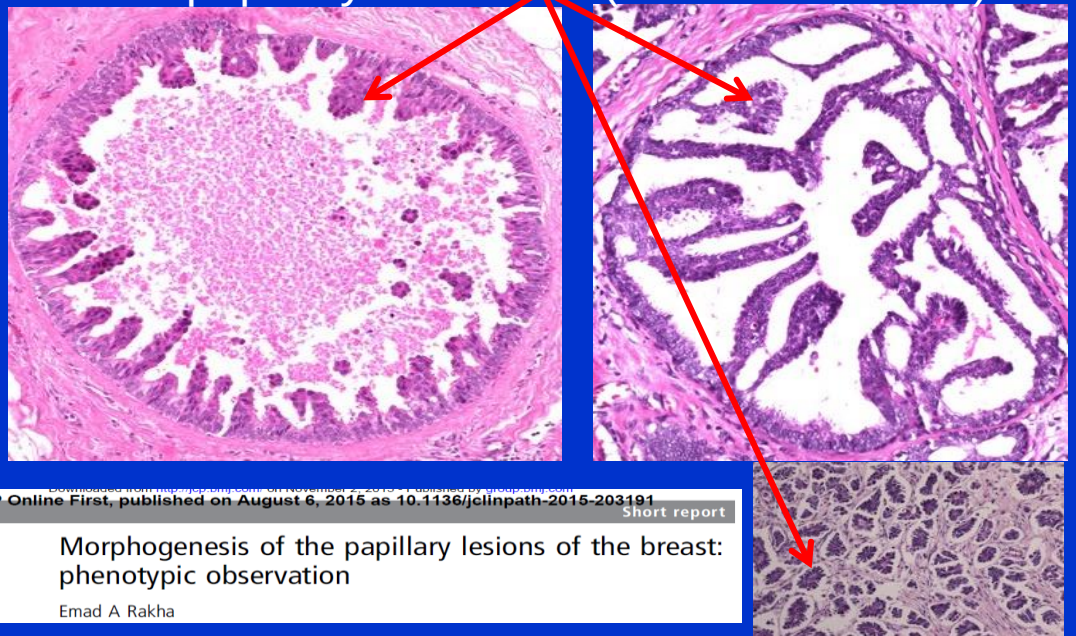
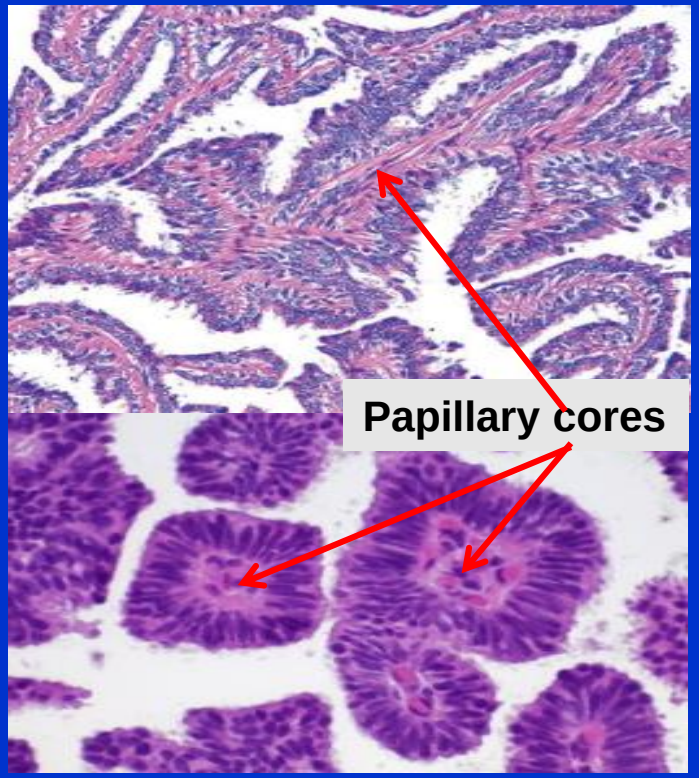
Papillary lesions of the breast are a heterogeneous group of disease, which are characterised by neoplastic epithelial proliferation supported by fibrovascular stalks

Micropapillary structures (no stromal cores)





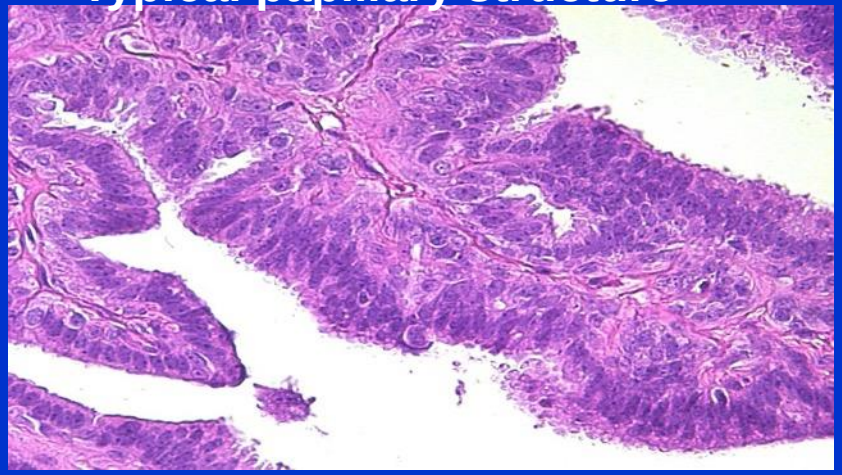
JCP Online First, published on August 6, 2015 as 10.1136/jclinpath-2015-203191

Short report

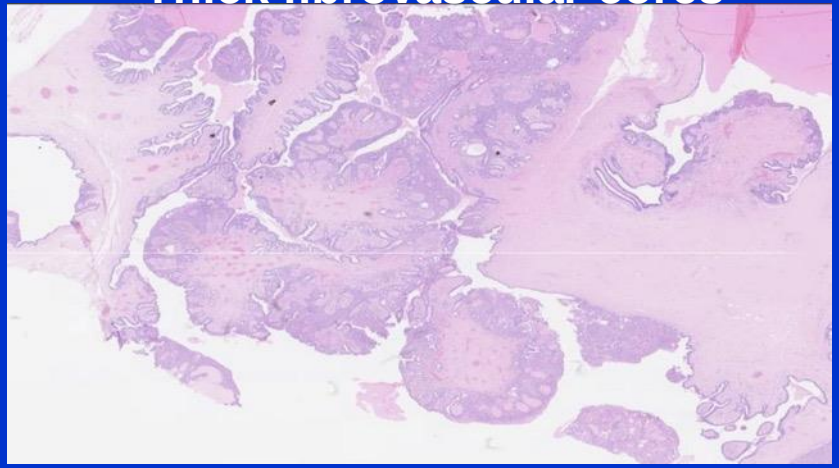
Morphogenesis of the papillary lesions of the breast: phenotypic observation

Emad A Rakha

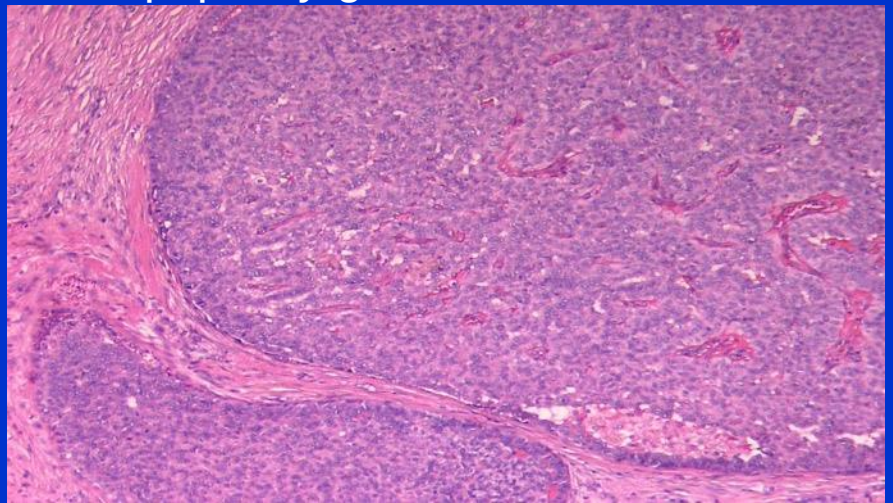
Typical papillary structure

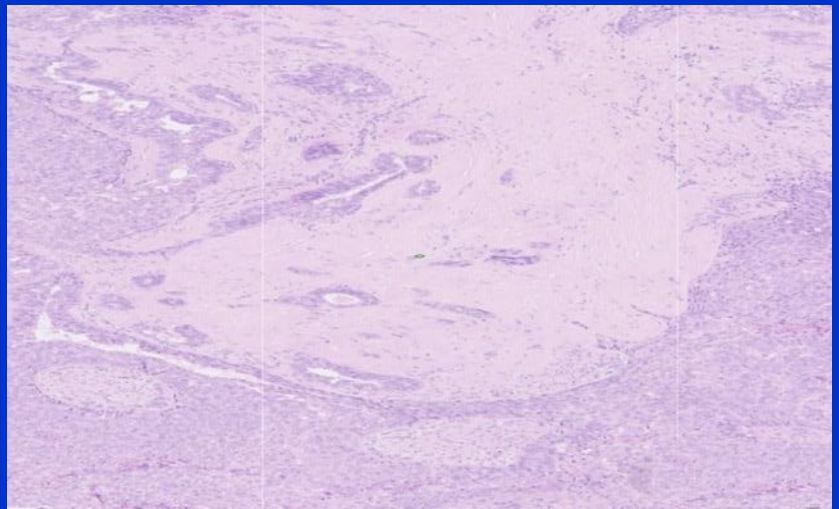


Thick fibrovascular cores

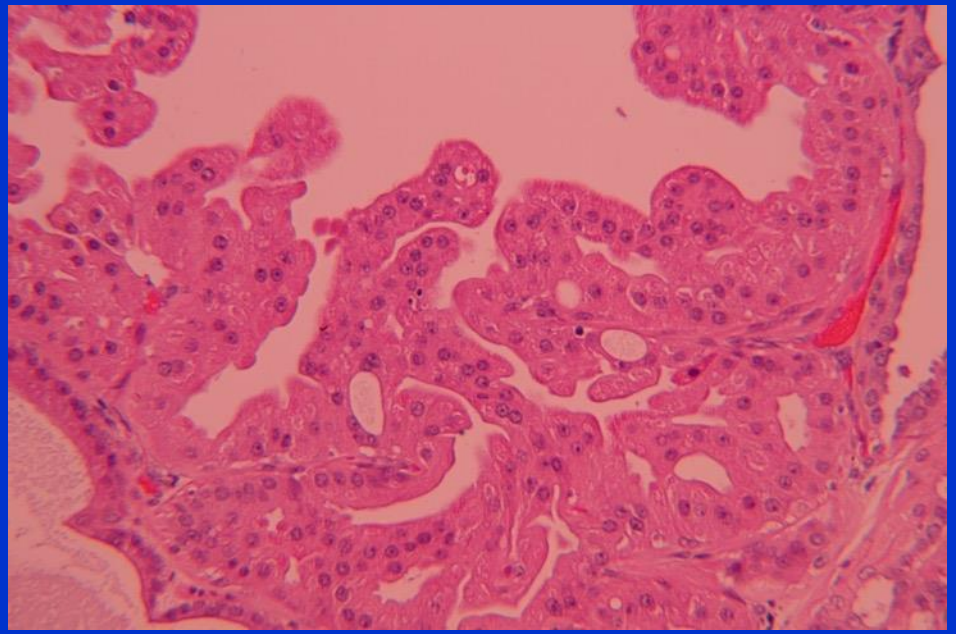


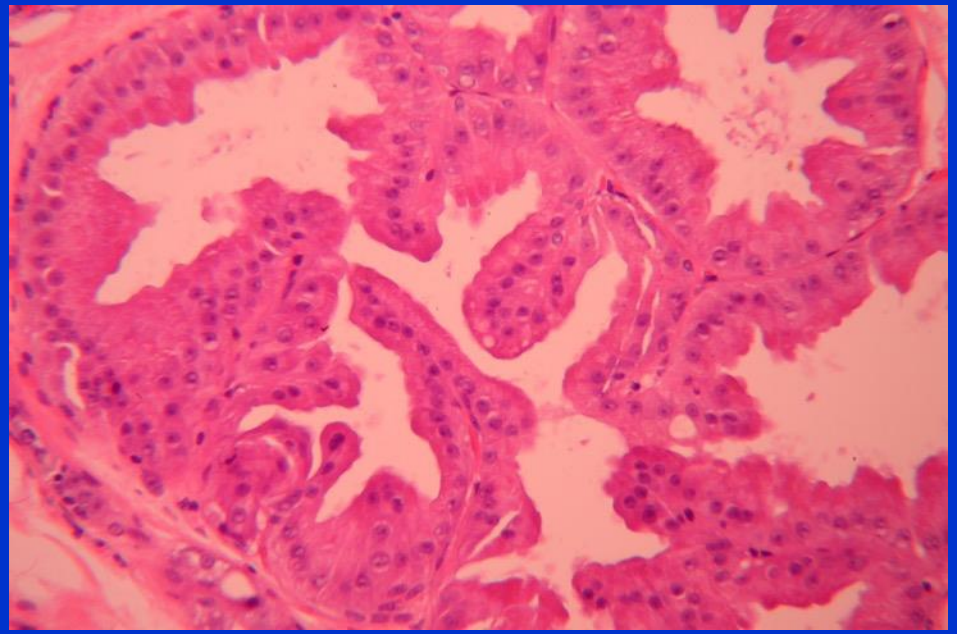
Solid papillary growth with indiscernible cores

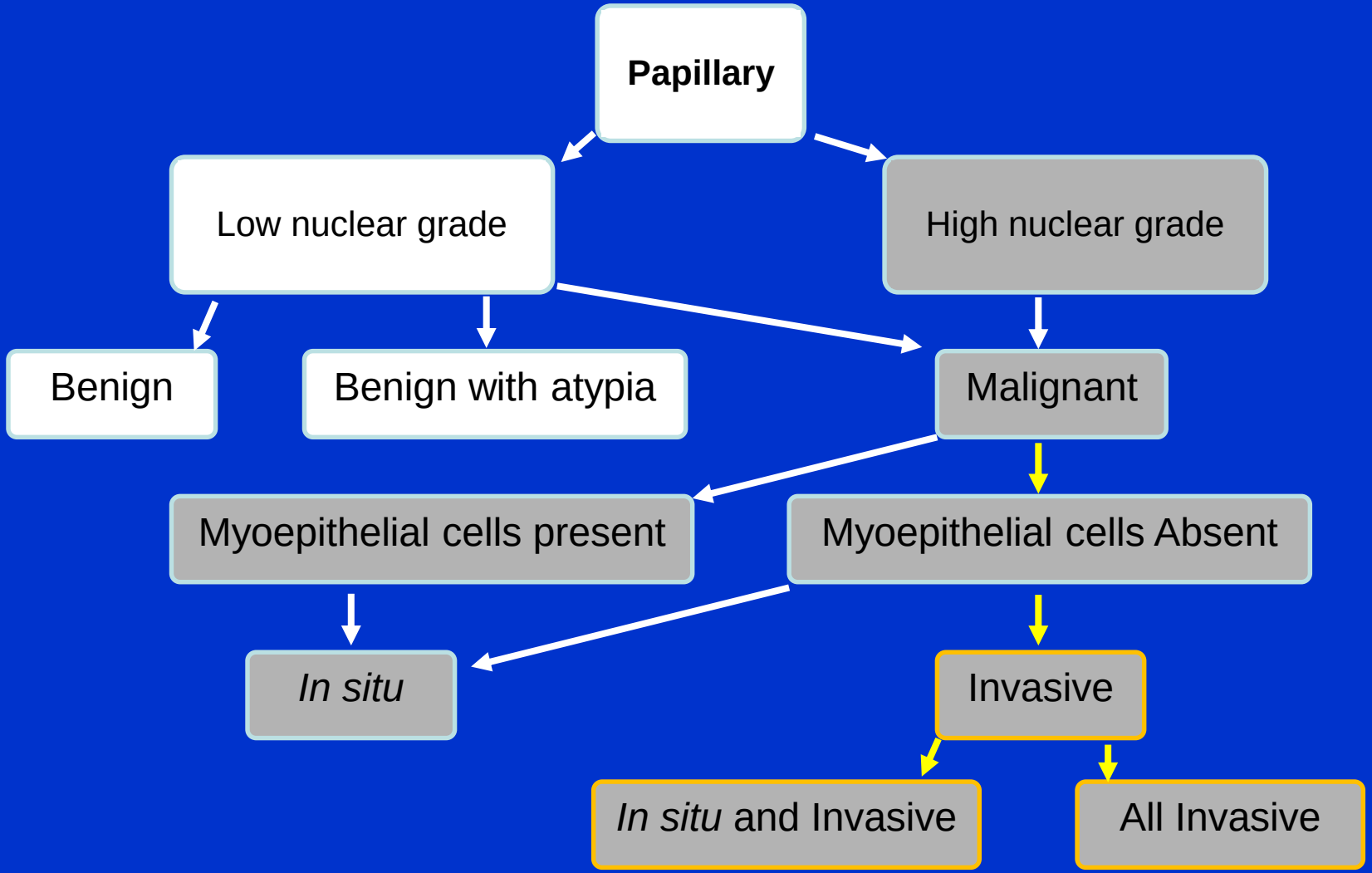




Papillary apocrine hyperplasia





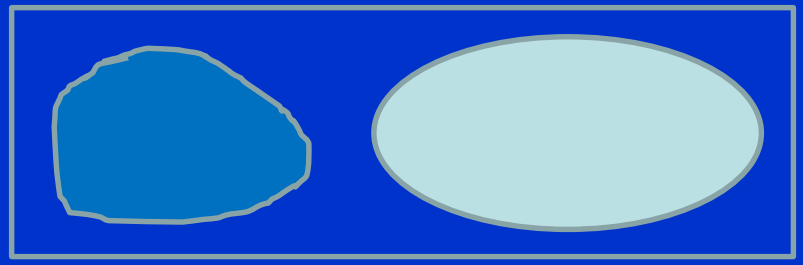

Papillary
Low nuclear grade
High nuclear grade
Benign
Benign with atypia
Malignant
Myoepithelial cells present
Myoepithelial cells Absent
In situ
Invasive
In situ and Invasive
All Invasive

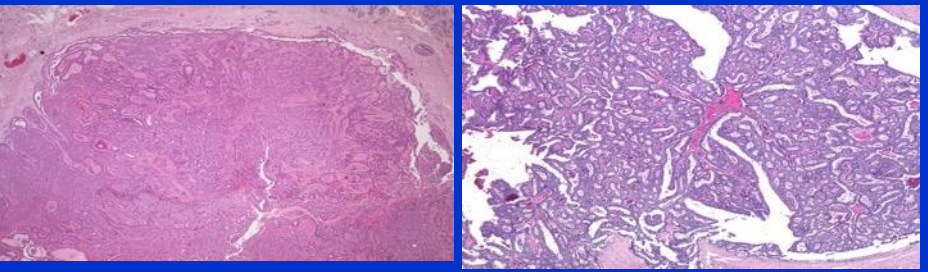
Classification

1- Location and number of involved ducts

Large ducts

Intraductal papilloma | **Papillary carcinoma**

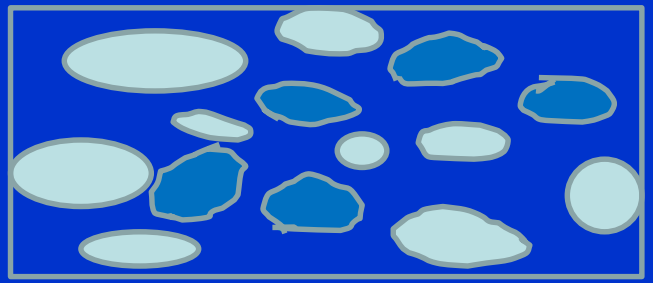


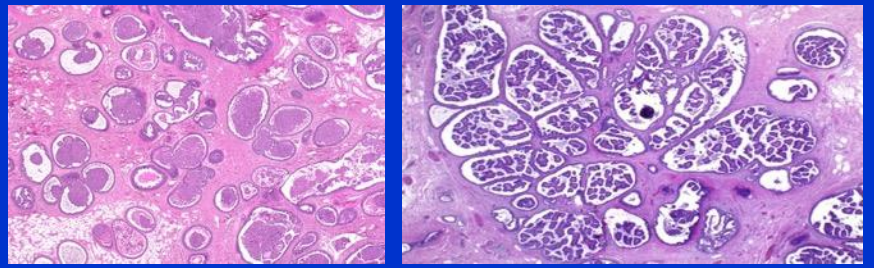


**Invasive papillary carcinoma*

Small ducts

Multiple papillomas | **Papillary DCIS**



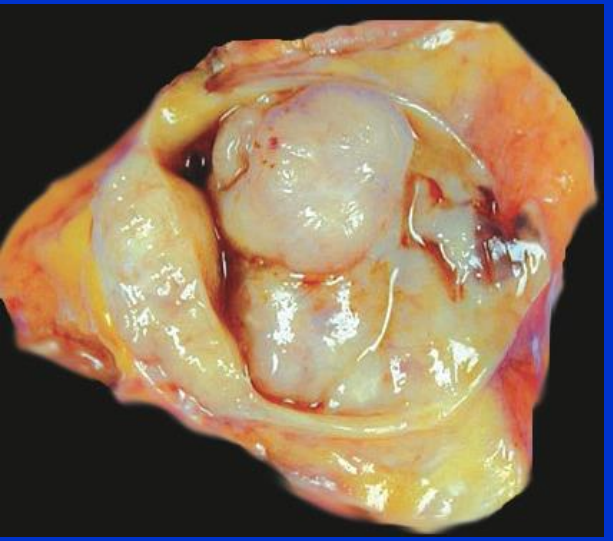


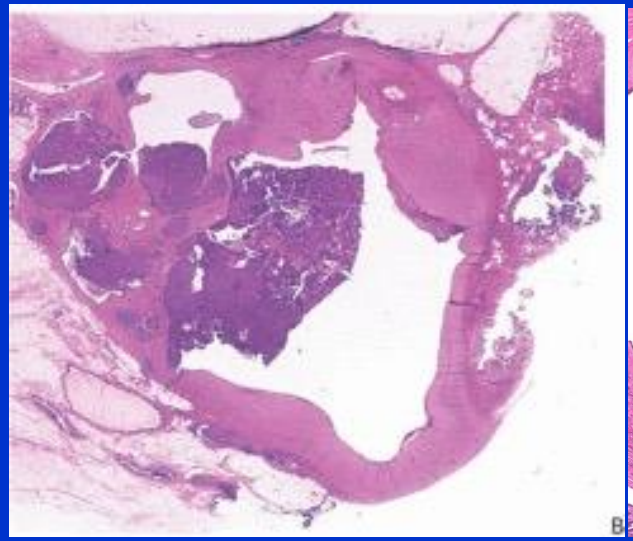
**Invasive papillary carcinoma*

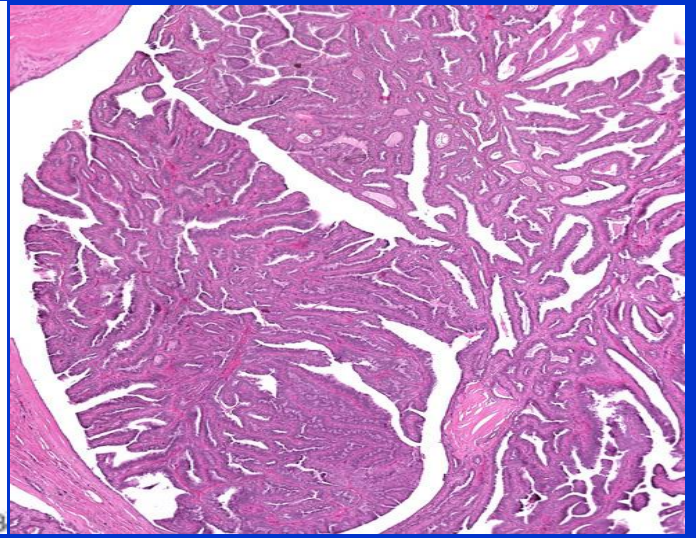
A-Large duct papilloma (Intraductal papilloma)

Usually Central, solitary; well-defined margin, cystic +/-solid areas.
usually present as a mass or nipple discharge

~ 5% of benign breast biopsies





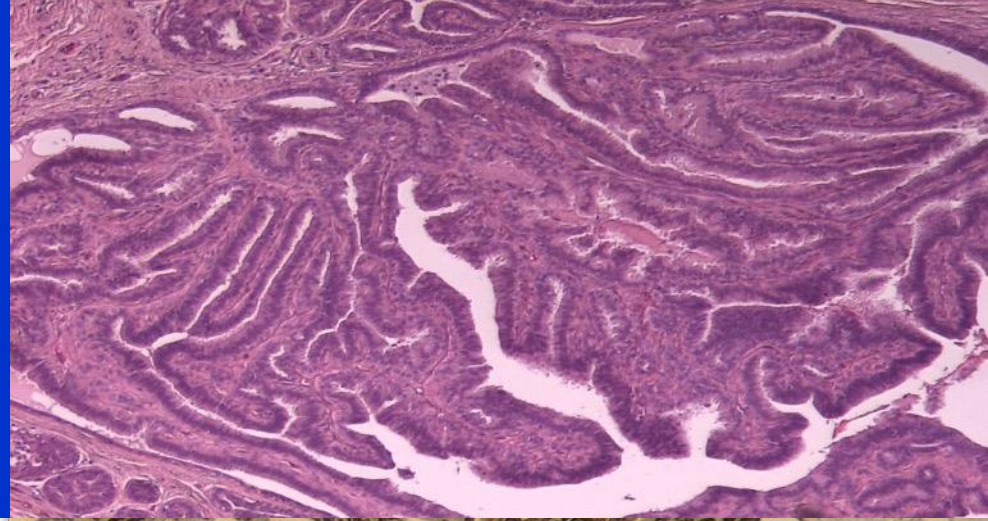


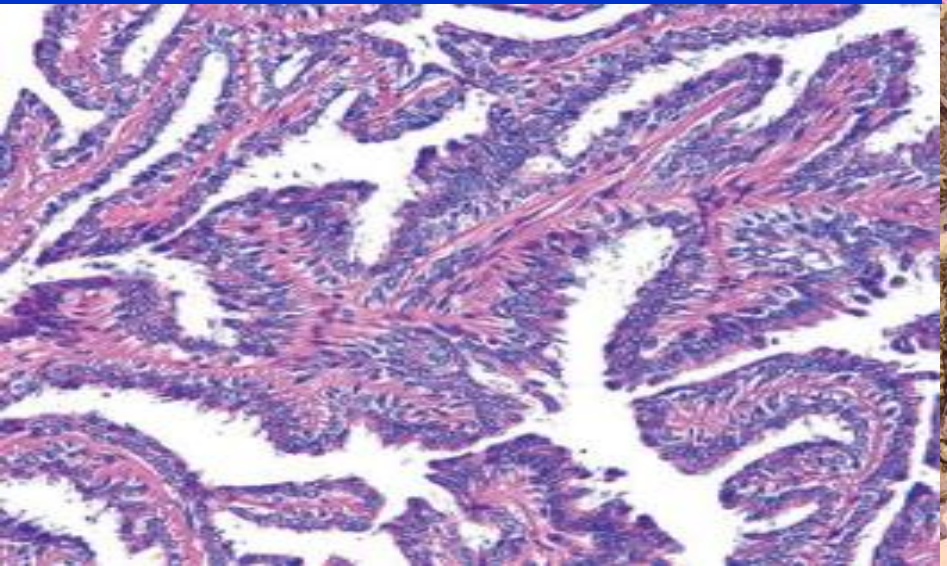
Well developed CT cores

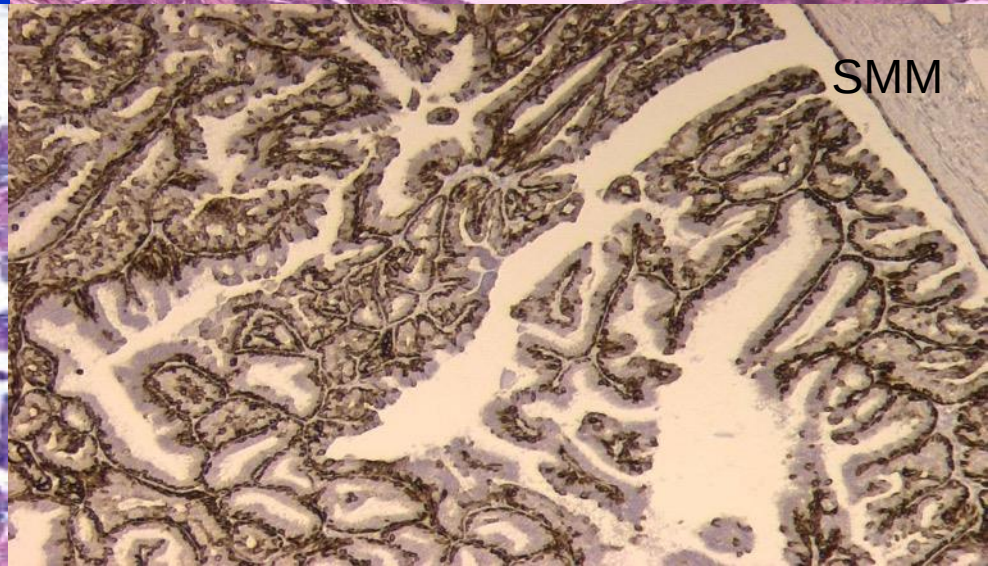
Myoepithelial cells throughout

Epithelial cell layer single or multiple but no atypia

Surrounding tissue is usually benign

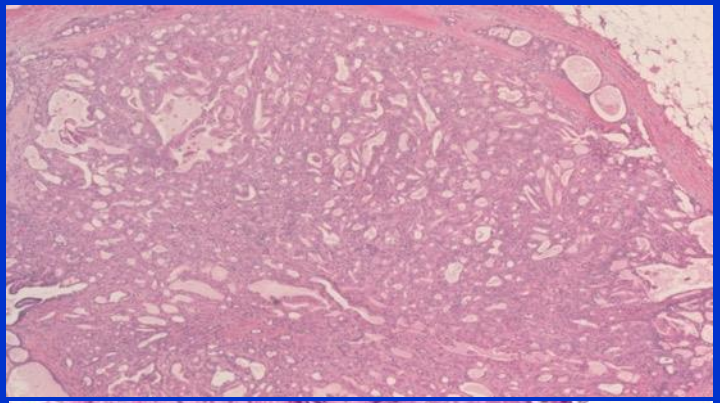


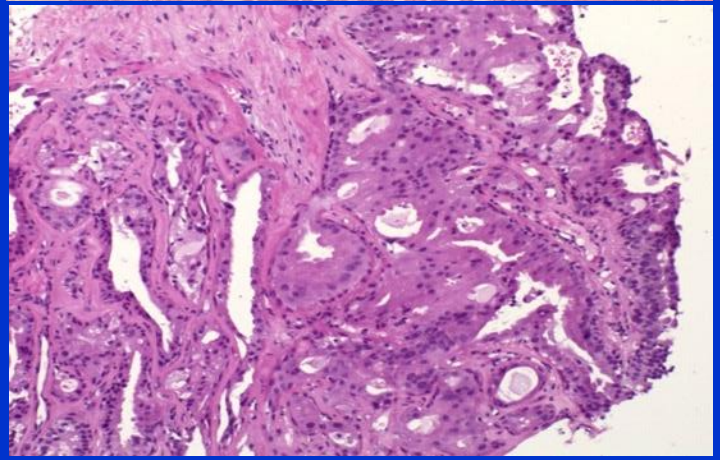


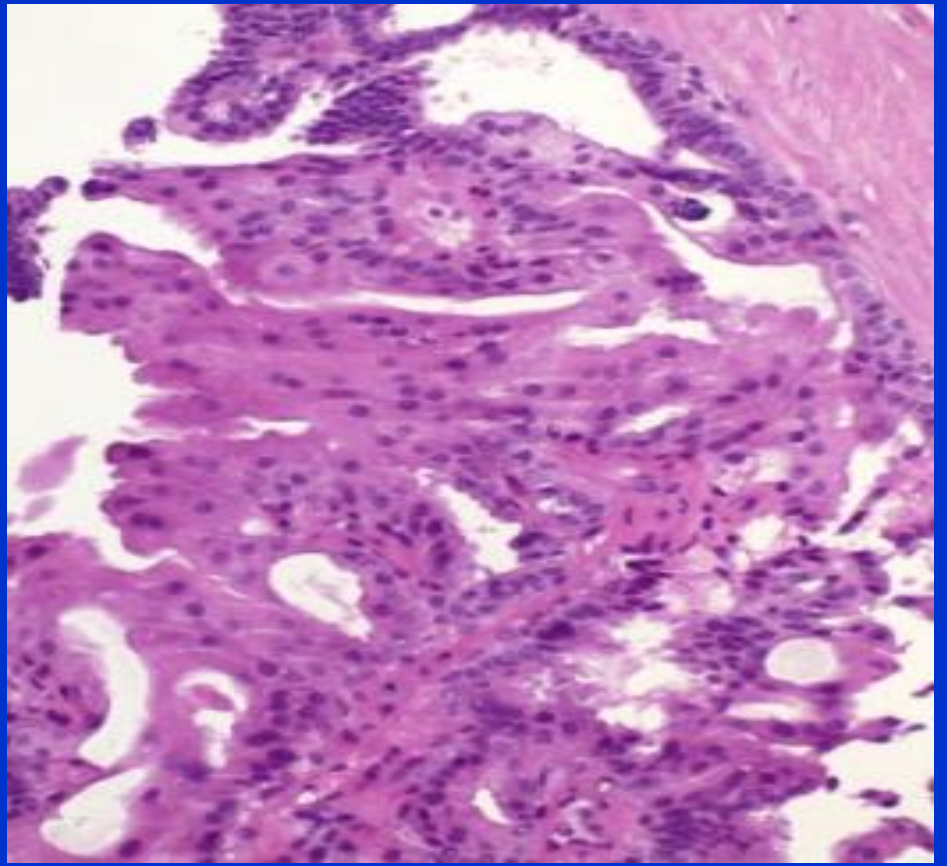


A-Large duct papilloma (Intraductal papilloma)

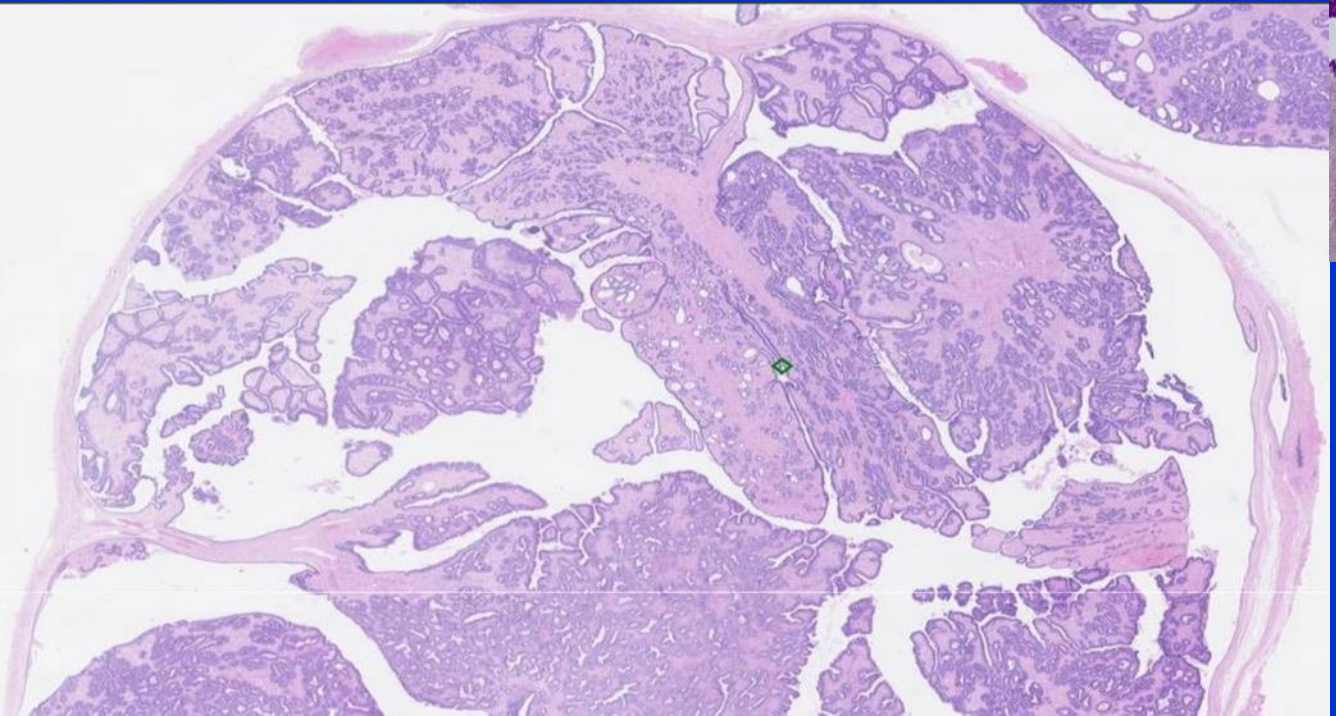
May show benign apocrine metaplasia (when present, it favours benign)

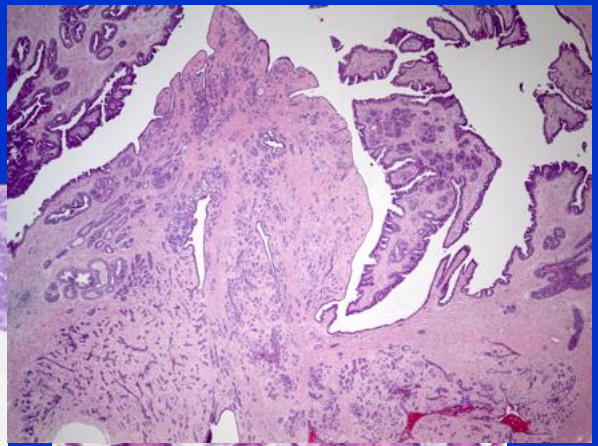


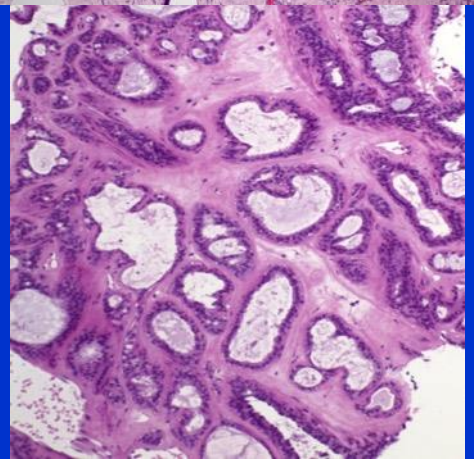




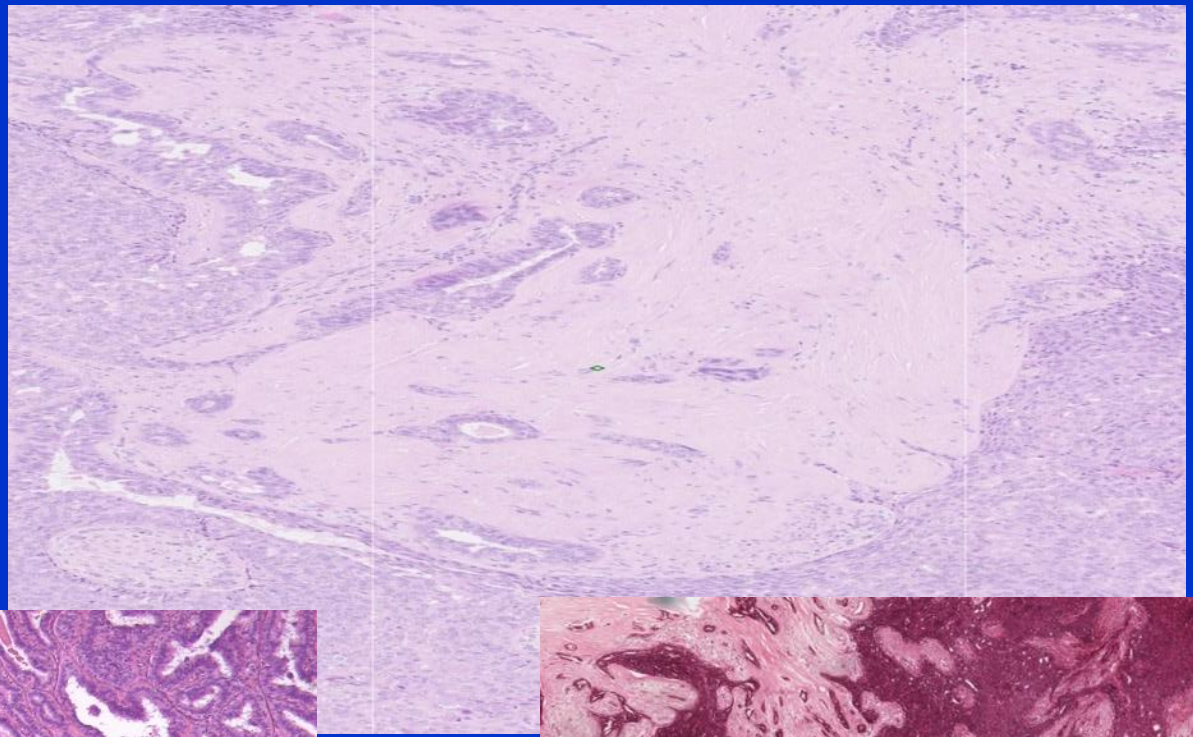
Papilloma may show florid adenotic and fibrotic pattern mimicking fibroepithelial lesion (FA)

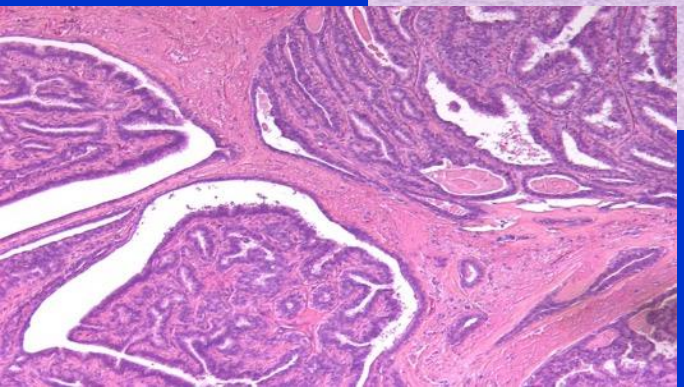


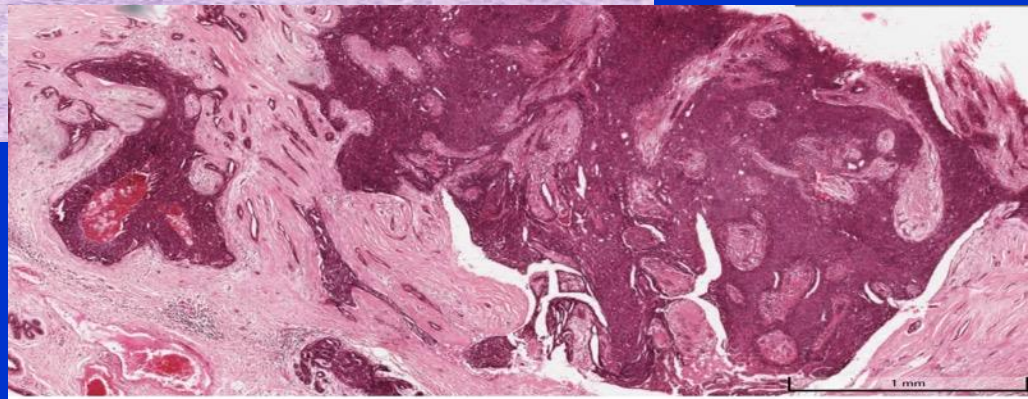


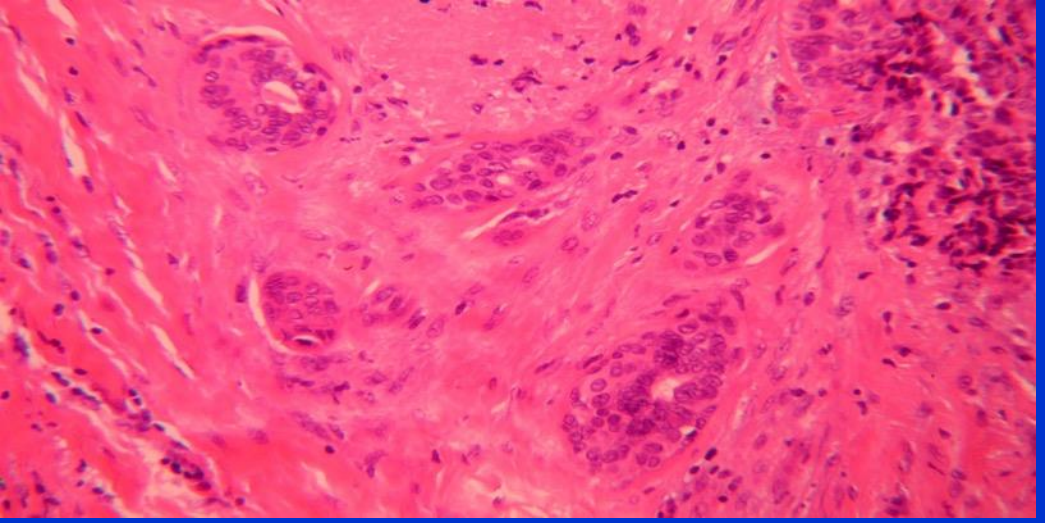


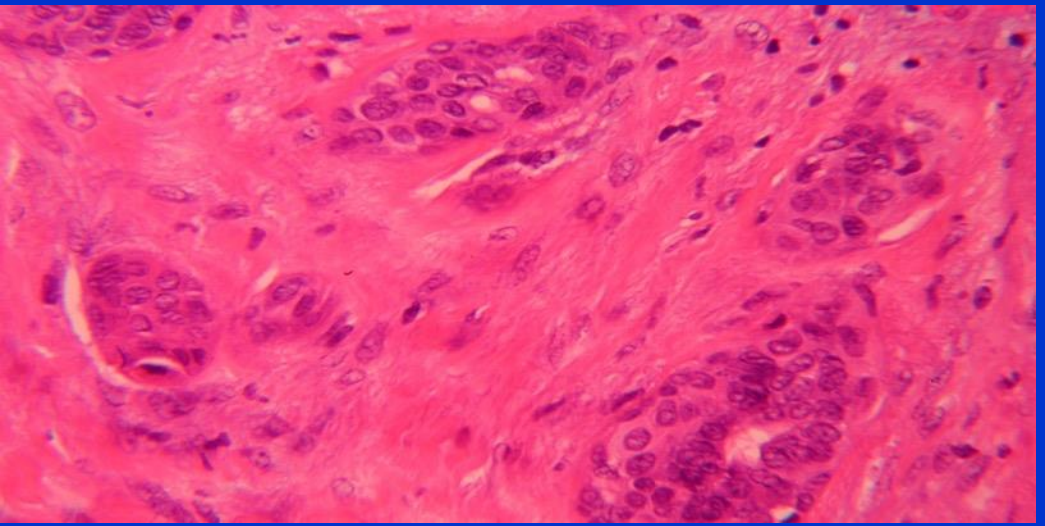
Fibrosis with entrapped glands and epithelium

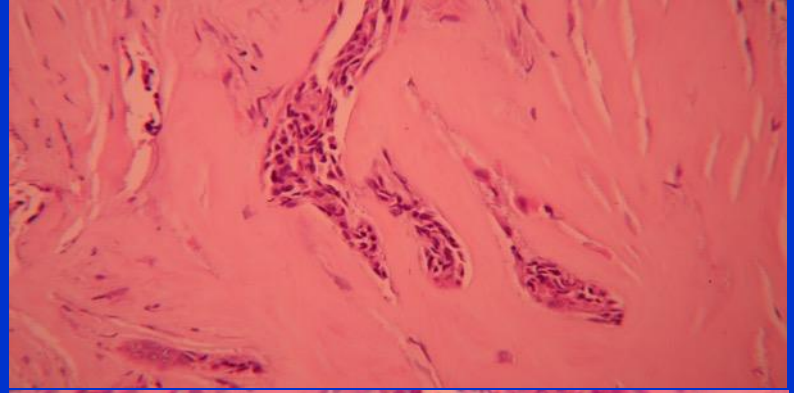


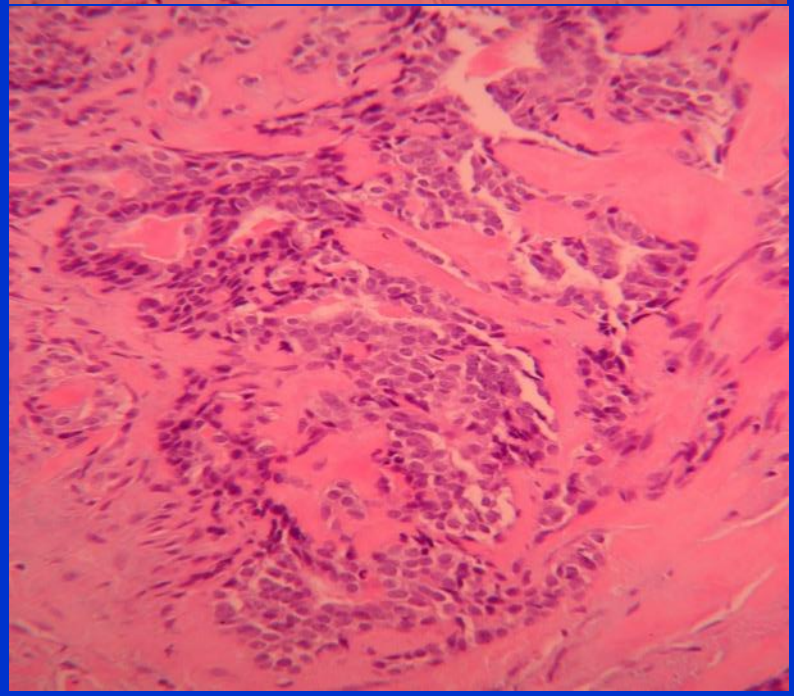




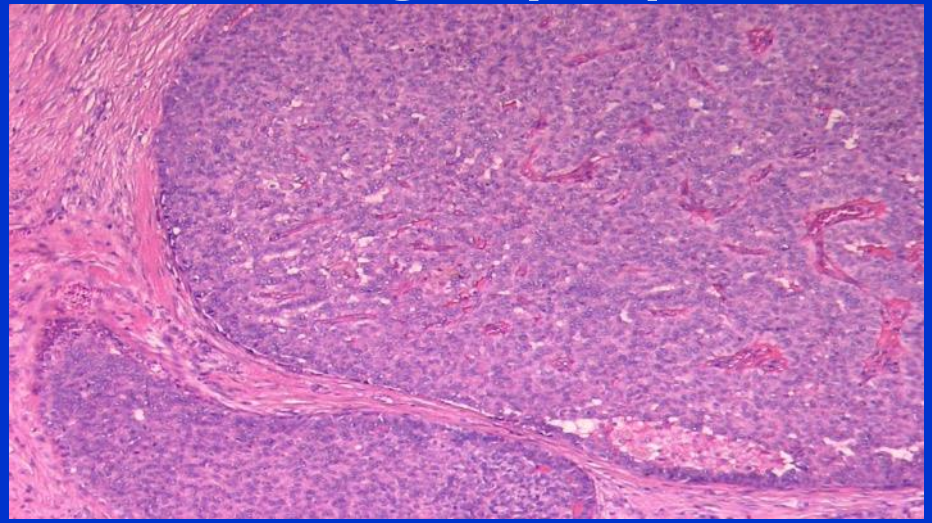


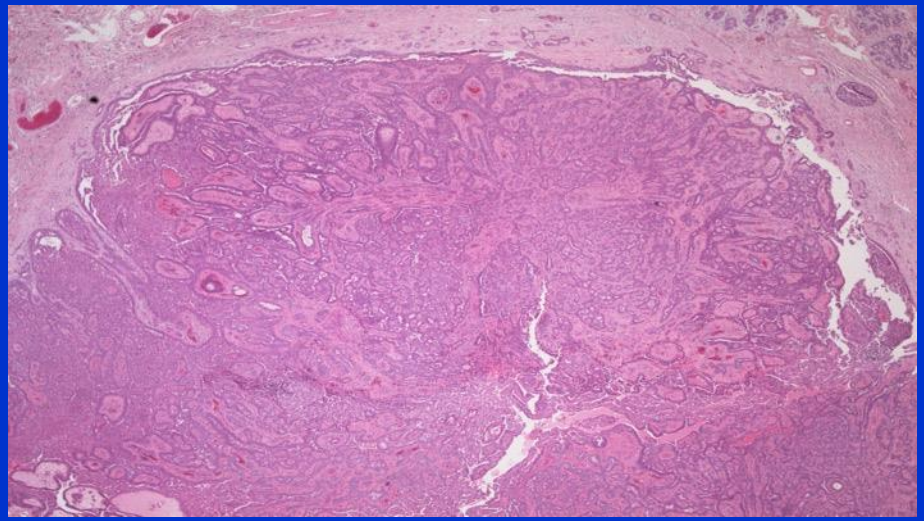


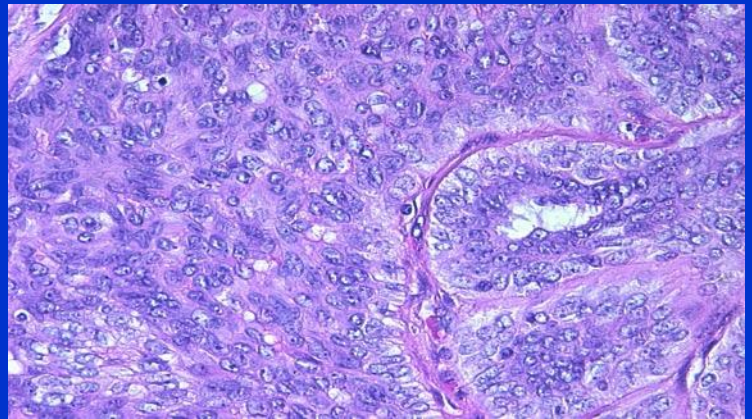


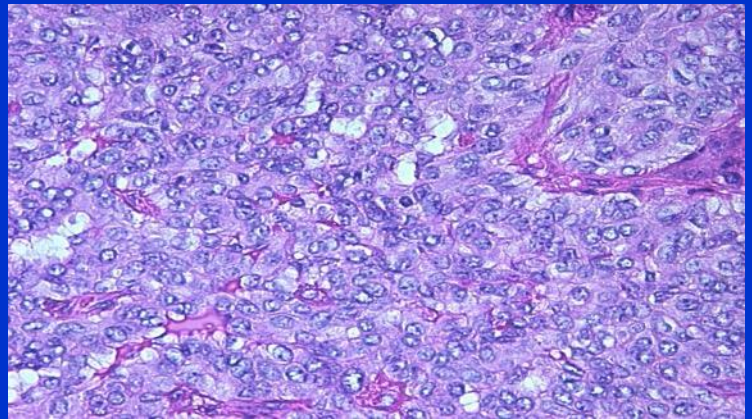


Benign papilloma with florid HUT

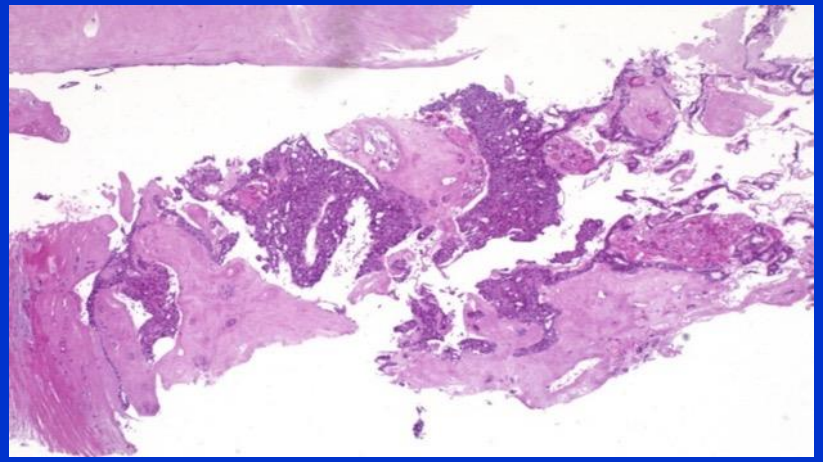


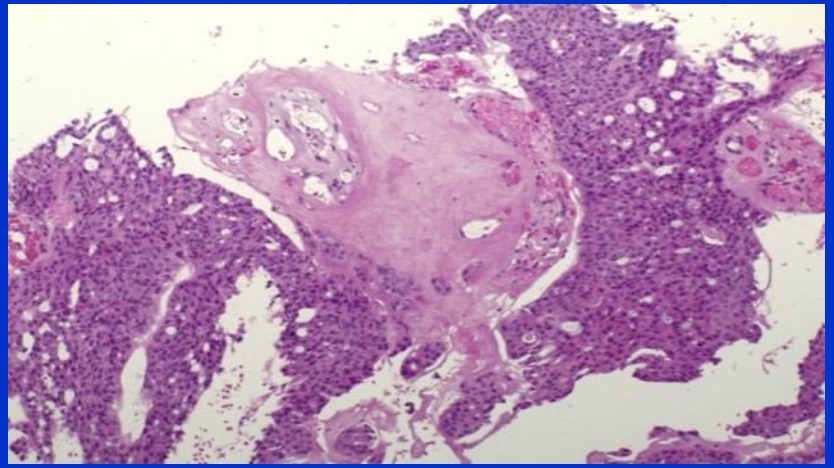




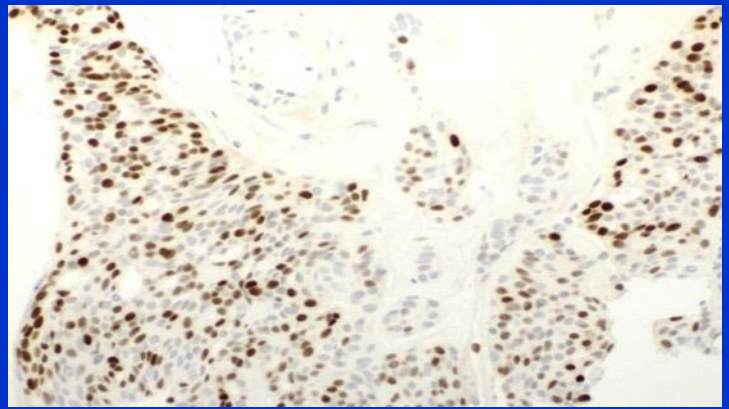


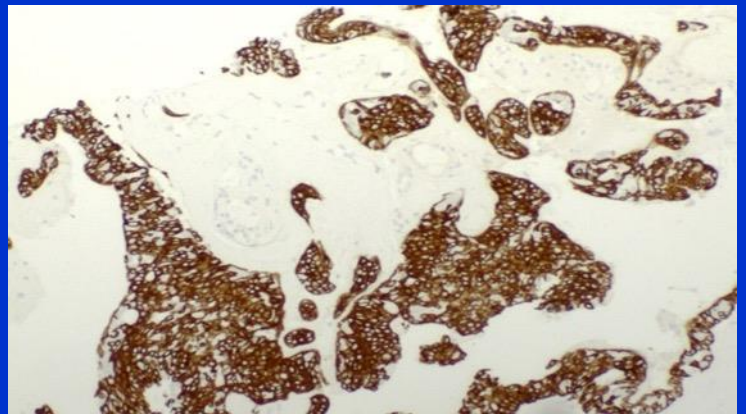
Papilloma with HUT- IHC





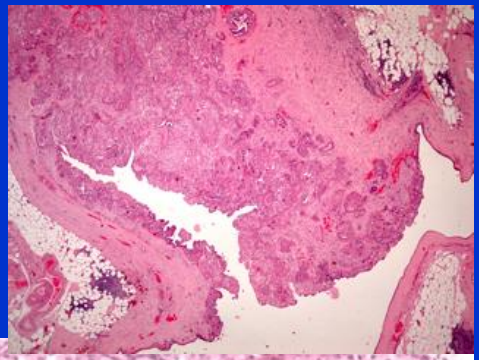
ER

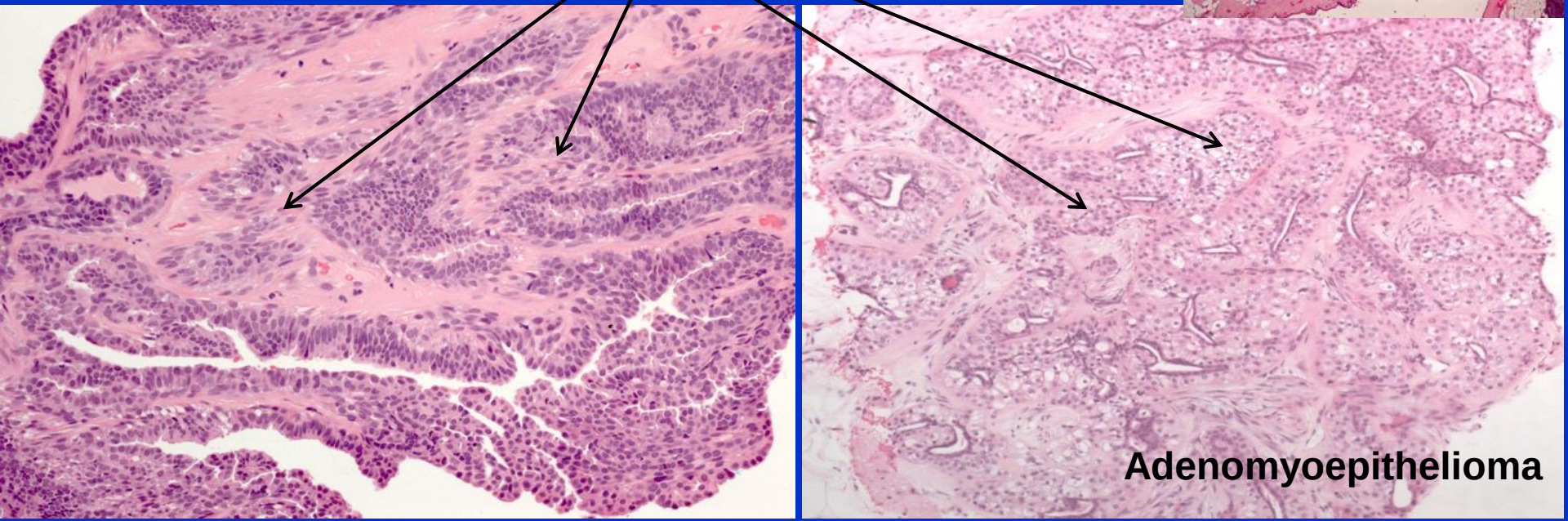




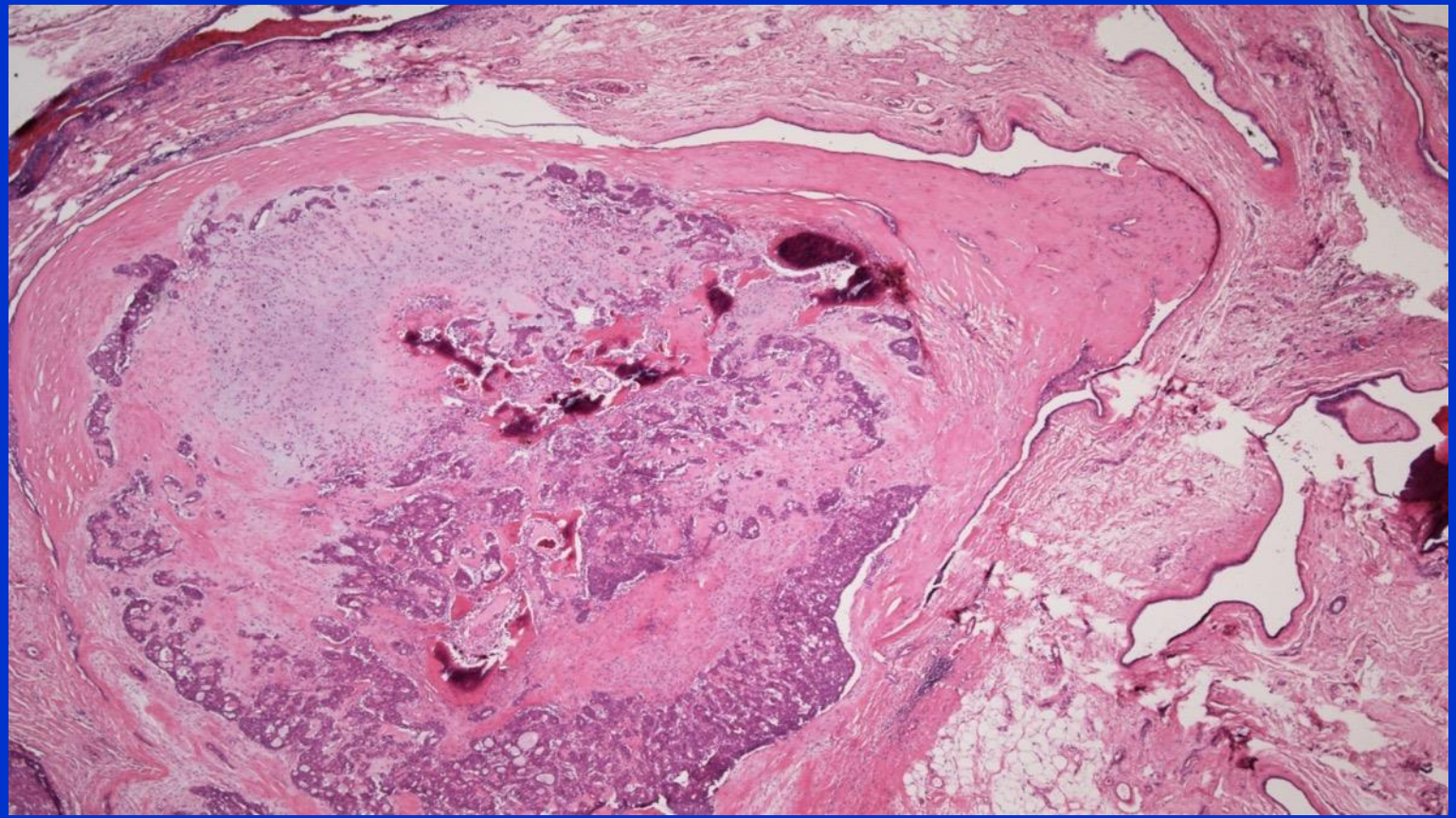
CKs

* ME cells may show hyperplasia BUT if marked: DD from adenomyoepithelioma





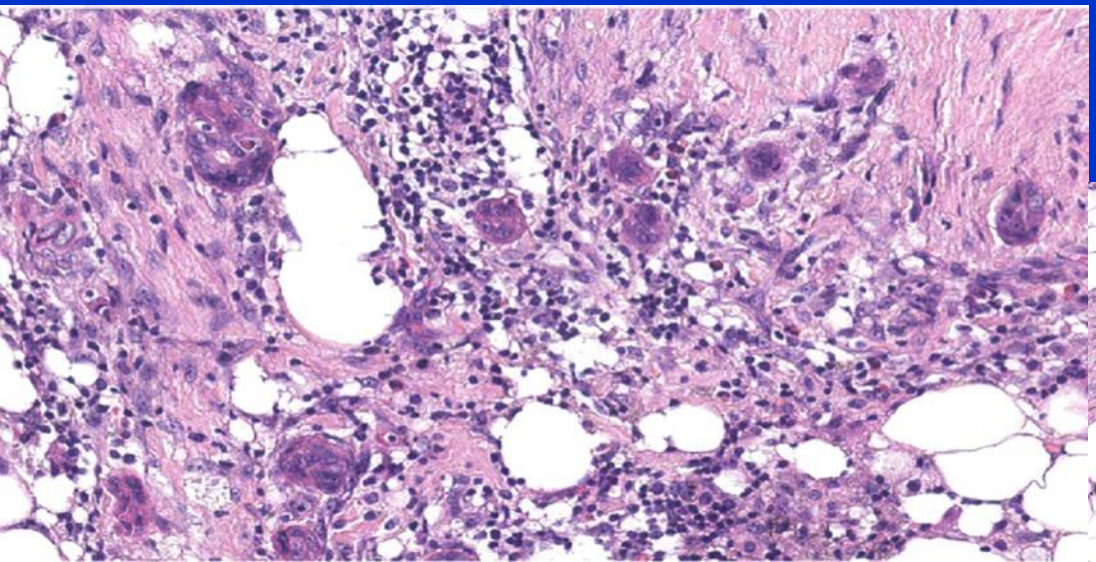
* Papilloma may show chondroid/chondromyxoid metaplasia: DD Pleomorphic Adenoma / MP MBC

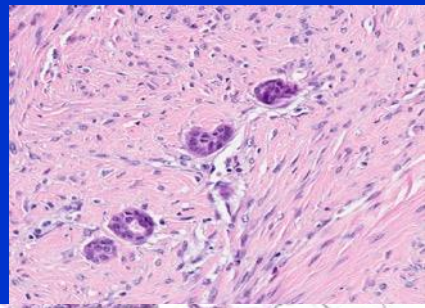


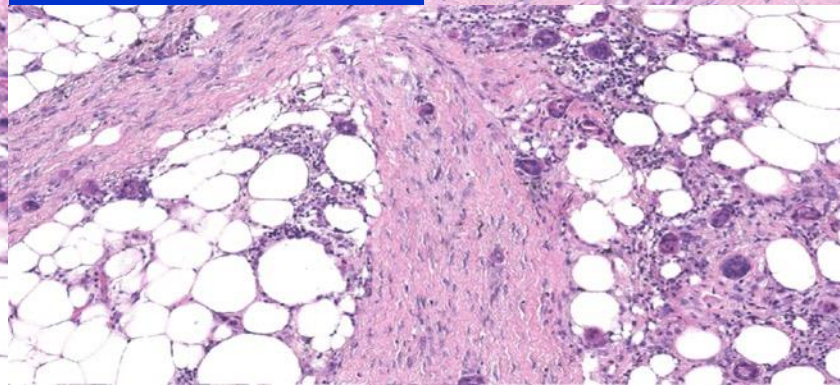
* Papillary lesion may show epithelial displacement

May lack peripheral ME cells: DD from invasive:

- Usually associated with biopsy site.
- No DCIS or invasive carcinoma in surrounding tissue
- Benign cytological features [ER, Ki67, Ck5/6, Ck14]

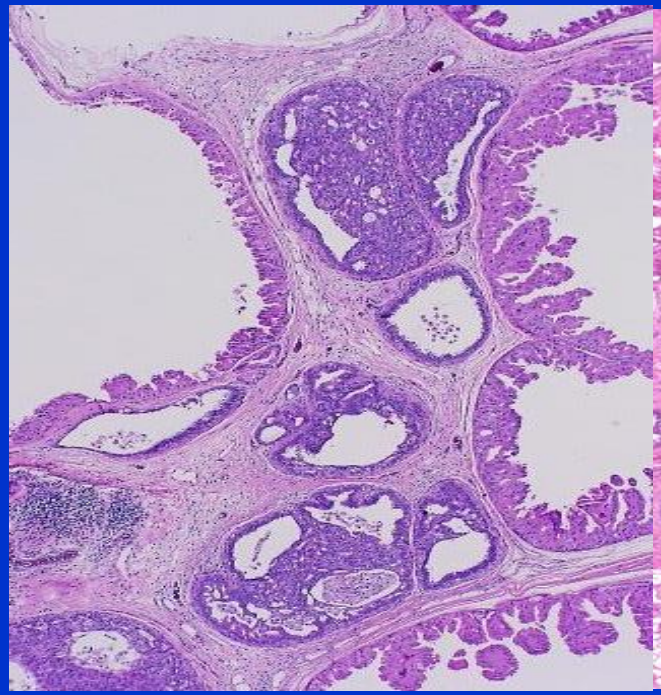


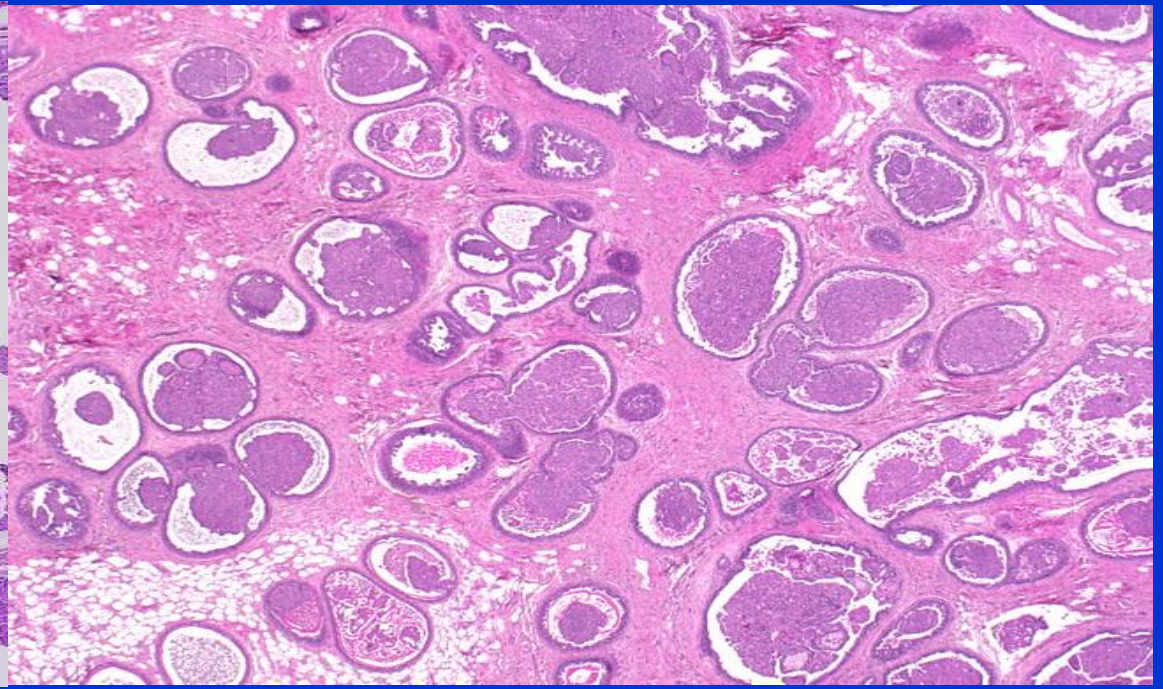


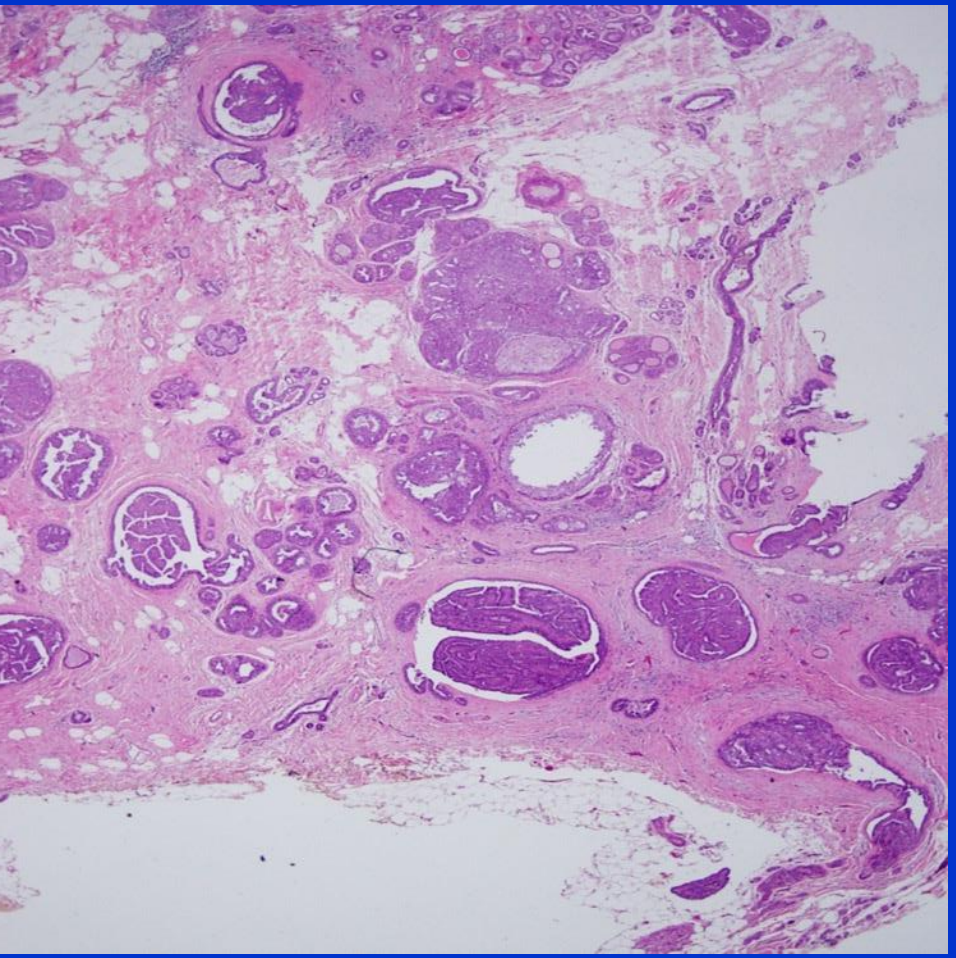


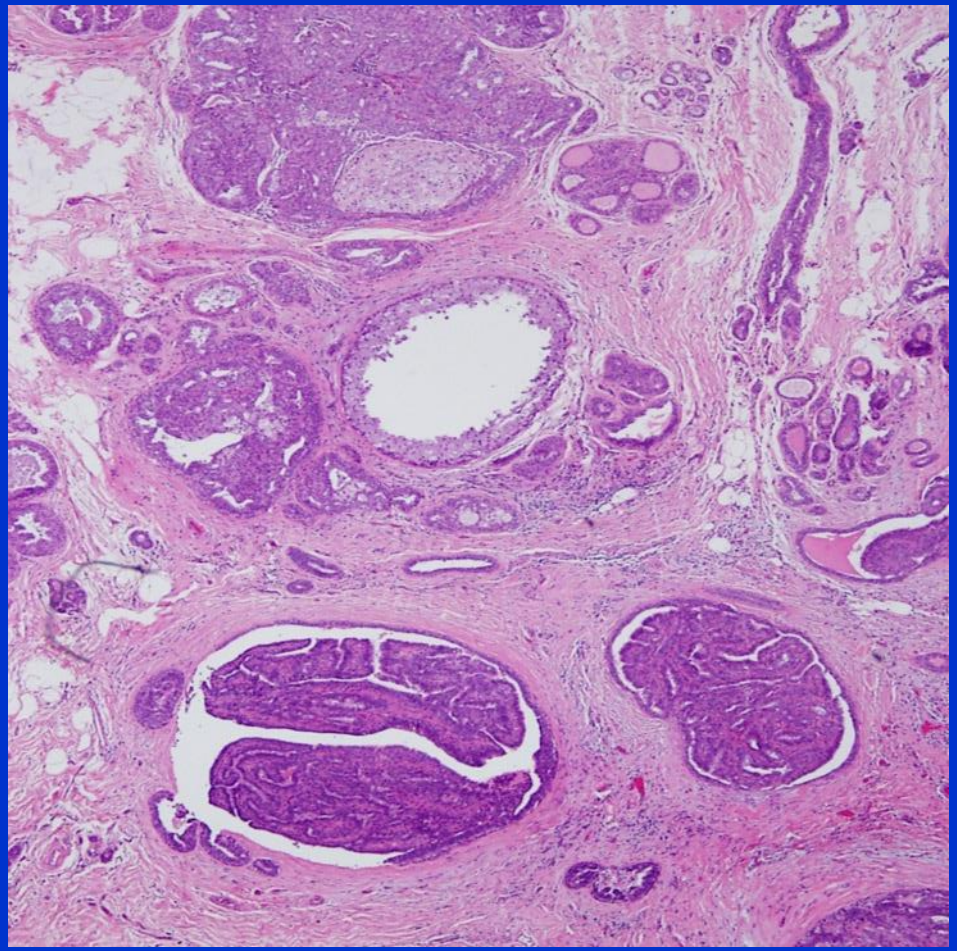
B-Multiple (microscopic) papillomas

- **Peripheral multiple** papillomas (TDLU), not mass forming.
- Less common than large duct papilloma but more frequently associated with epithelial hyperplasia and atypia
- Benign epithelium and myoepithelium +/- fibrocystic change, HUT









Acceptable terminology
Central papilloma: large duct papilloma; major duct papilloma.

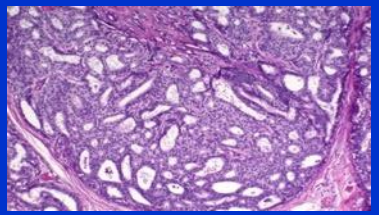
Peripheral papilloma: microscopic papilloma.

Not recommended
Papillomatosis.

C-Benign papilloma with atypia

1- Low grade atypical Proliferation

Benign papilloma containing solid or cribriform areas of uniform low-grade nuclei devoid of basal/ME cells akin to ADH/low grade DCIS



≤3mm (Papilloma with ADH)

>3mm (Papilloma with low grade DCIS)

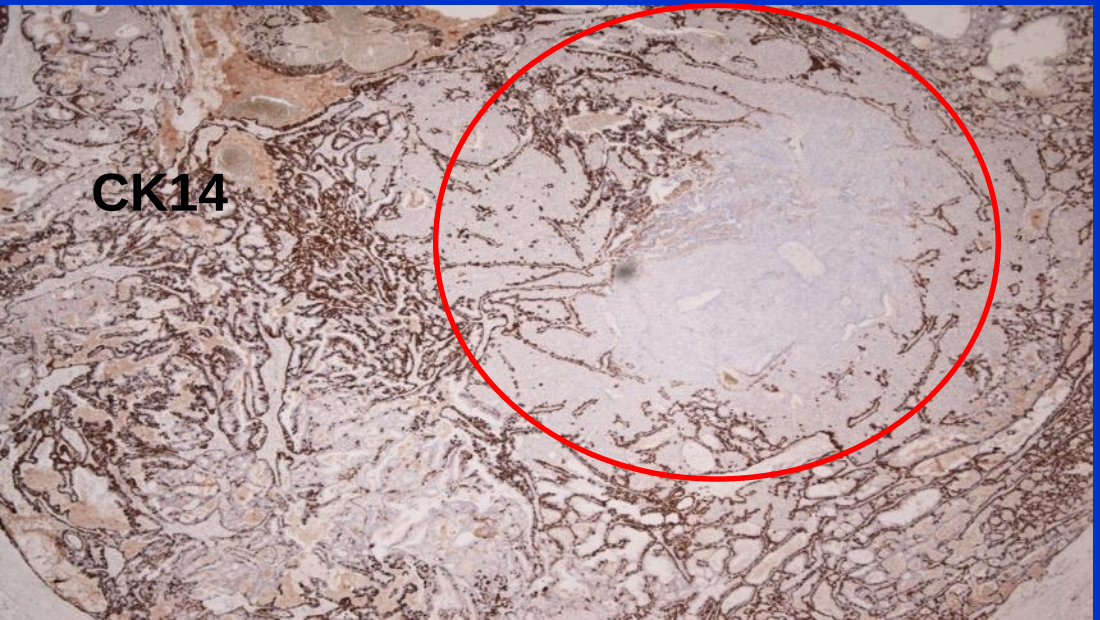
2- High grade atypical proliferation (Papilloma with DCIS regardless of the size of the atypical focus)

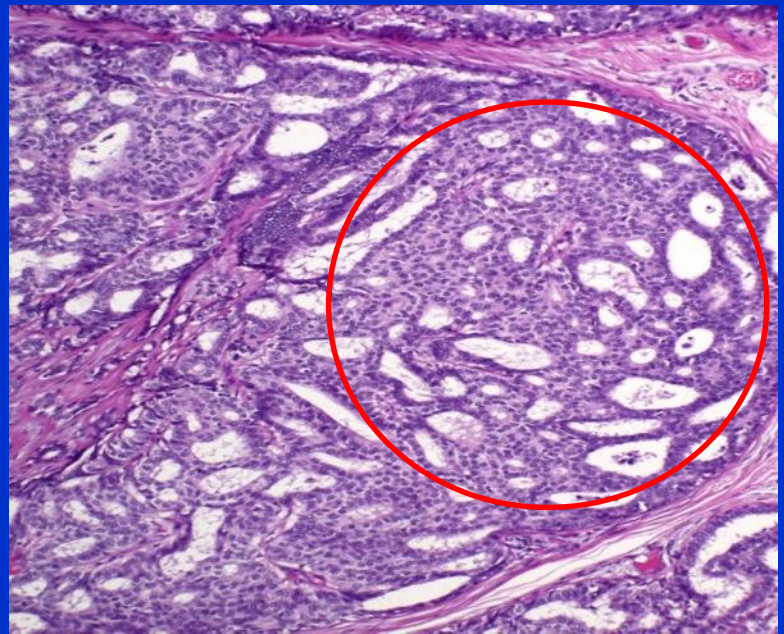
Diagnosis: DCIS involving a Papilloma

3- CCC / Flat Eptheial Atypia (FEA)-type

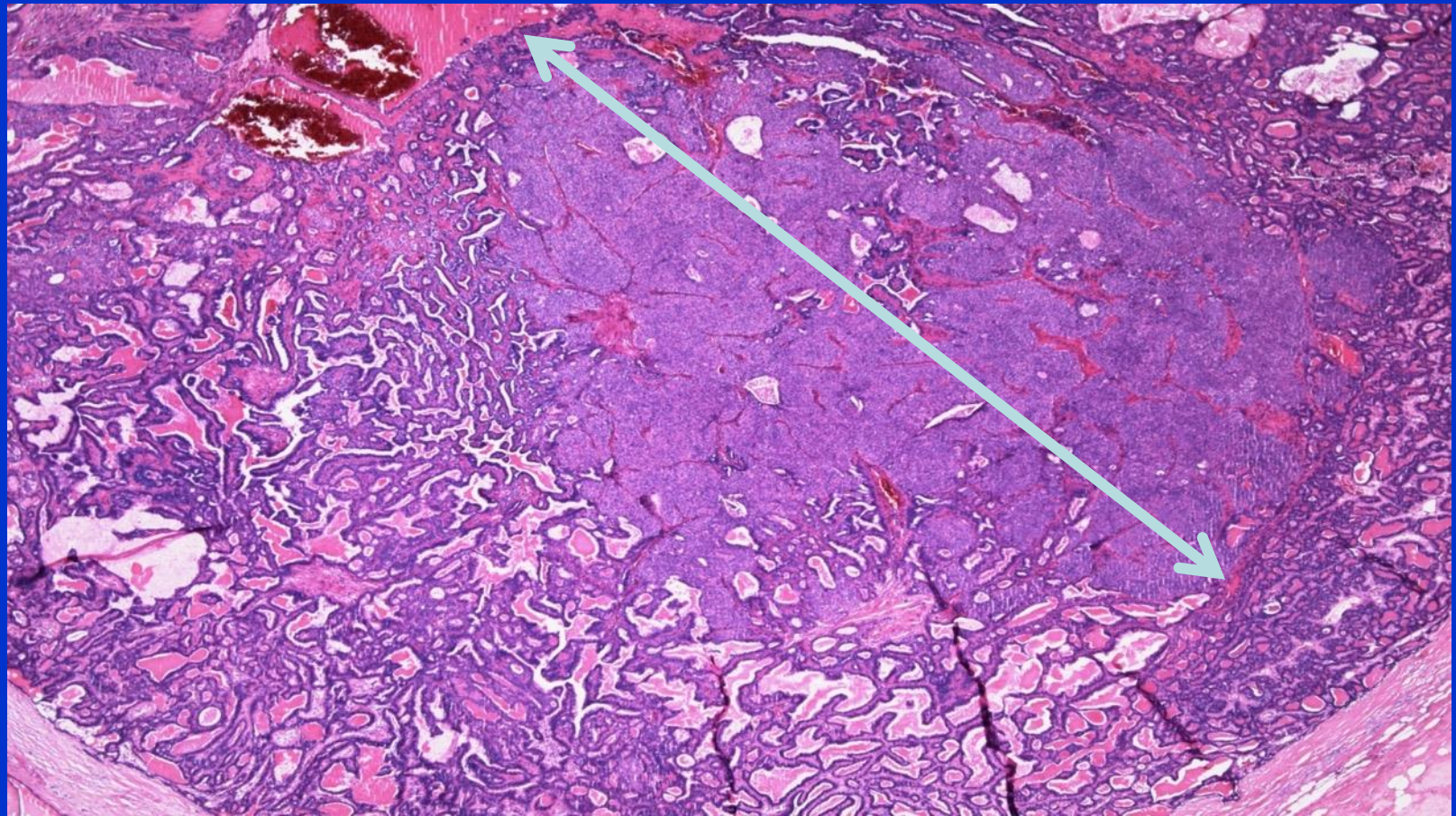
C-Benign papilloma with ADH

Small (<3mm) area of atypical epithelial hyperplasia : ER+, basal CKs negative

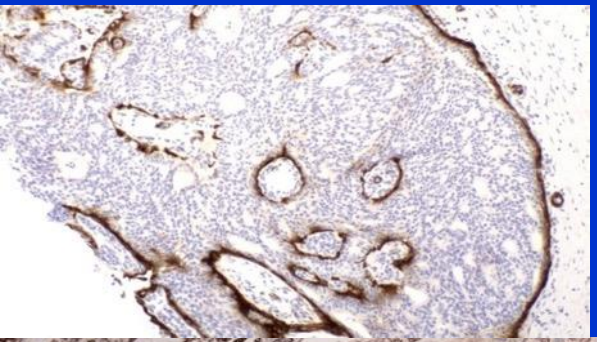


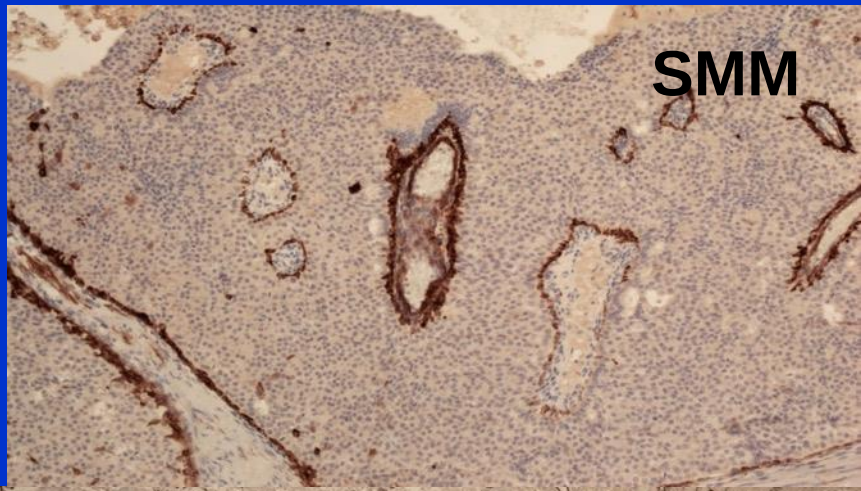


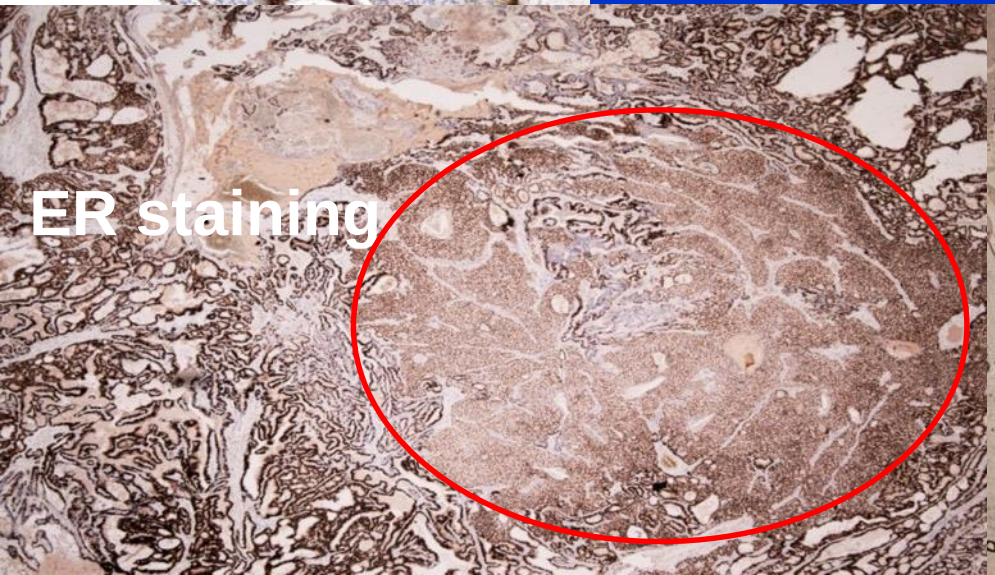
C-Benign papilloma with LG DCIS

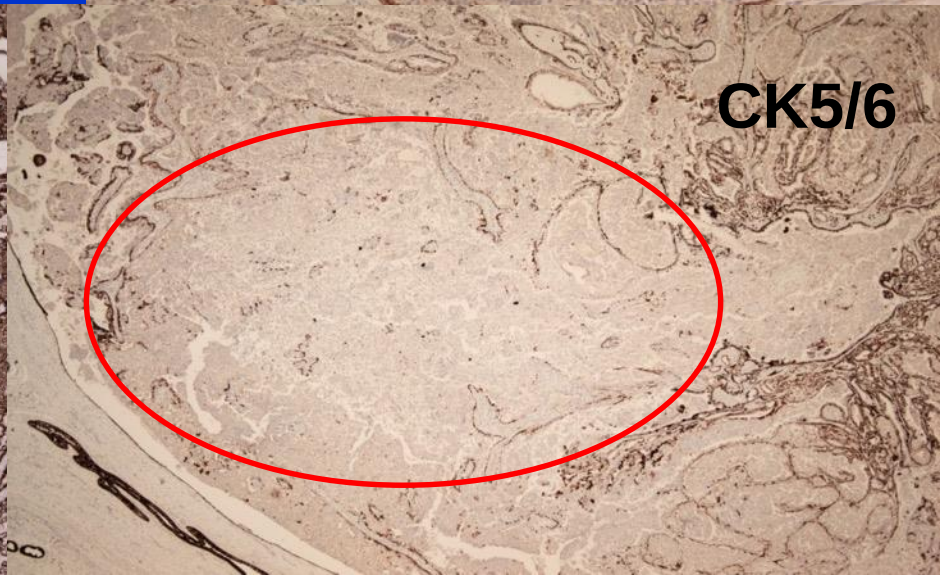


C-Benign papilloma with LG DCIS









D-Papillary carcinoma (0.5-1% of breast cancer)

- Papillary DCIS (malignant counterpart of multiple papillomas) peripheral, multiple, associated with other types of DCIS

- Large duct papillary carcinoma (Central and usually solitary)

  *Encapsulated (*Intracystic/Encysted) PC

  Solid PC (SPC)

- invasive PC with or without *in situ* PC component

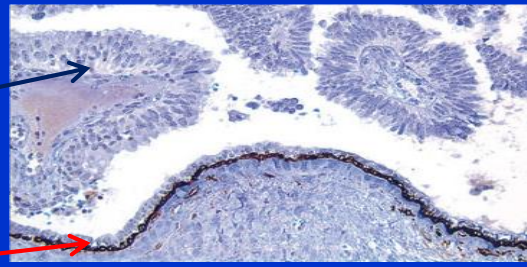
Papillary DCIS

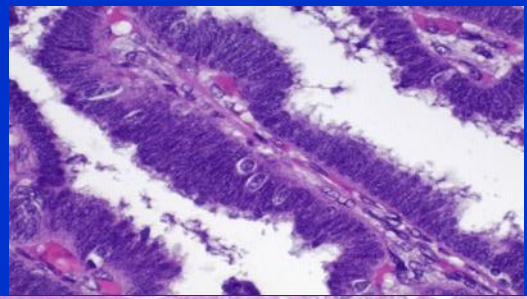
Less common form of PC. It is usually:

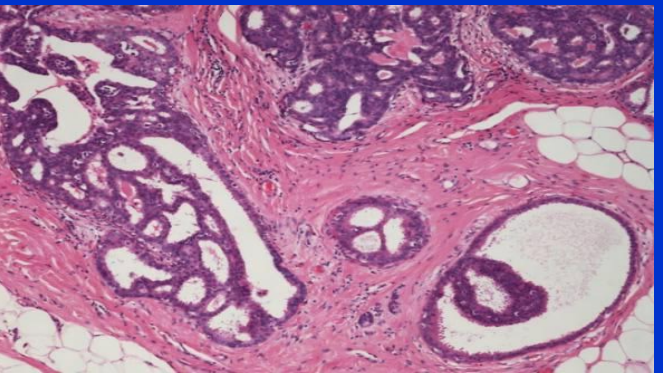
- **Peripheral and multiple (TDLU)**
- **Malignant epithelium**
- **ME absent in the papillae**
- **ME preserved at epithelial stroma interface**

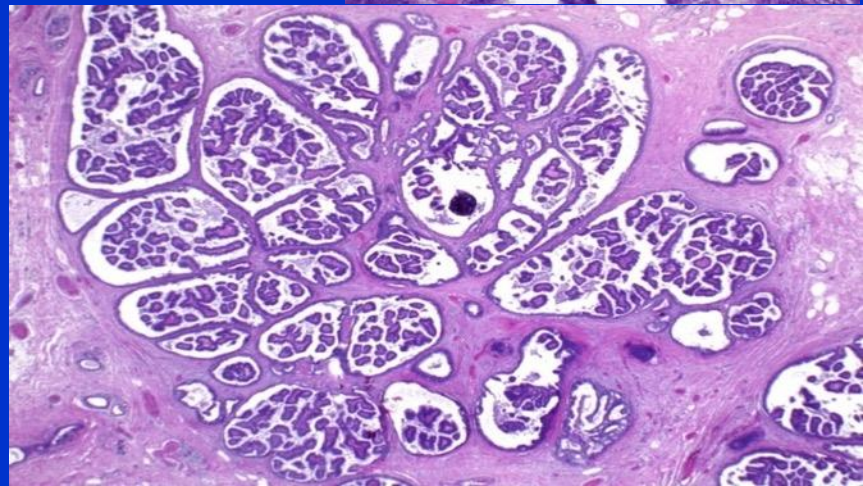
No evidence of pre-existing benign papilloma

*** Usually associated with other types of DCIS**
*** Low to intermediate nuclear grade**
*** No peripheral fibrous capsule**

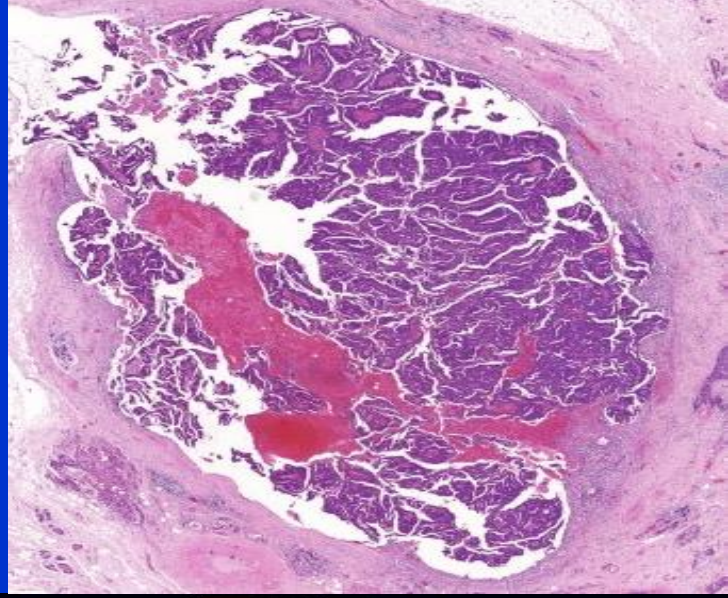


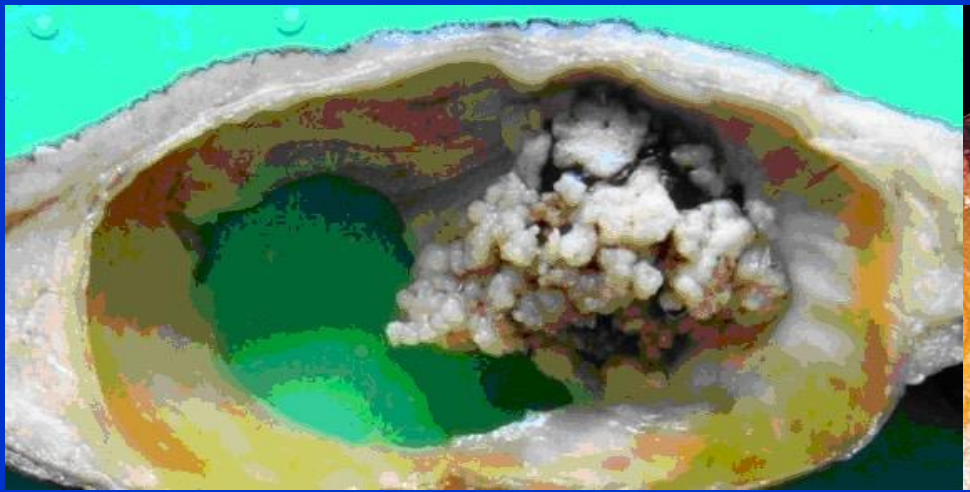


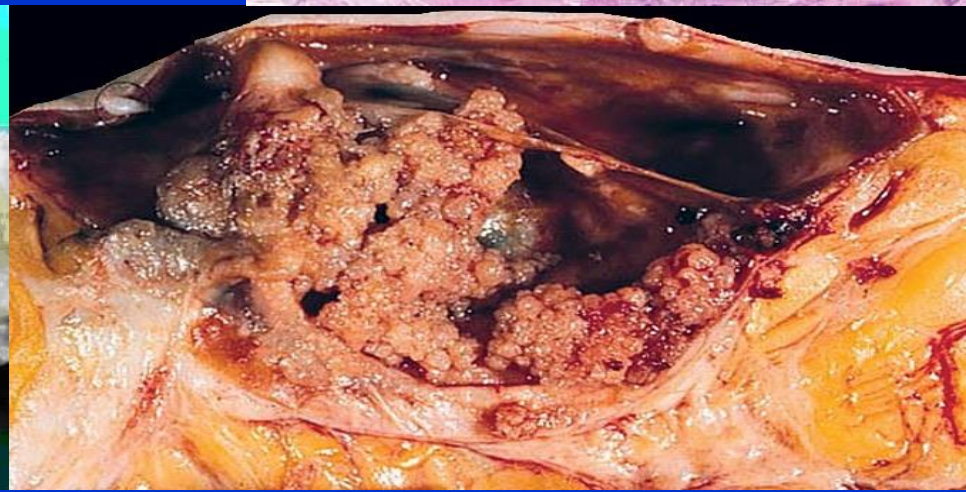




Encapsulated PC
(encysted / intracystic PC)



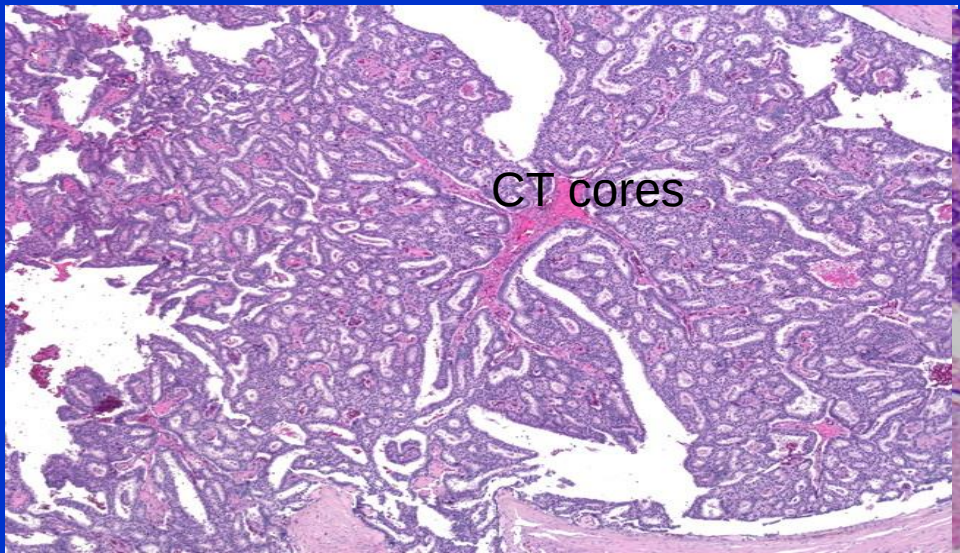


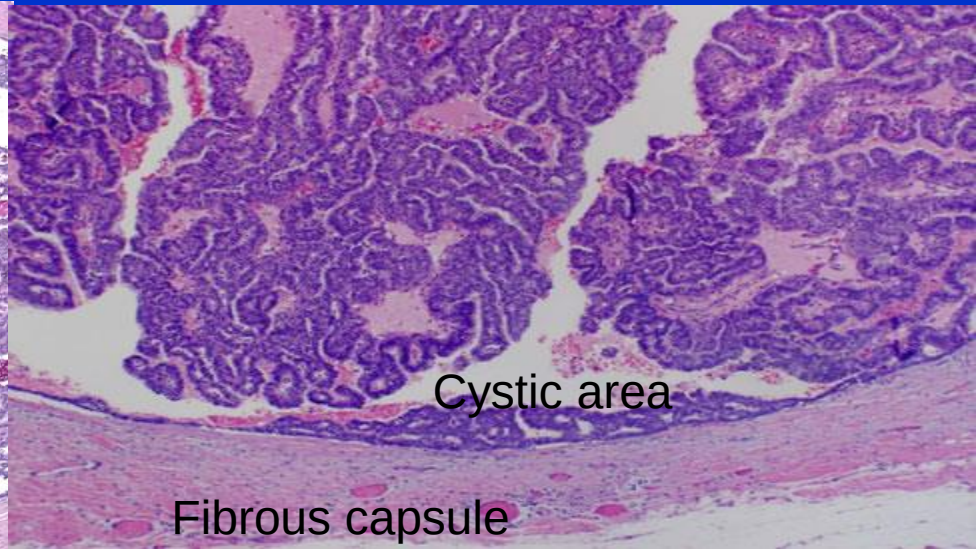


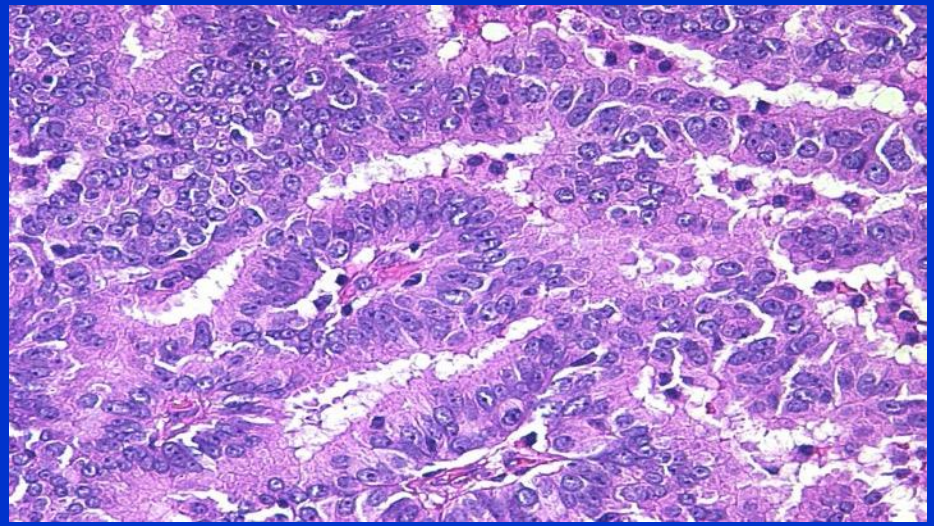
Encapsulated (encysted/intracystic) PC

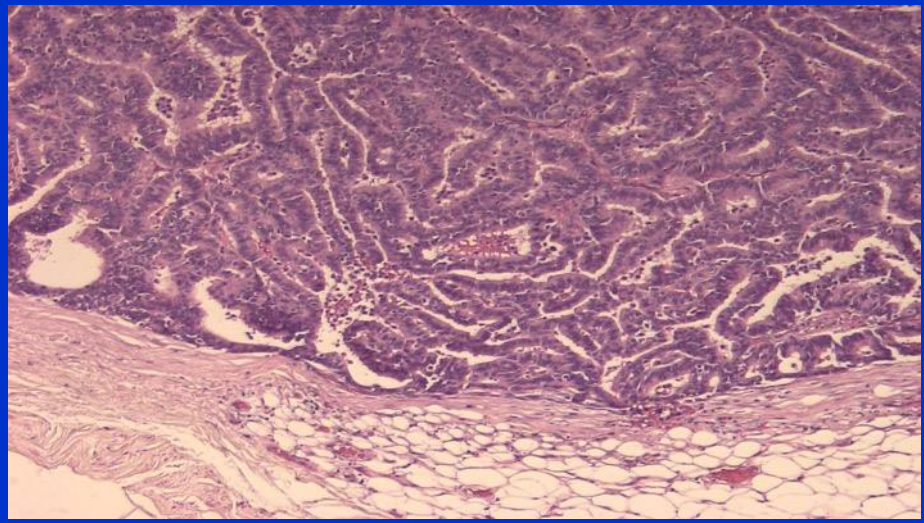
Usually central and solitary, cystically dilated ducts +/- solid areas

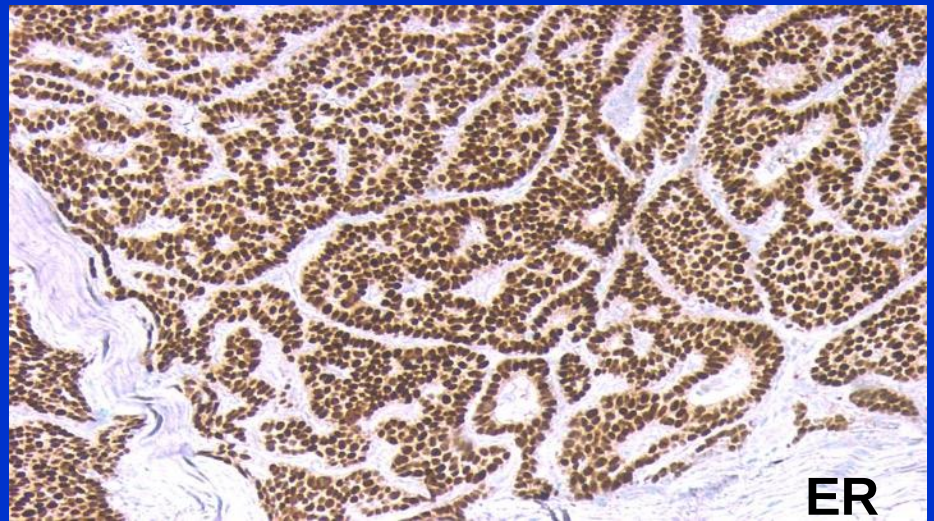
Malignant/atypical cytology/architecture
Surrounded by thick fibrous capsule
Absent ME in centre (100%) and periphery (complete absence in >80%)







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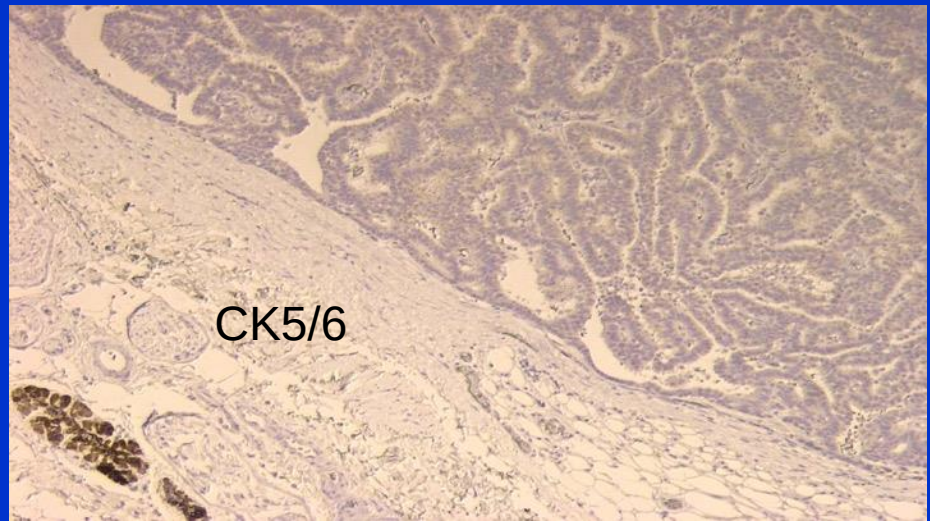
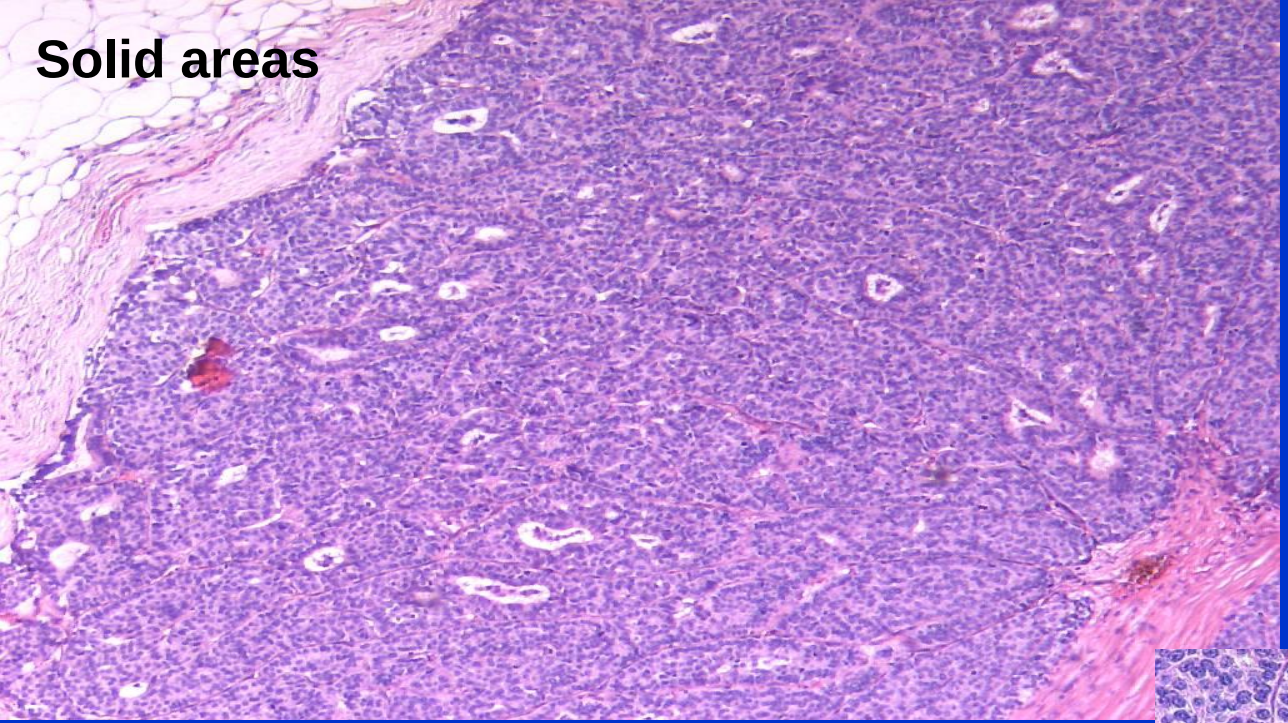
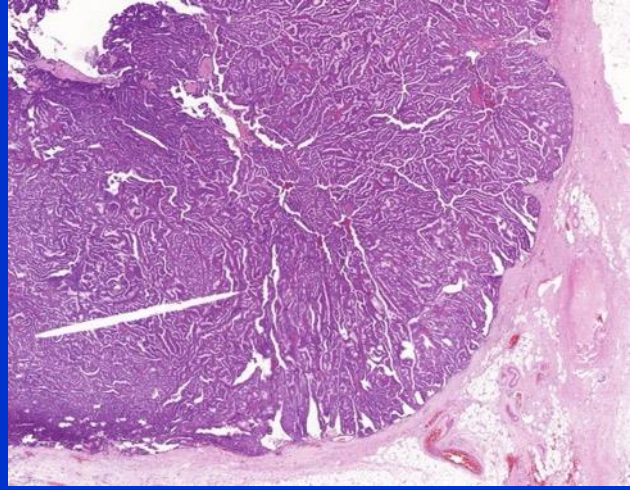
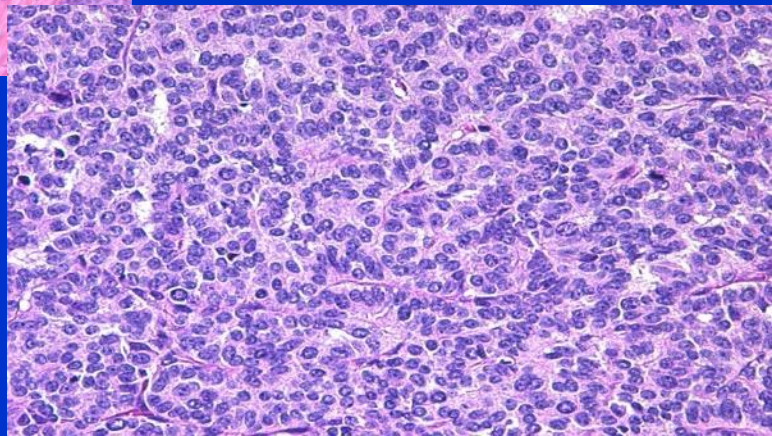

CK5/6

Solid areas







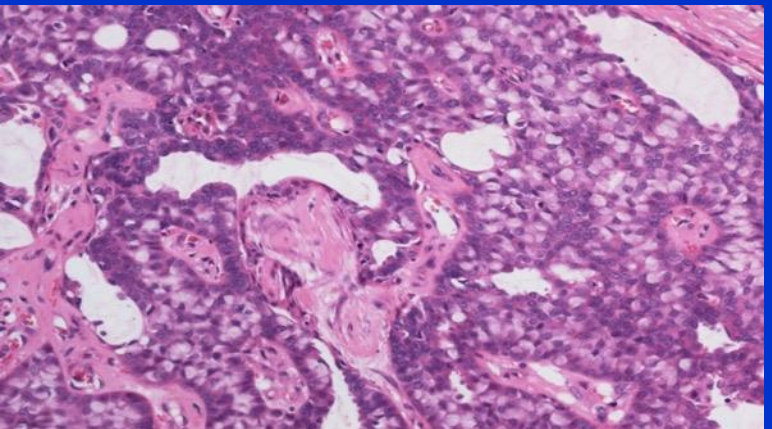
Solid PC

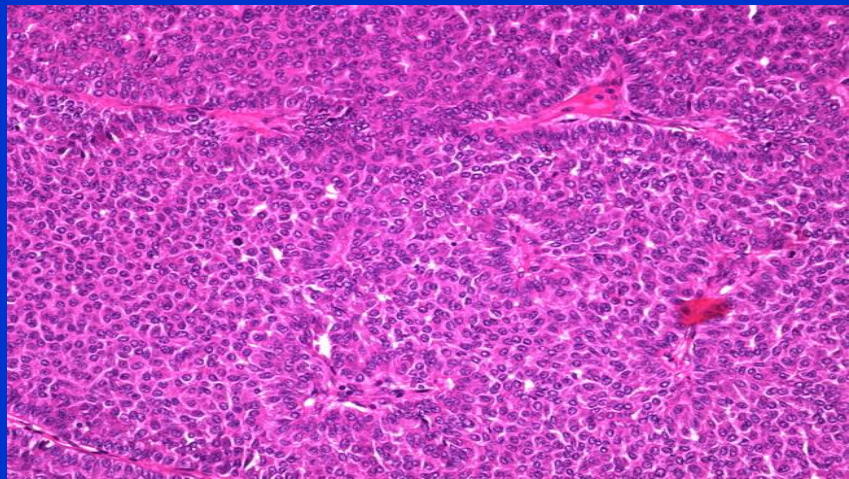
Composed almost entirely of solid epithelial proliferation

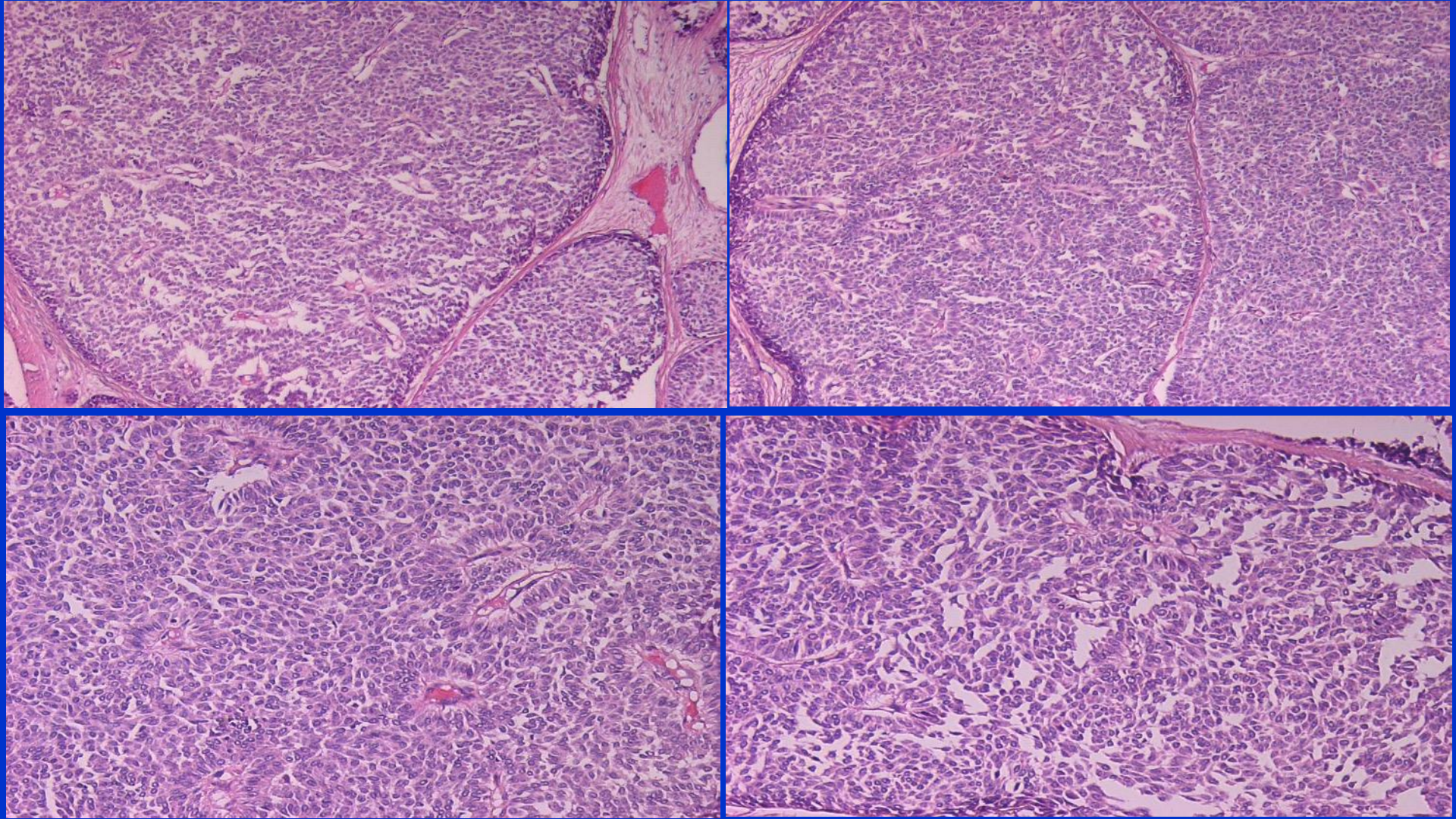
Small cords of fibrovascular stroma (H&E or IHC) make it possible to recognize it as papillary carcinoma. Often central multinodular

Spindle areas, focal mucin production, low-nuclear grade NE features (~70%), and peripheral palisading. Often lack thick fibrous capsule
Frequently assoc. with invasion: mucinous carcinoma

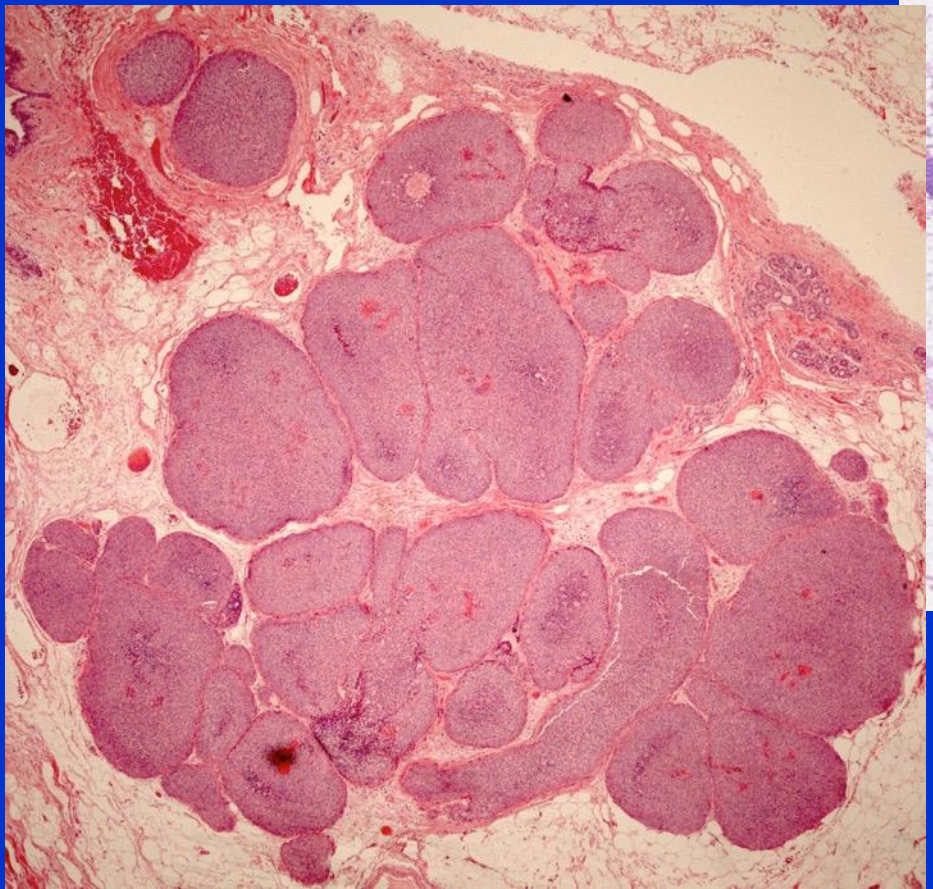
Synonyms: Spindle, NE / Endocrine DCIS

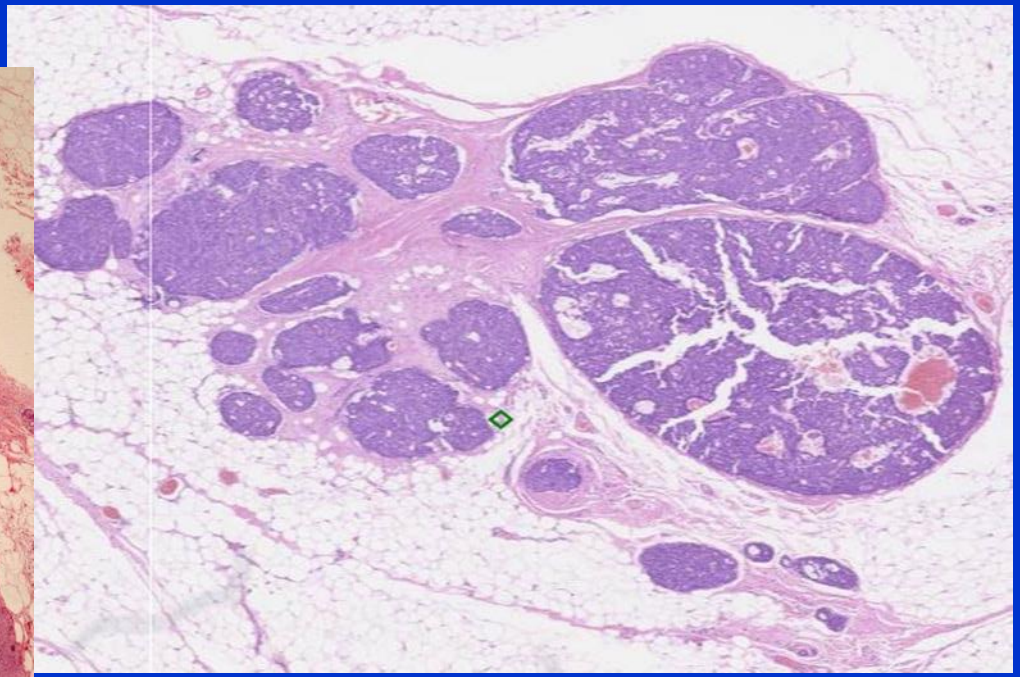


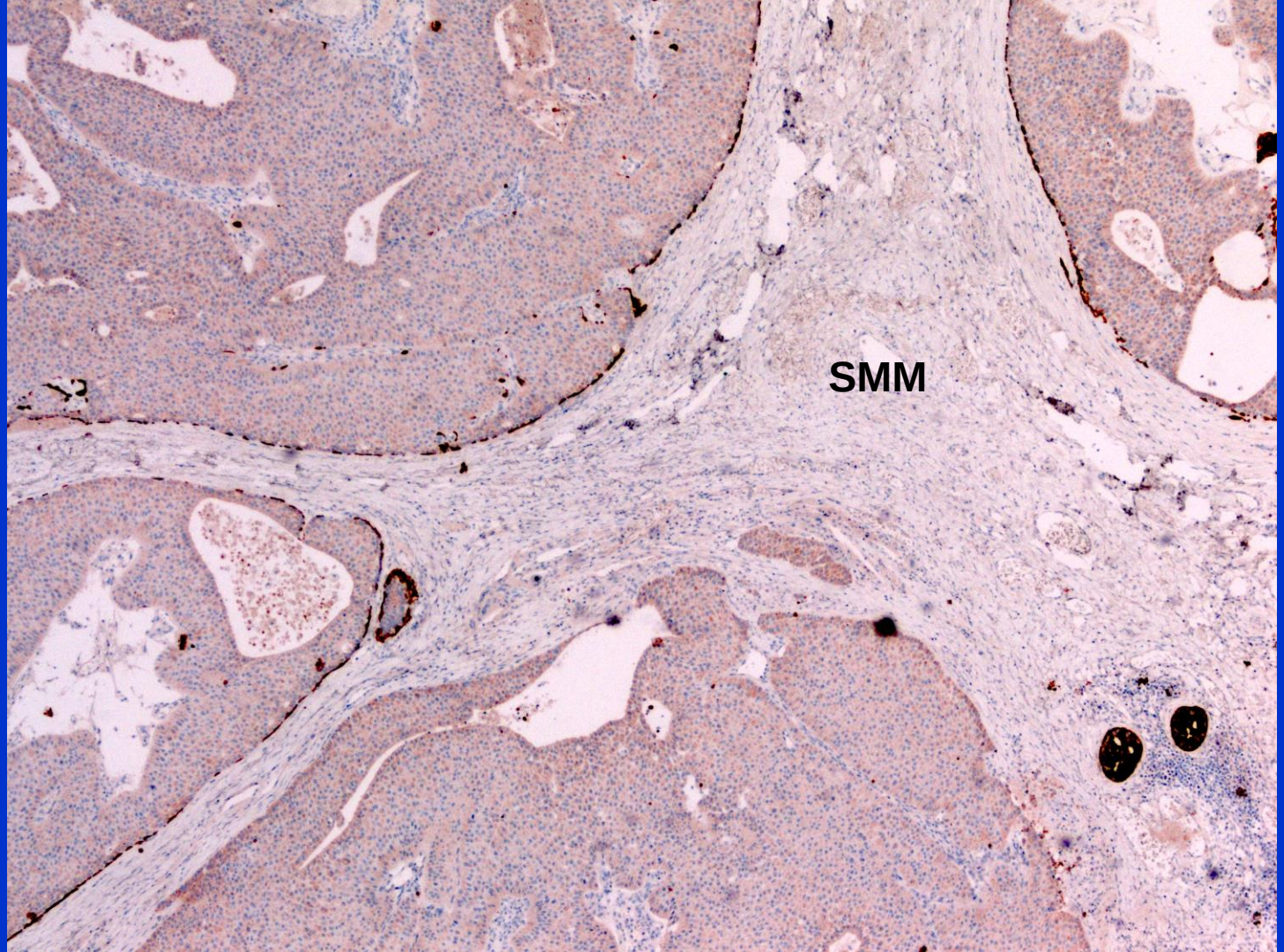


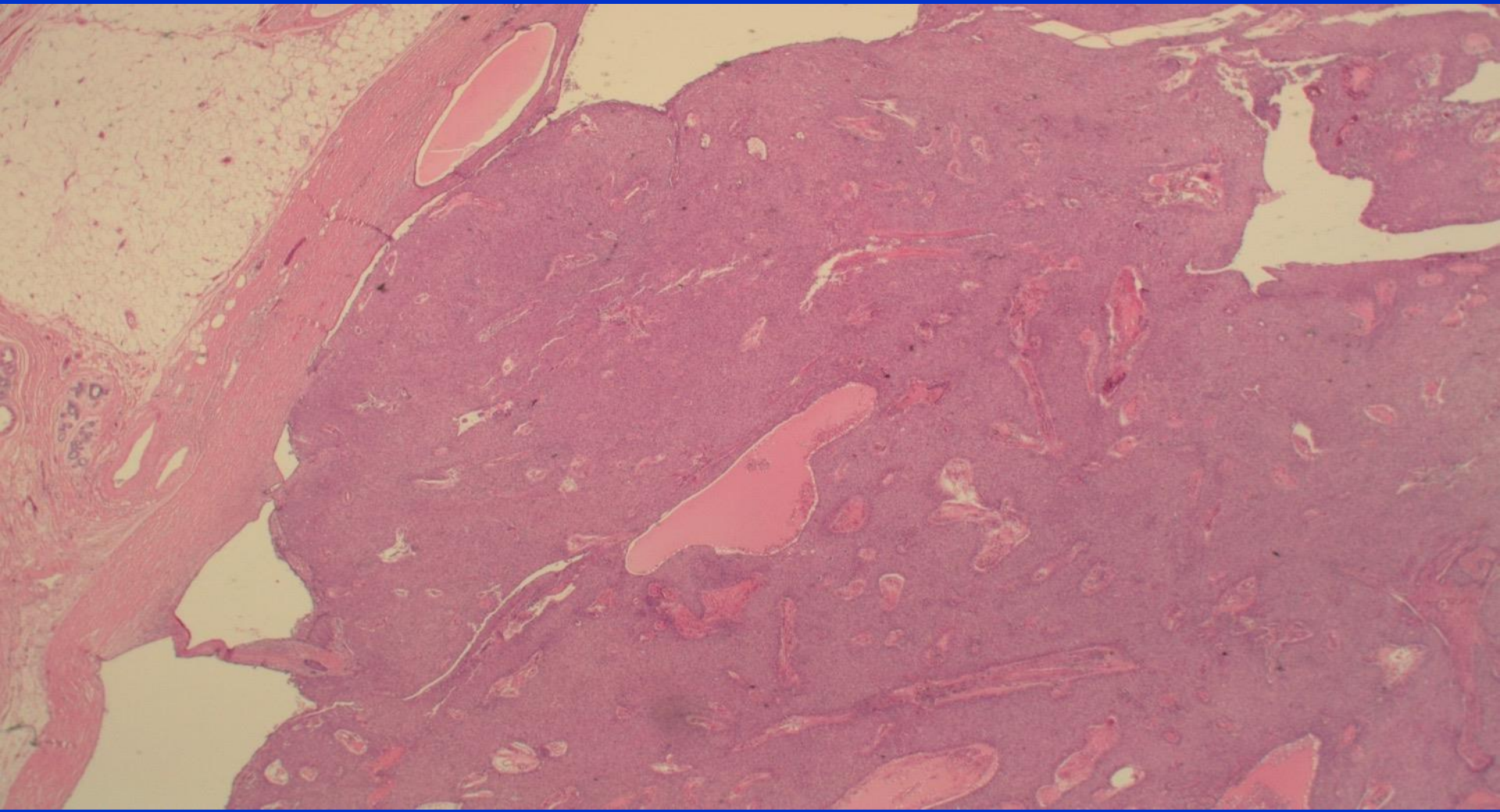


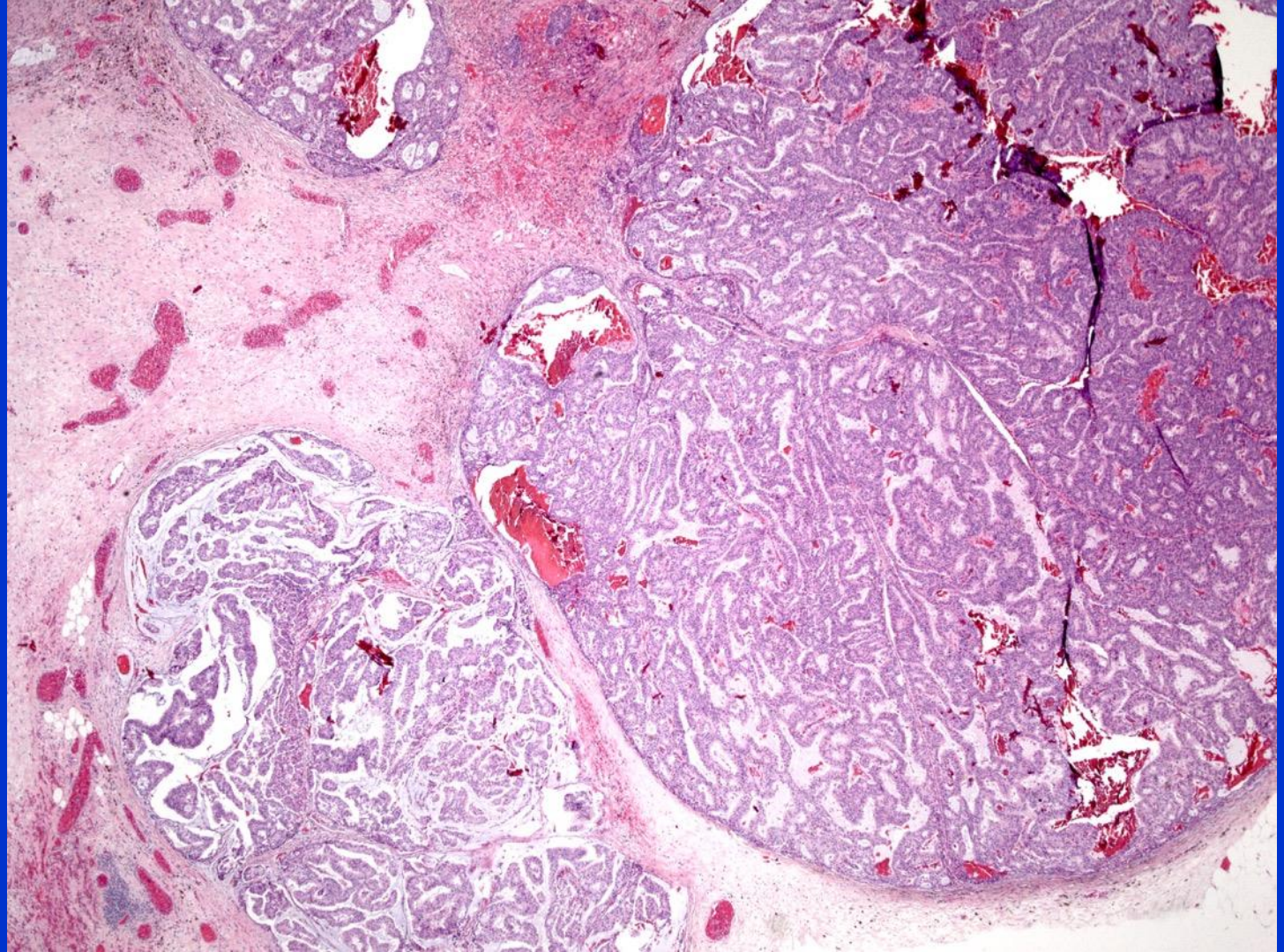
More often multi-nodular



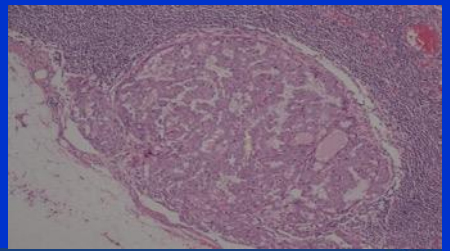


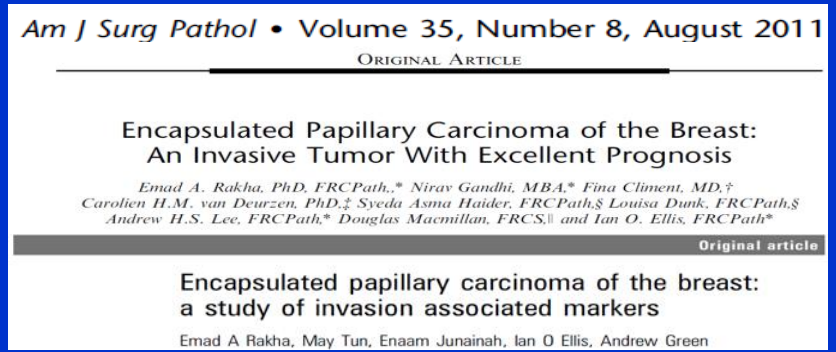

SMM





- **Papillary DCIS: behave as conventional DCIS**
- **EPC and SPC have the potential to behave as an indolent form of invasive BC *with low volume LN mets in few cases*, but the excellent outcome justify managing them as a form of *in-situ* disease**
- **WHO recommends staging EPC and SPC as DCIS [pTis]**





Am J Surg Pathol • Volume 35, Number 8, August 2011

ORIGINAL ARTICLE

Encapsulated Papillary Carcinoma of the Breast:
An Invasive Tumor With Excellent Prognosis

Emad A. Rakha, PhD, FRCPath, Nirav Gandhi, MBA,* Fina Climent, MD,† Carolien H.M. van Deurzen, PhD,‡ Syeda Asma Haider, FRCPath,§ Louisa Dunk, FRCPath,§ Andrew H.S. Lee, FRCPath,* Douglas Macmillan, FRCS,‖ and Ian O. Ellis, FRCPath**

Original article

Encapsulated papillary carcinoma of the breast:
a study of invasion associated markers

Emad A Rakha, May Tun, Enaam Junainah, Ian O Ellis, Andrew Green

Histopathology

Histopathology 2016, 68, 45–56. DOI: 10.1111/his.12861

REVIEW

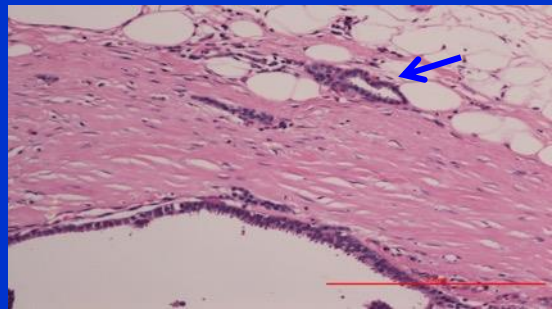
Breast lesions of uncertain malignant nature and limited metastatic potential: proposals to improve their recognition and clinical management

Emad A Rakha, Sunil Badve,[1] Vincenzo Eusebi,[2] Jorge S Reis-Filho,[3] Stephen B Fox,[4] David J Dabbs,[5] Thomas Decker,[6] Zsolt Hodi, Shu Ichihara,[7] Andrew HS Lee, José Palacios,[8] Andrea L Richardson,[9] Anne Vincent-Salomon,[10] Fernando C Schmitt,[11] Puay-Hoon Tan,[12] Gary M Tse[13] & Ian O Ellis

Exceptions:

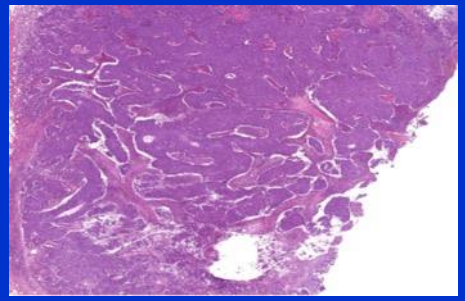
- **EPC and SPC showing *intact peripheral ME cell layer* (10-20%) is a true *in-situ* cancer both biologically and clinically and be confidently called PC *in-situ***
- **Although microinvasion/suspicion of invasion in typical PC seems to be of little clinical significance, if you are in doubt (ie malignant glands outside the fibrous capsule lacking ME cells), it may be safer to call it:**

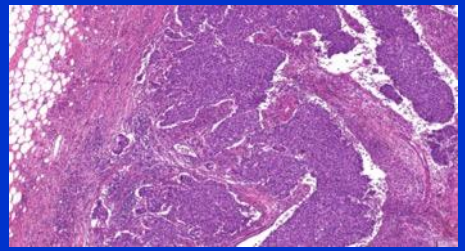
- **EPC with microinvasion or**
- **EPC, invasion cannot be excluded**
  BUT still treated as DCIS

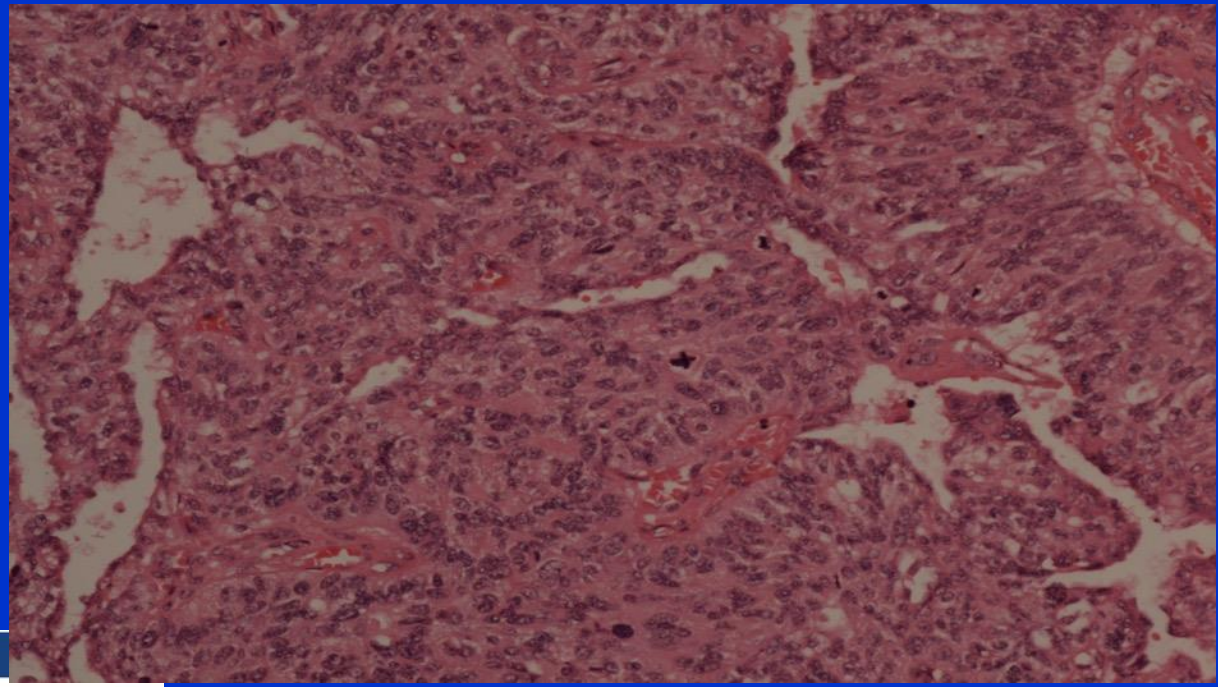


Exceptions in pure EPC:

- When PC shows high grade nuclei with frequent mitotic figures, we call them invasive as the number is insufficient to comment on behaviour





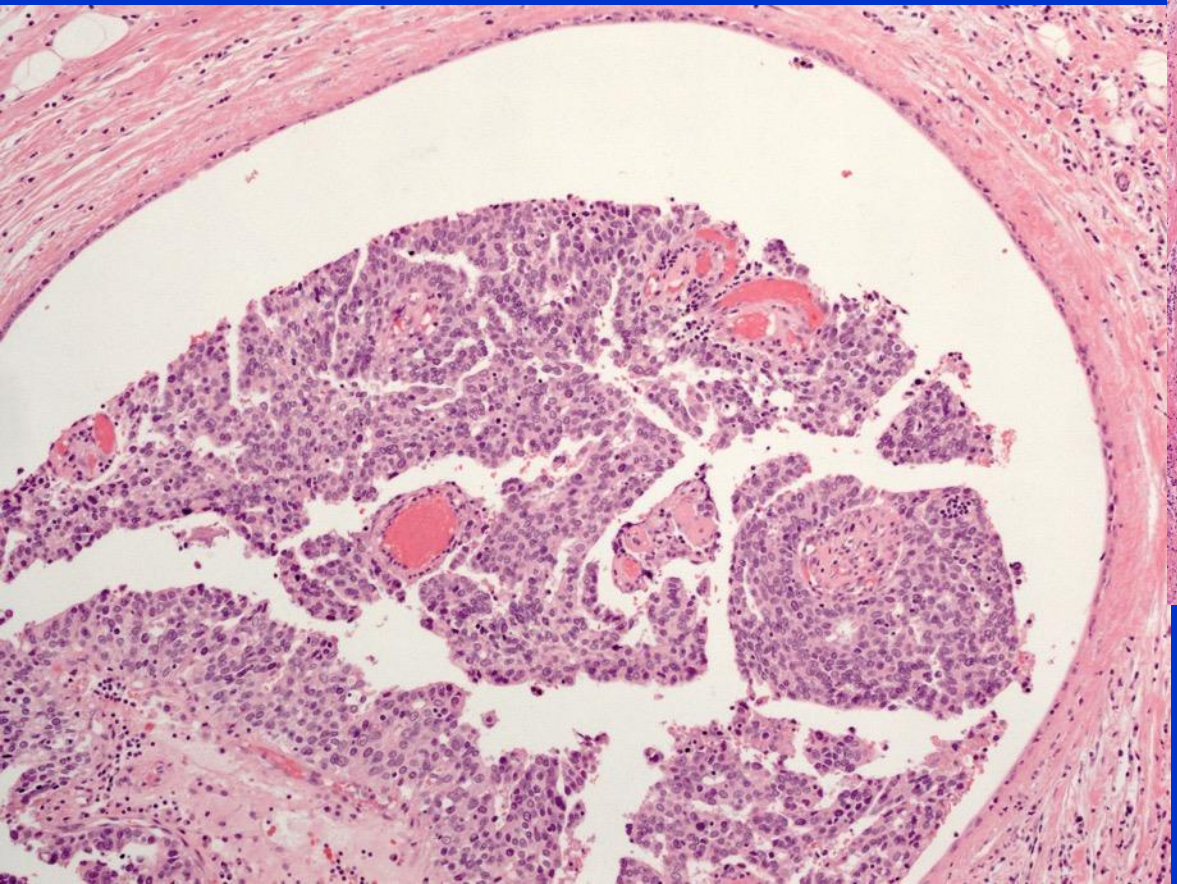


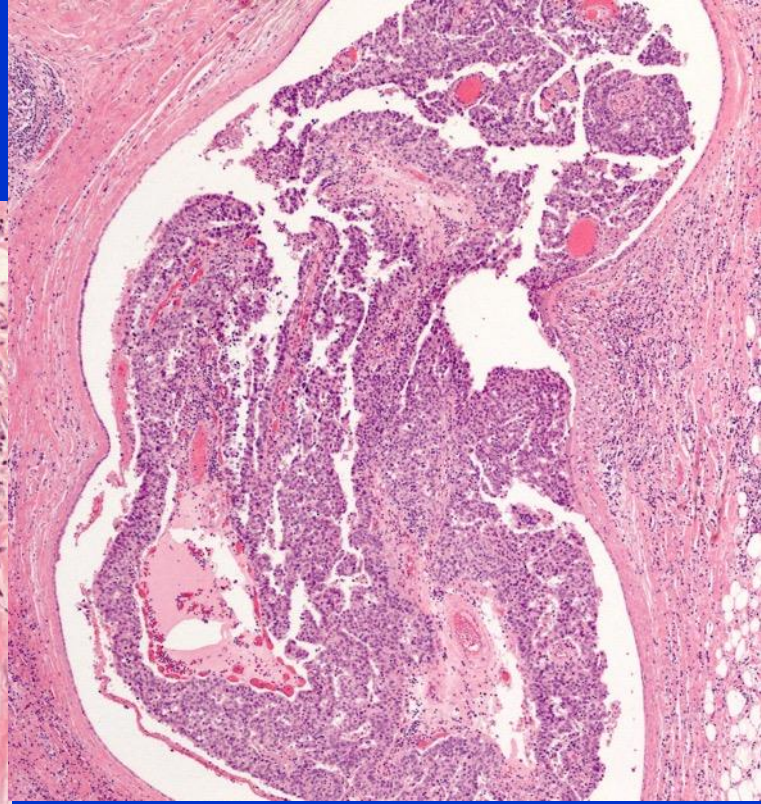
Histopathology

Histopathology 2015, **66**, 740–746. DOI: 10.1111/his.12591

High-grade encapsulated papillary carcinoma of the breast: an under-recognized entity

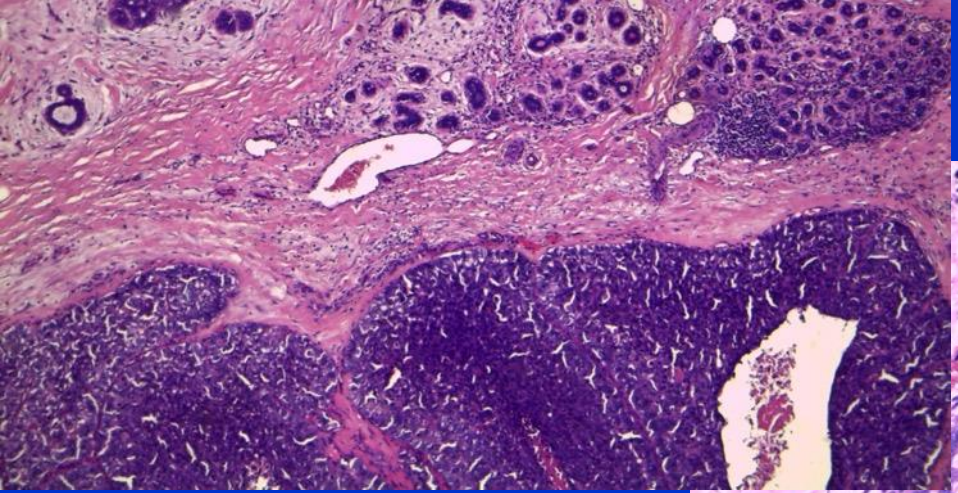
Emad A Rakha, Zsuzsanna Varga,[1] Somaia Elsheik & Ian O Ellis

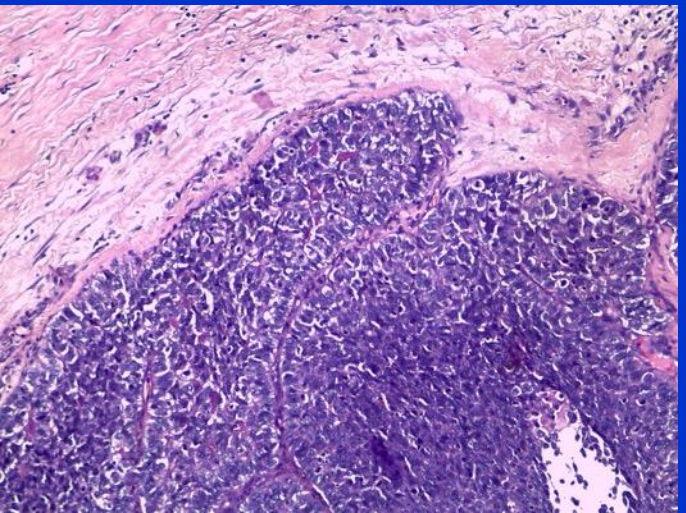


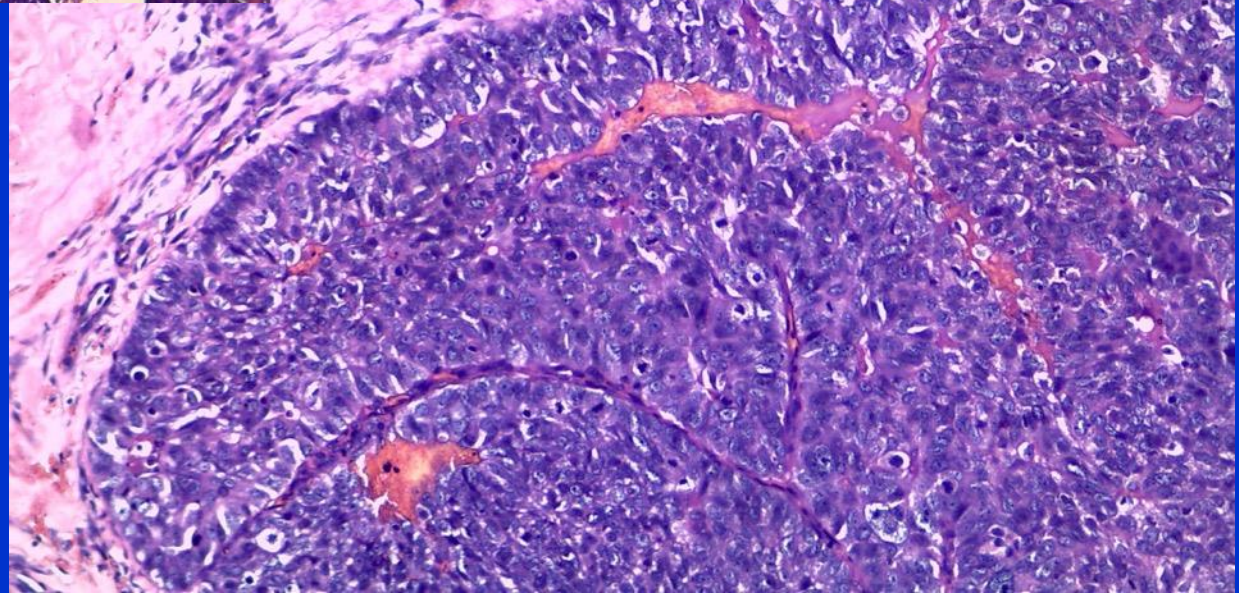


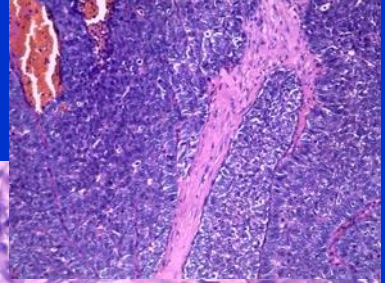
Intraductal high grade

Diagnosis??





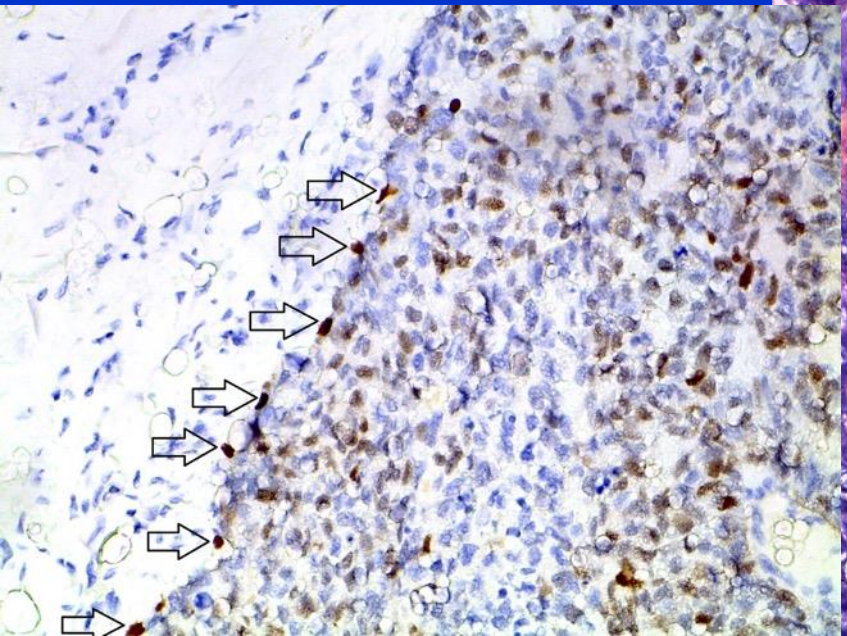




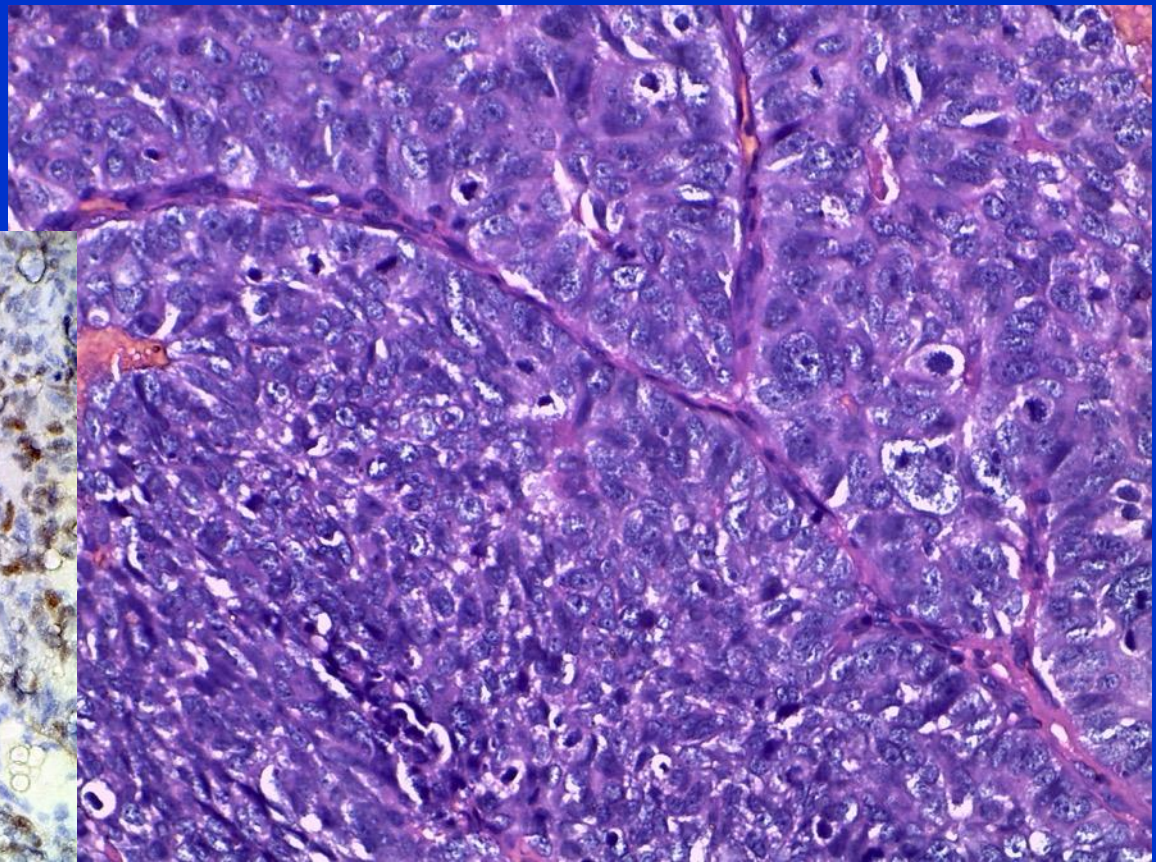
Triple negative

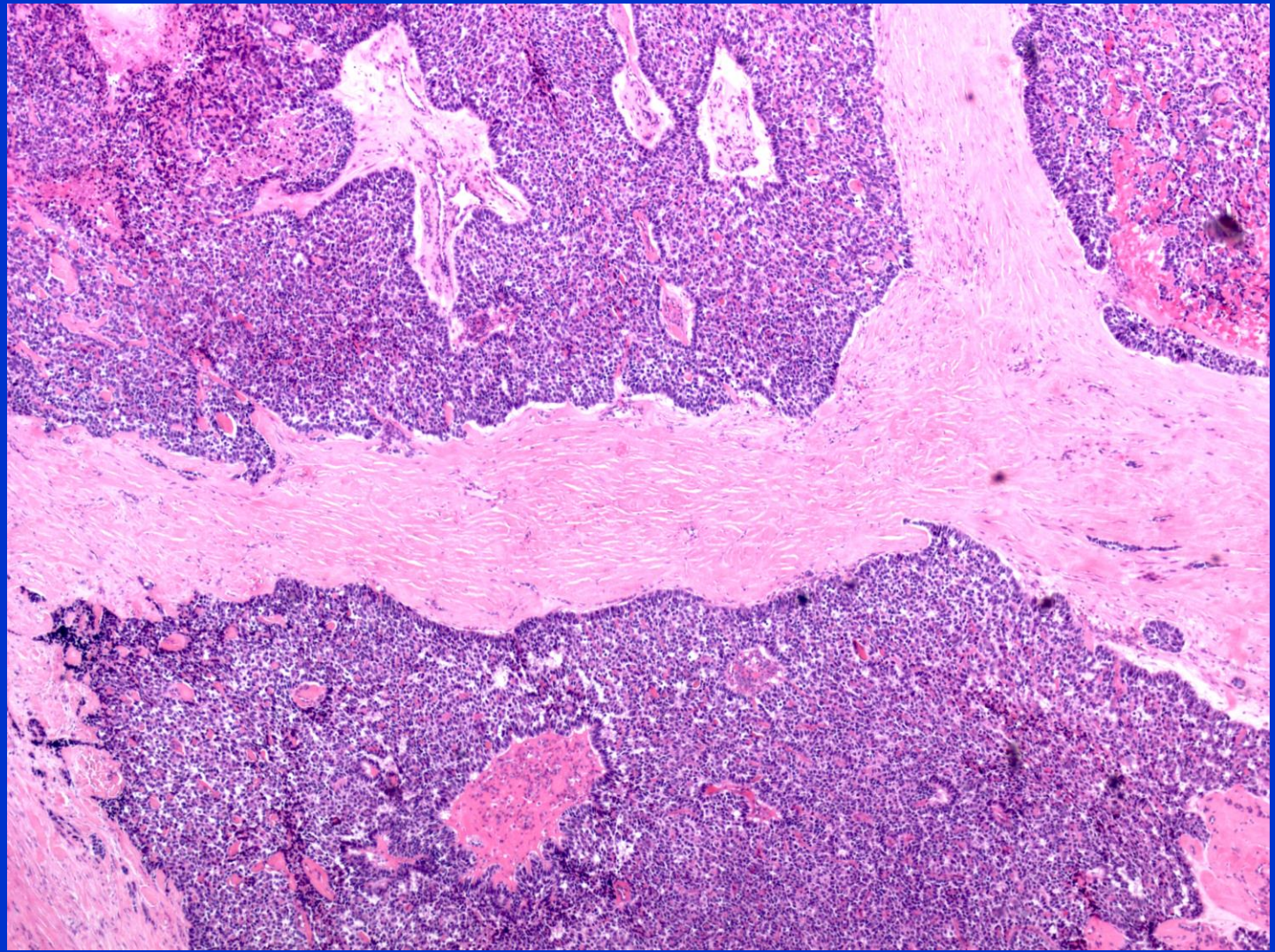
high grade Invasive carcinoma

p63

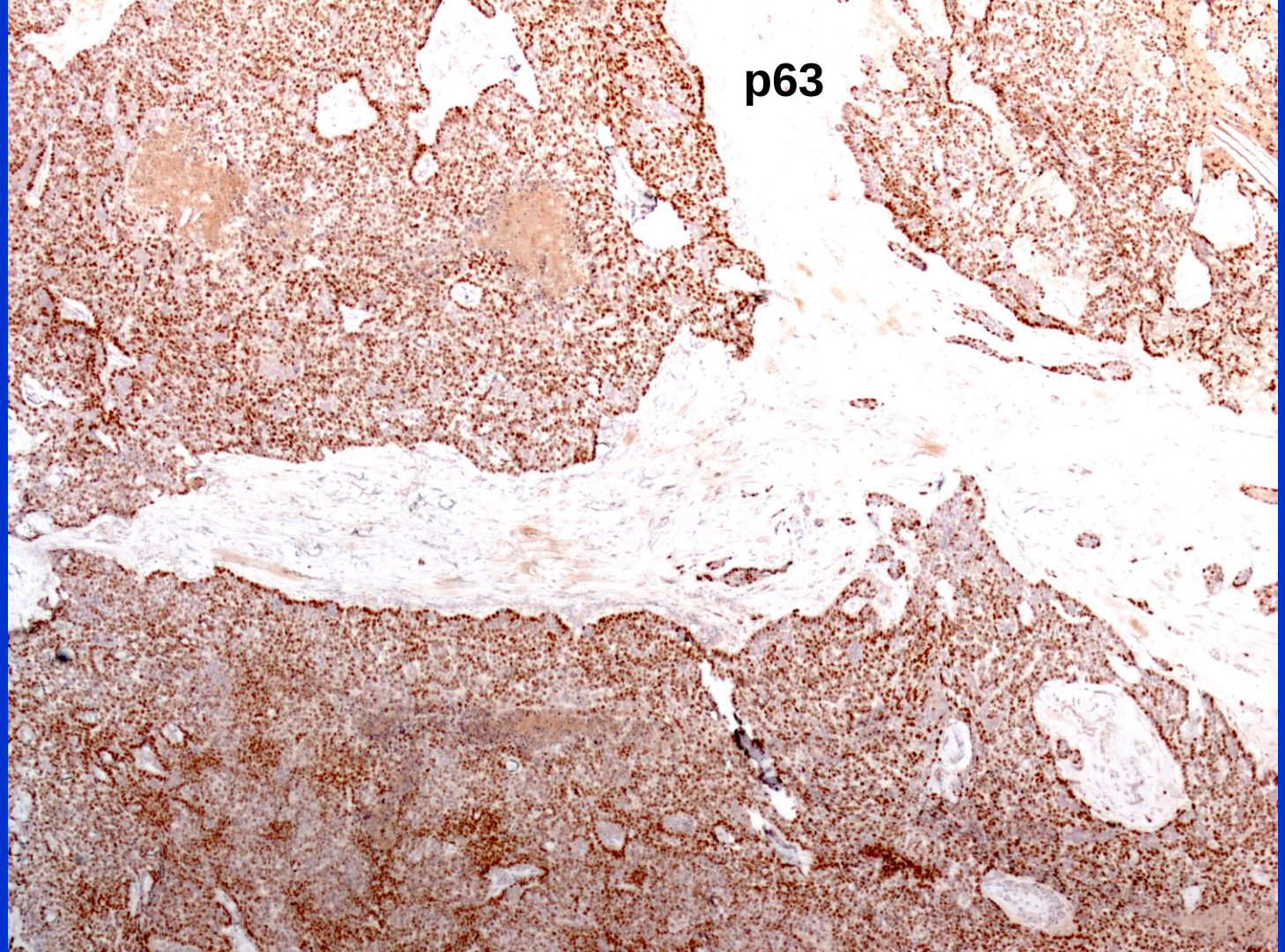


High grade cytology



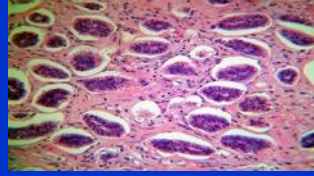


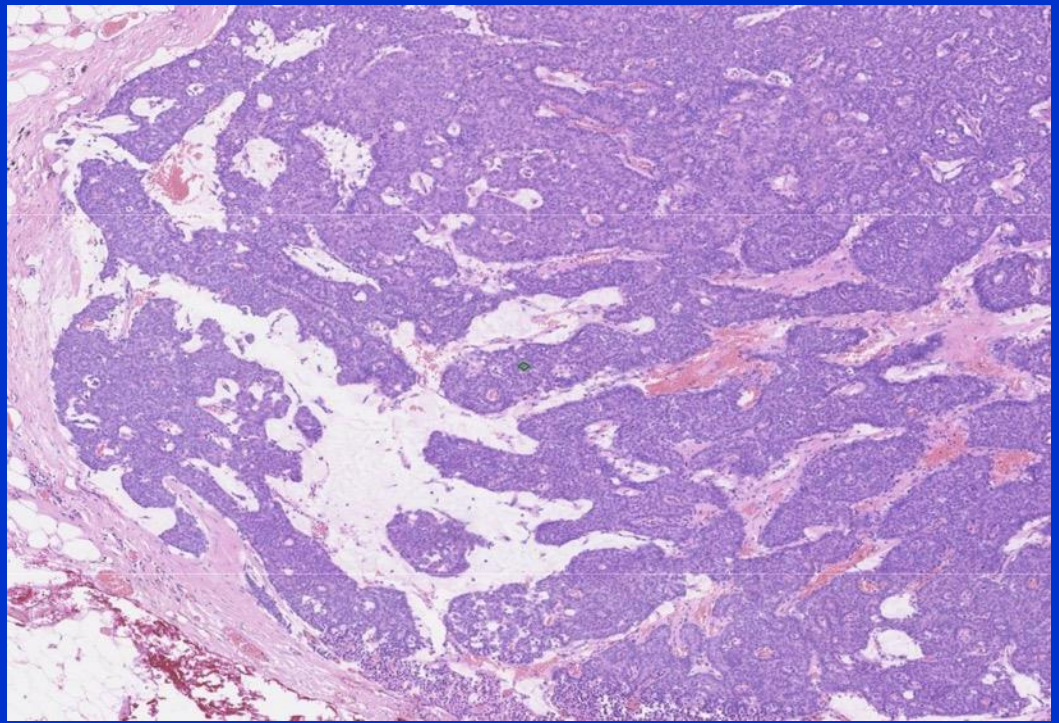
ER
negative

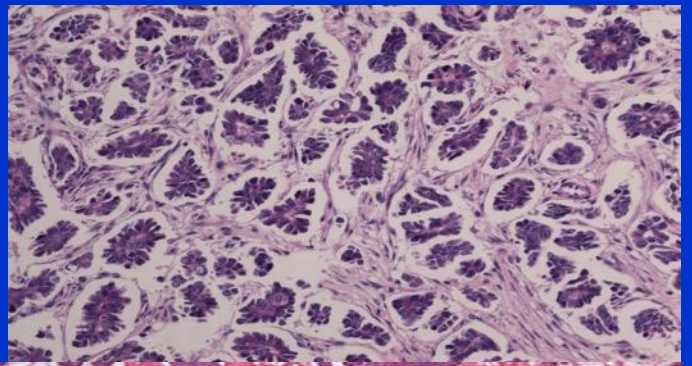


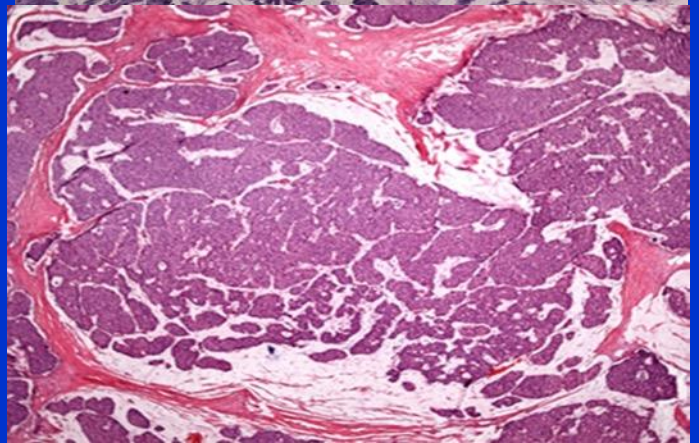
Exceptions in pure EPC:

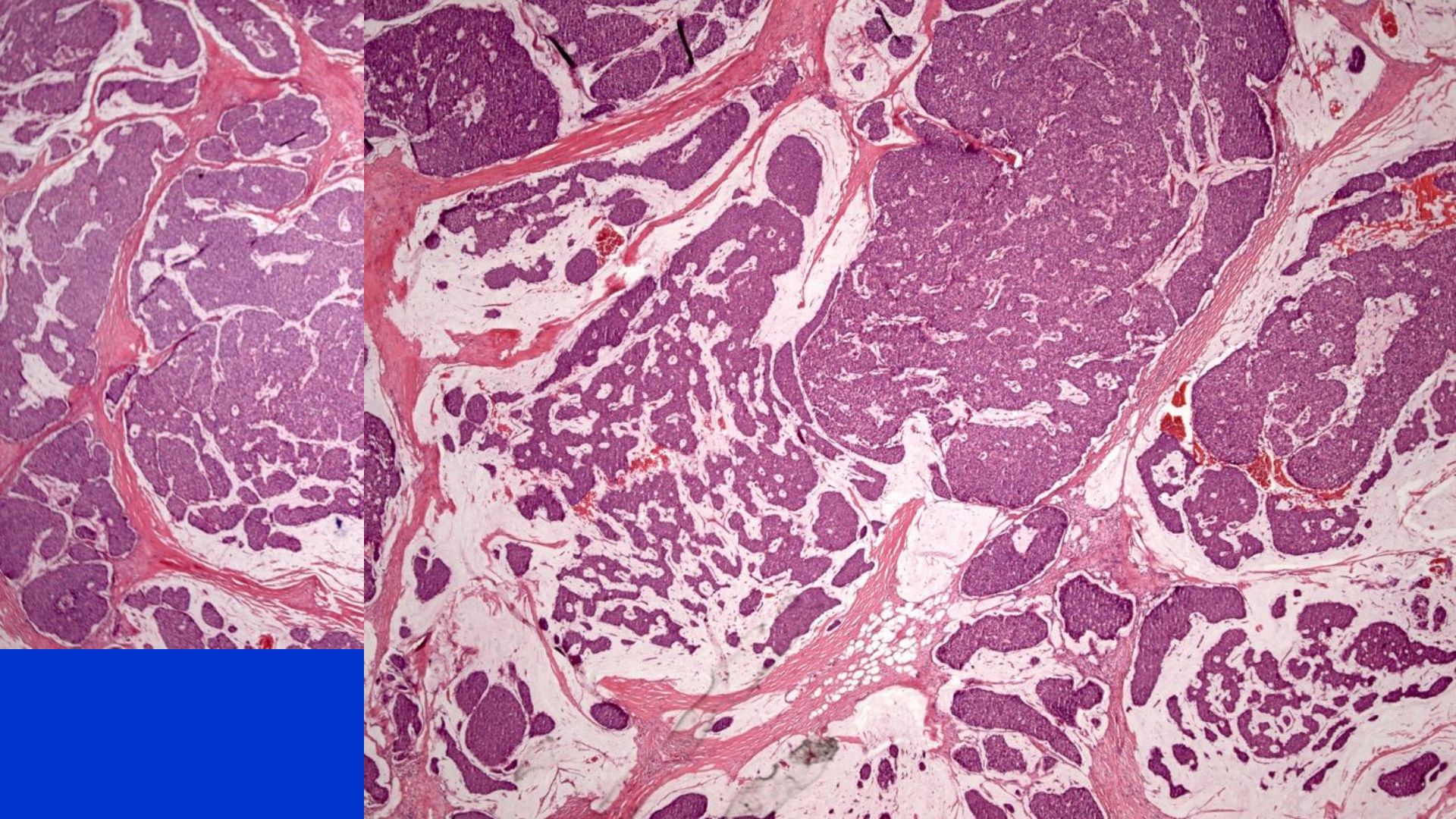
- EPC containing foci of invasive micropapillary carcinoma, or invasive mucinous carcinoma call it invasive carcinoma











Invasive Papillary carcinoma:

1- EPC / SPC associated with conventional type invasion

2- EPC / SPC with invasive features

3- Invasive PC (NOS) without EPC/SPC

EPC/SPC with frank conventional-type invasion

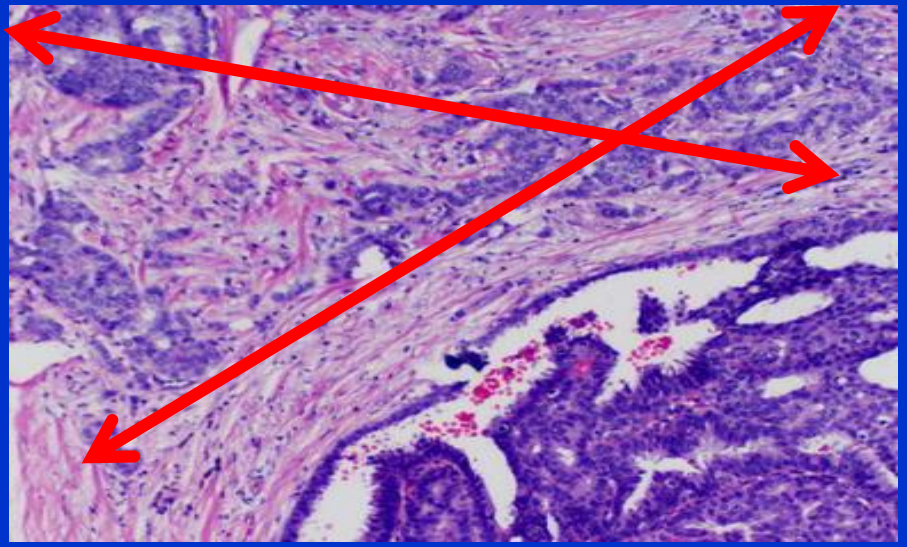
It is usually easy to identify frank invasion associated with PC (e.g., usually conventional carcinoma such as mucinous, NST or cribriform)

Type, grade ER, PR and HER only on invasive foci and not EPC

Invasive size = size of the invasive component while PC can be added to the whole tumour size

Few scattered foci, measure largest focus and call it multifocal

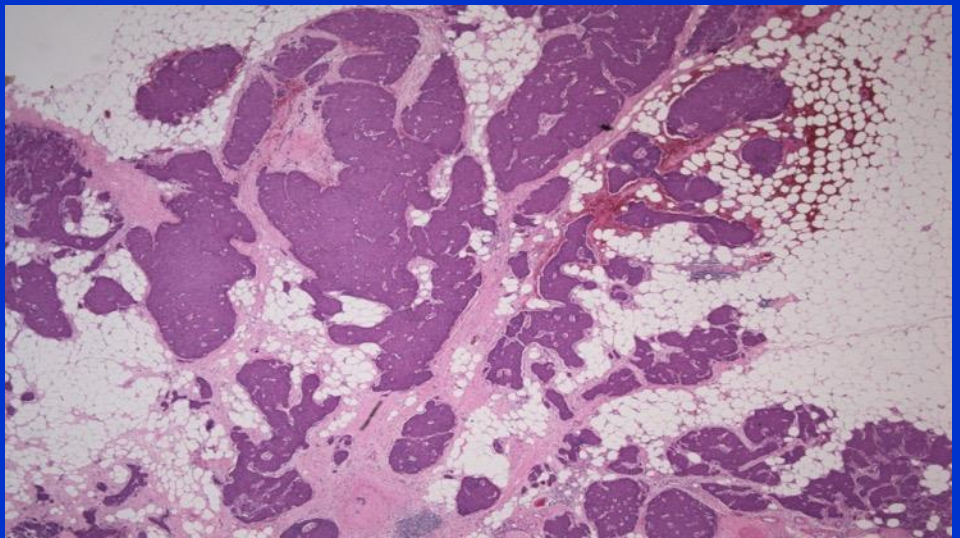
Many scattered foci, measure the whole area and mention this in the text

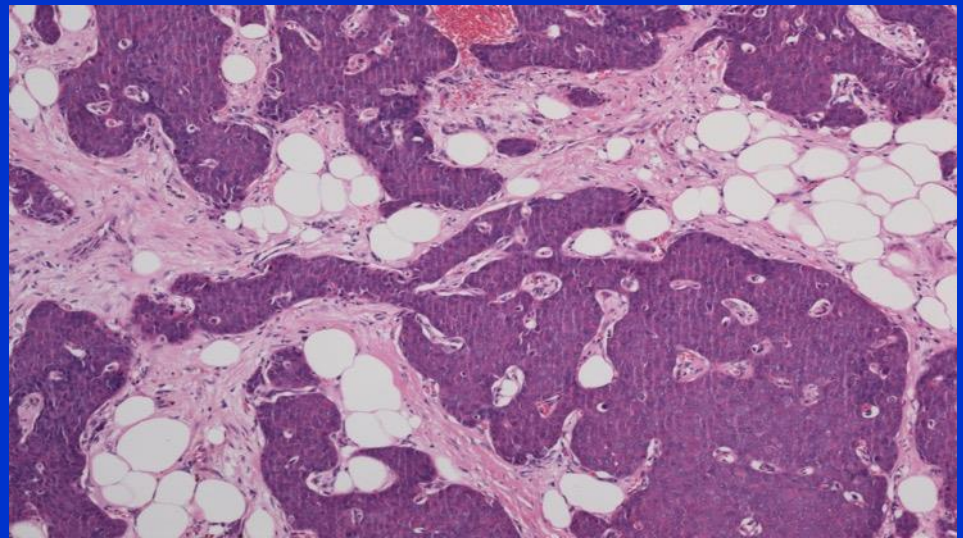


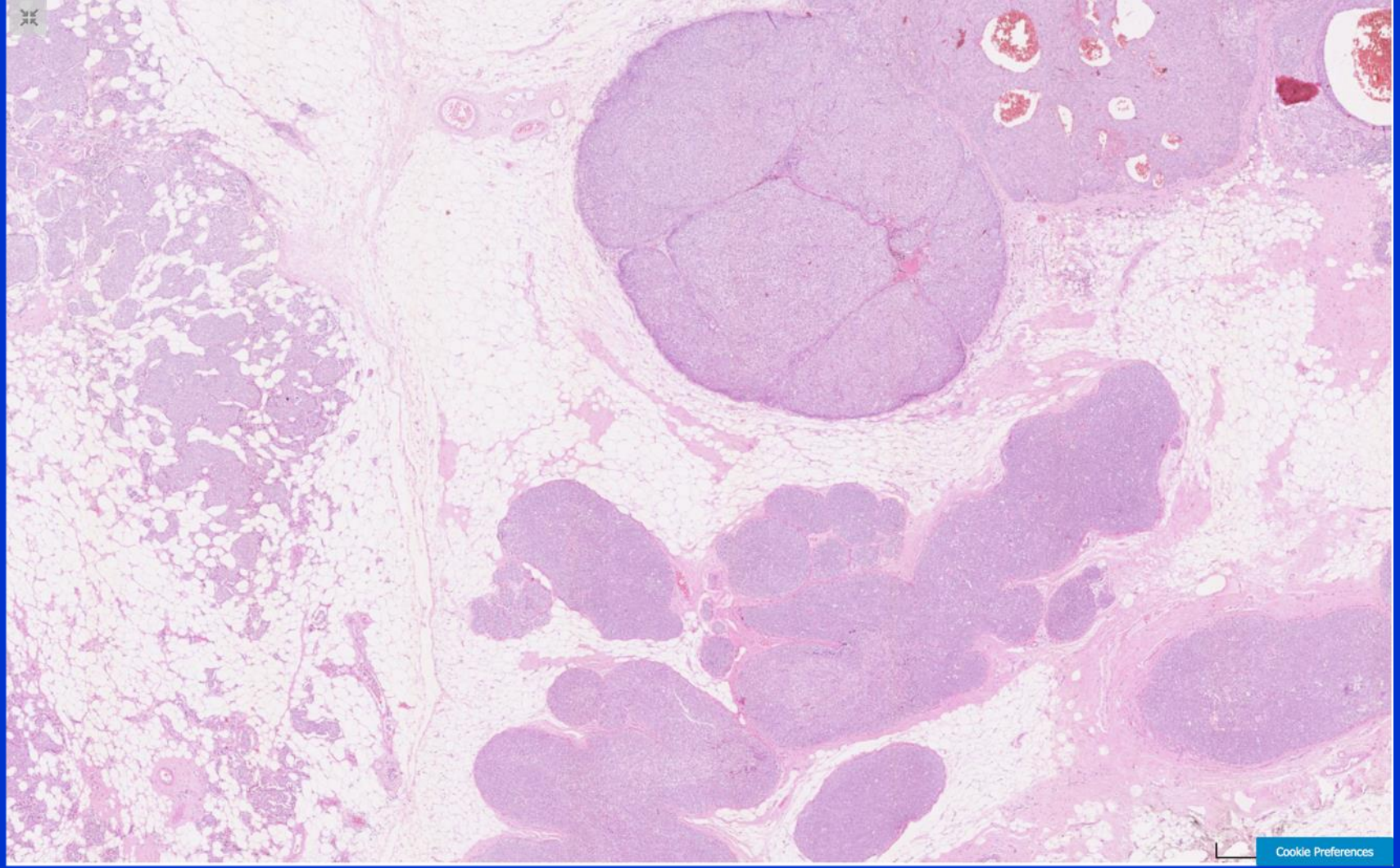
Invasive solid PC

WHO definition of invasion in SPC:

Geographic jigsaw pattern with ragged and irregular margins, + absence of ME cells +/- infiltrating fat







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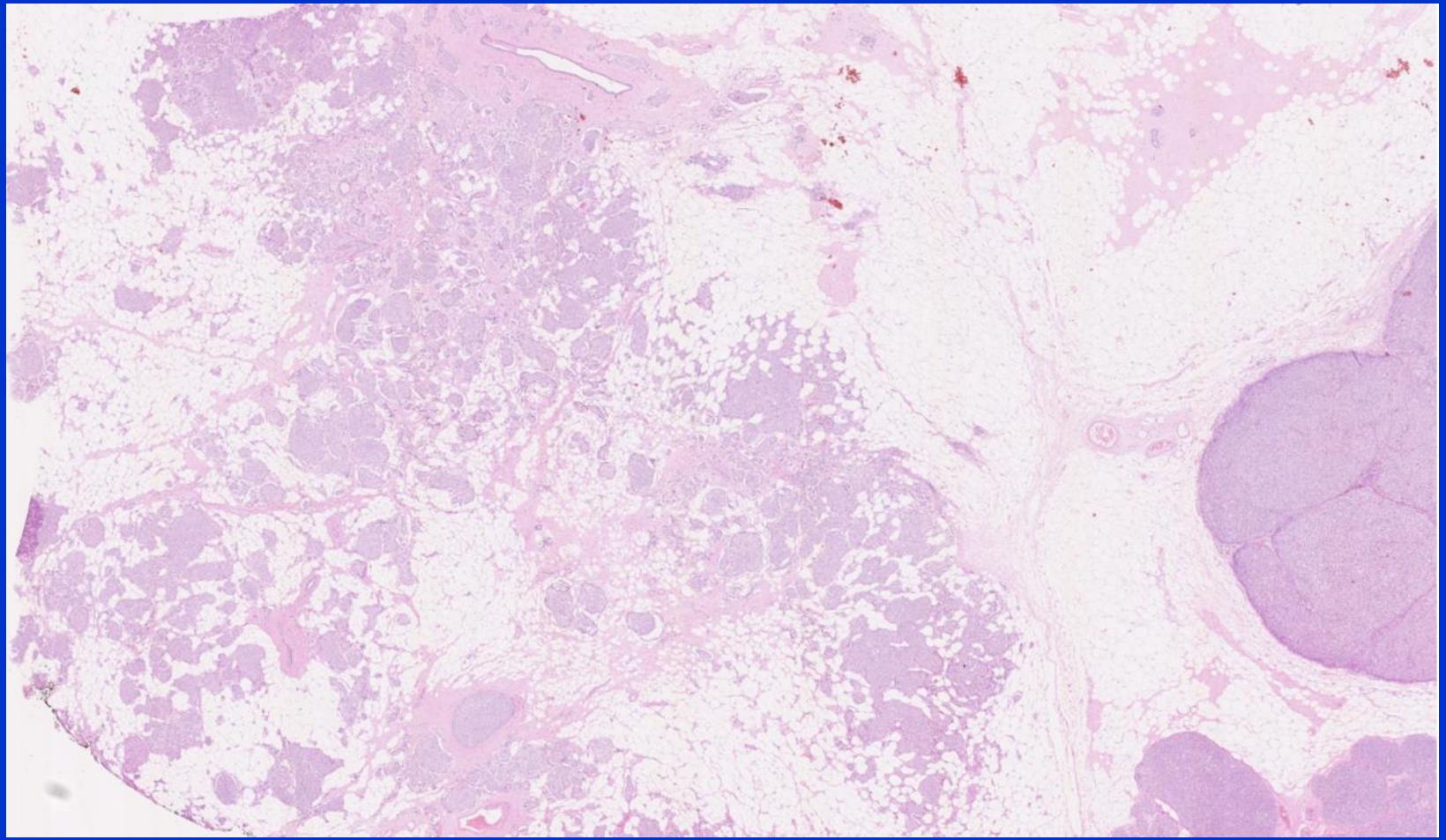
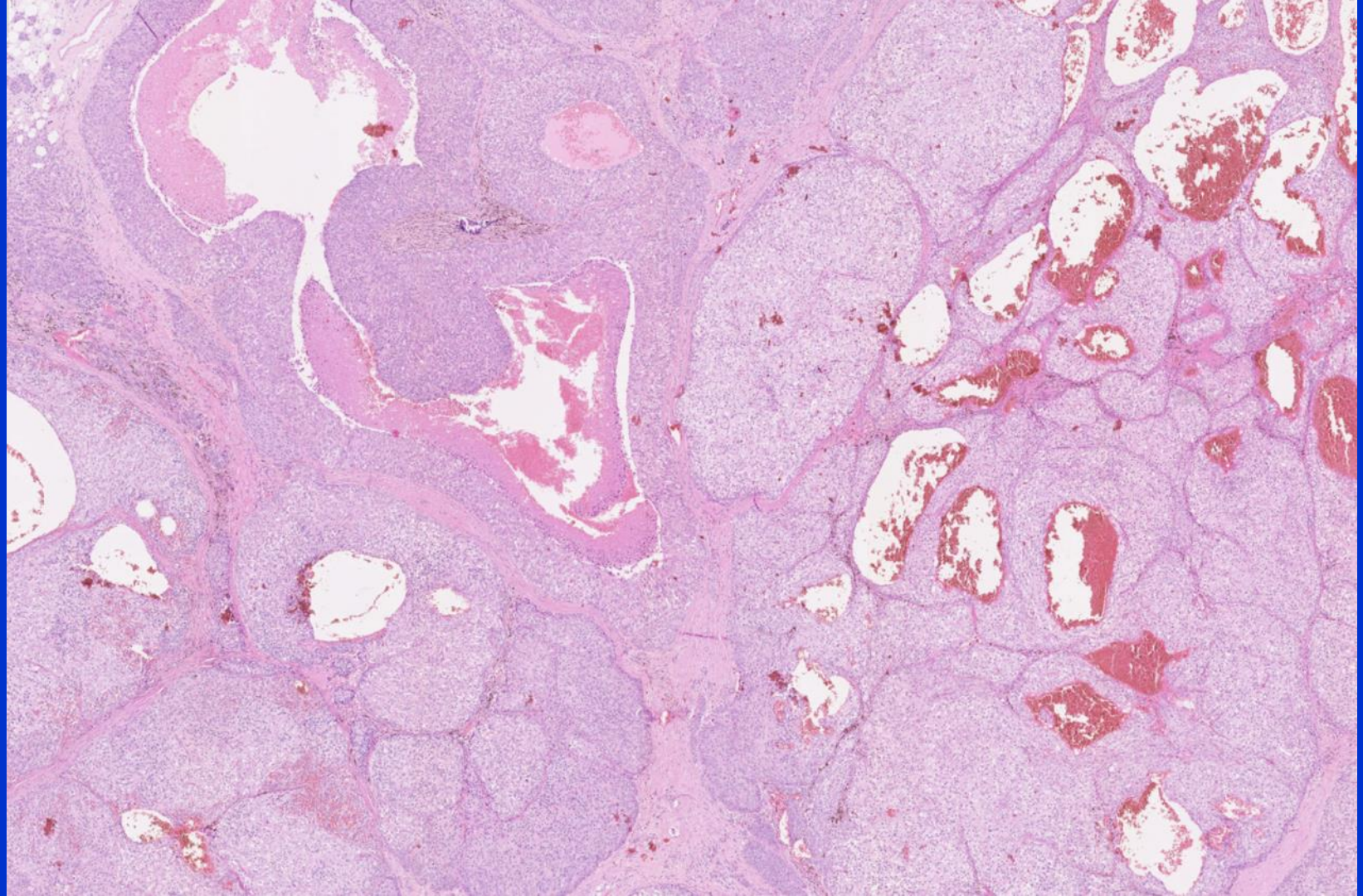
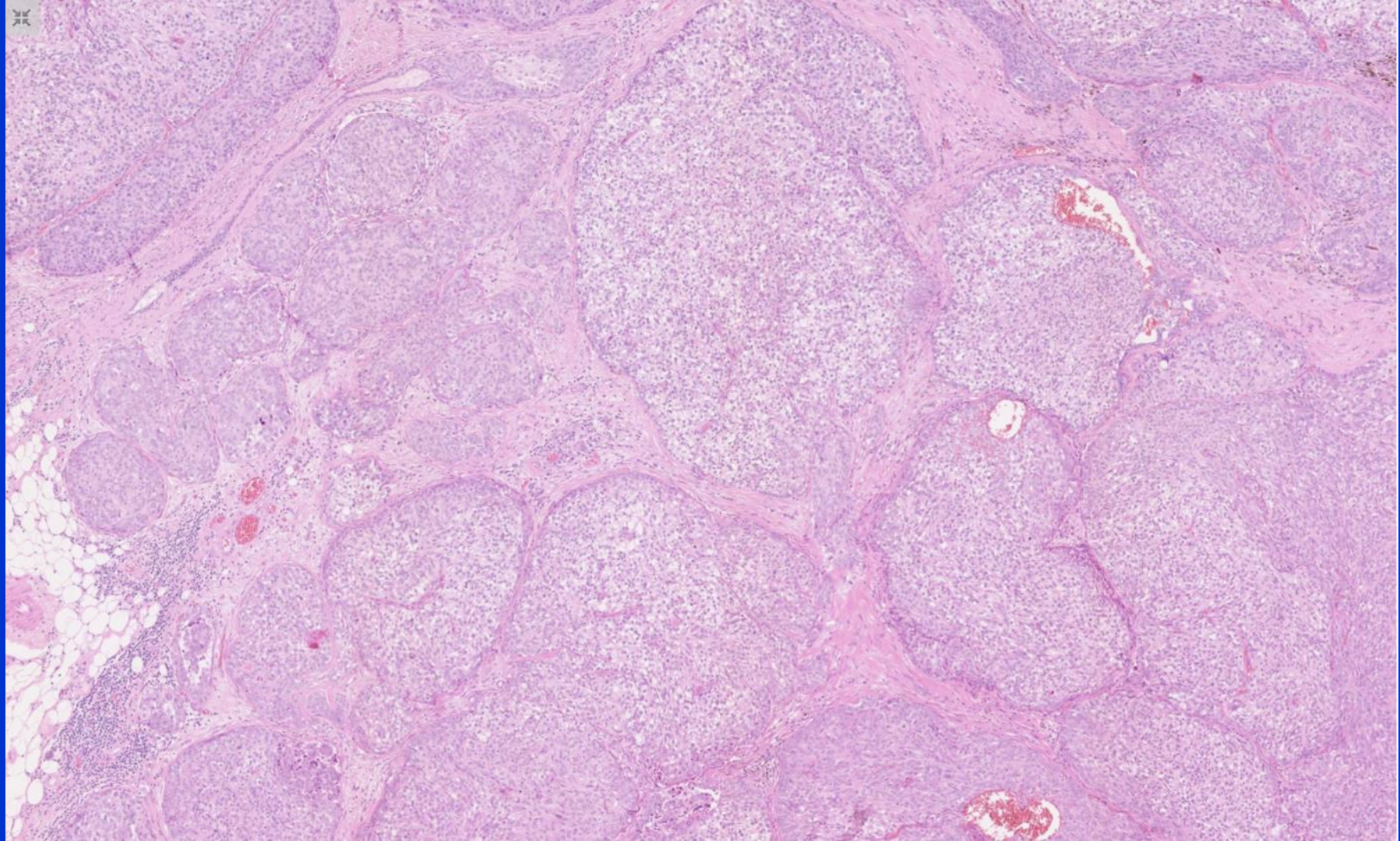
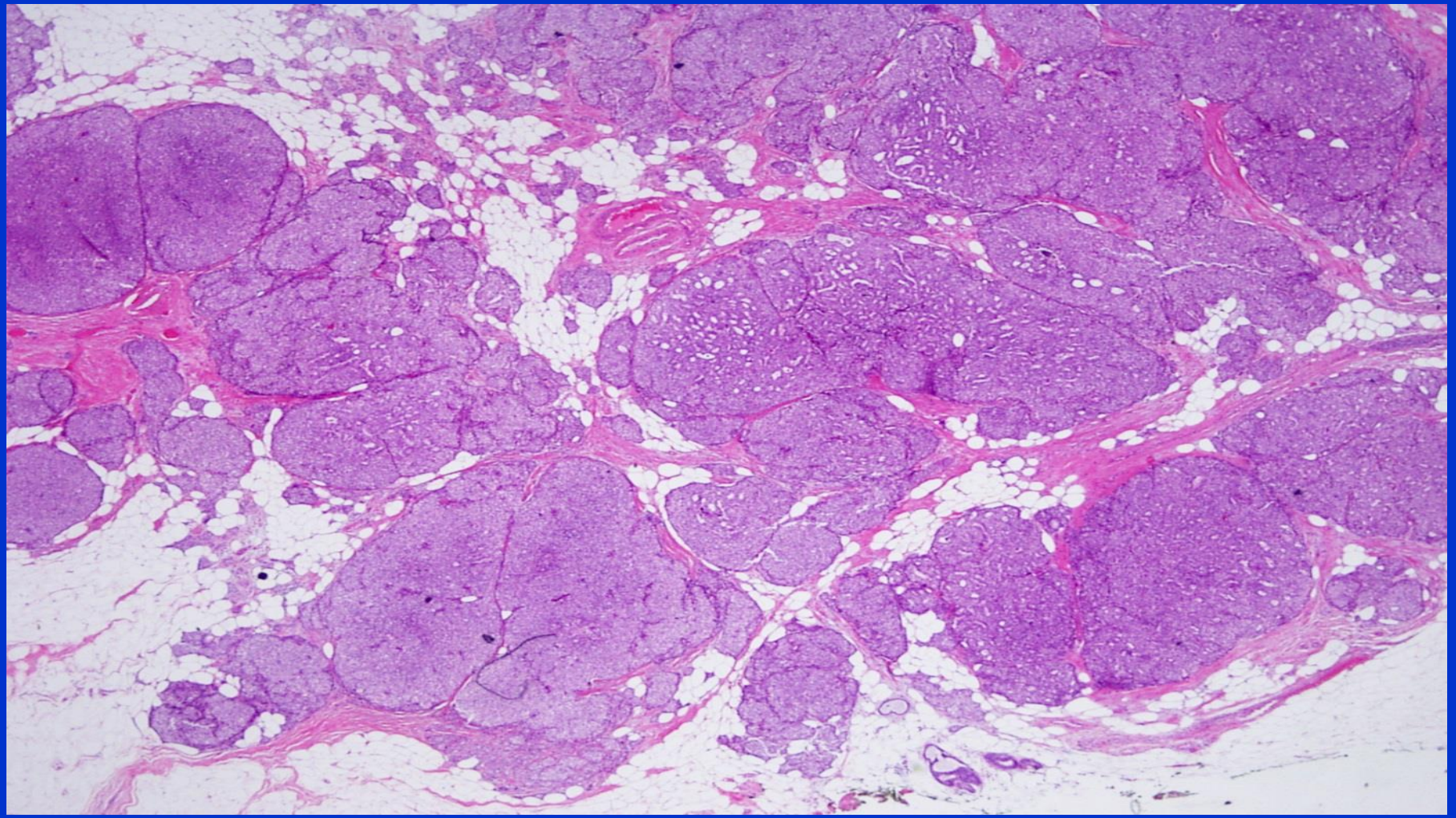
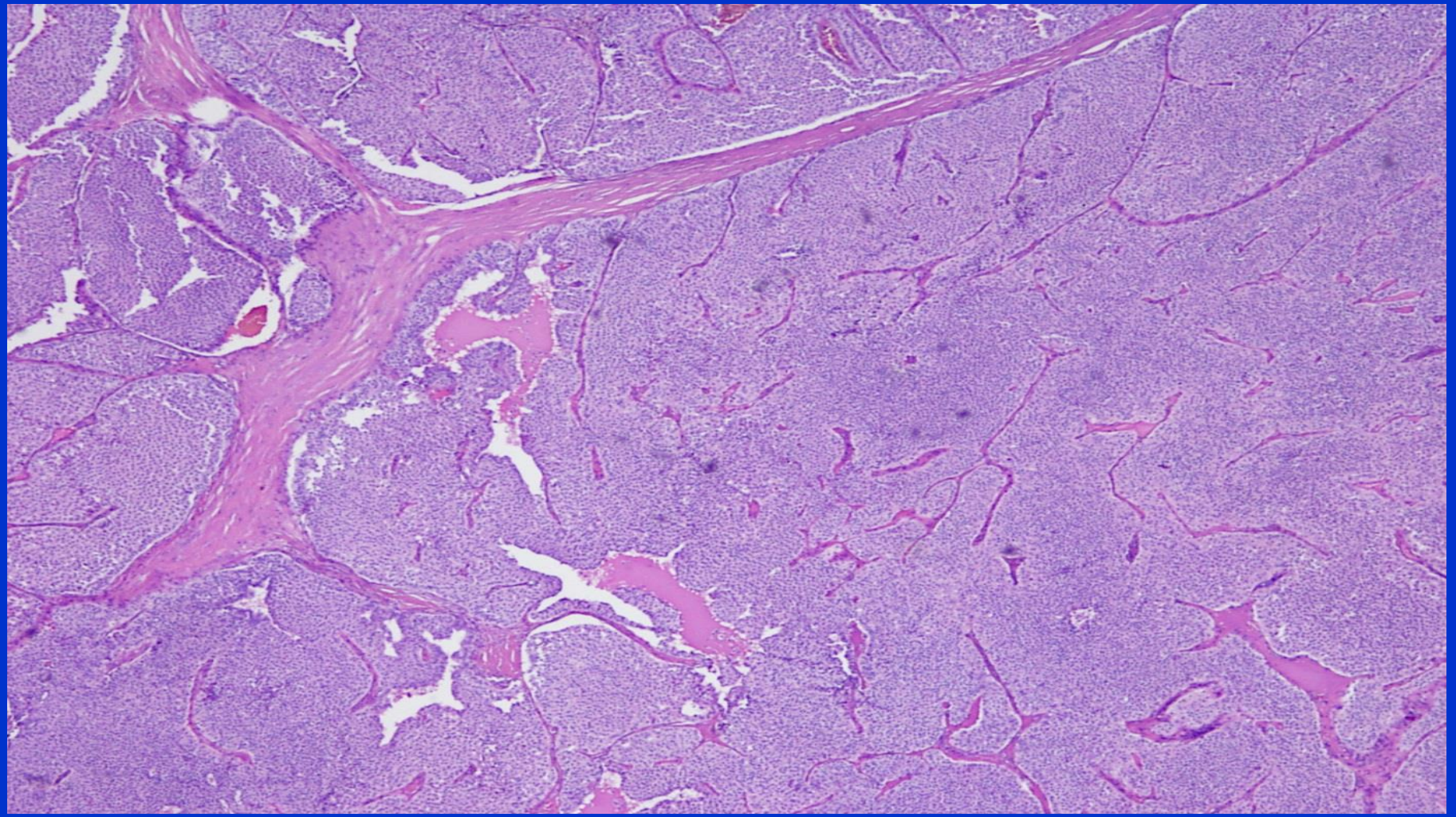








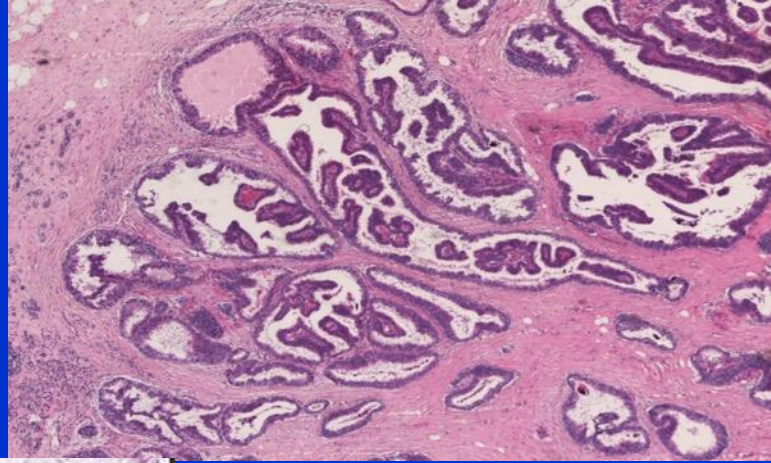


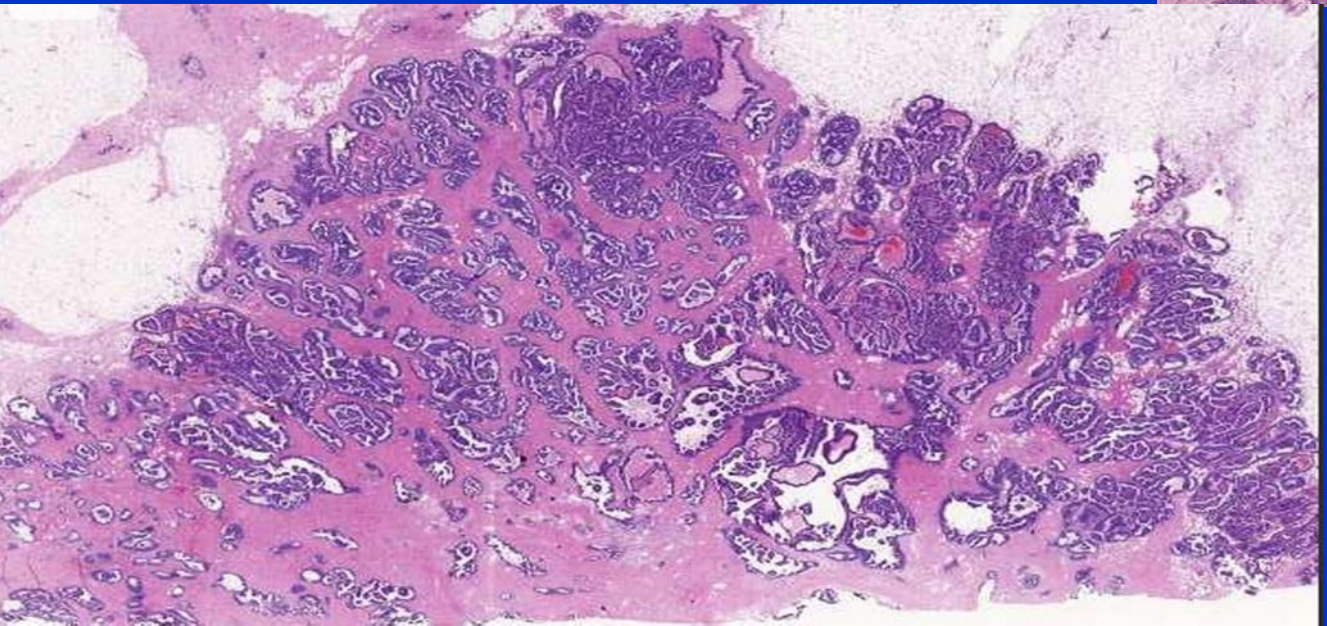
Invasive PC

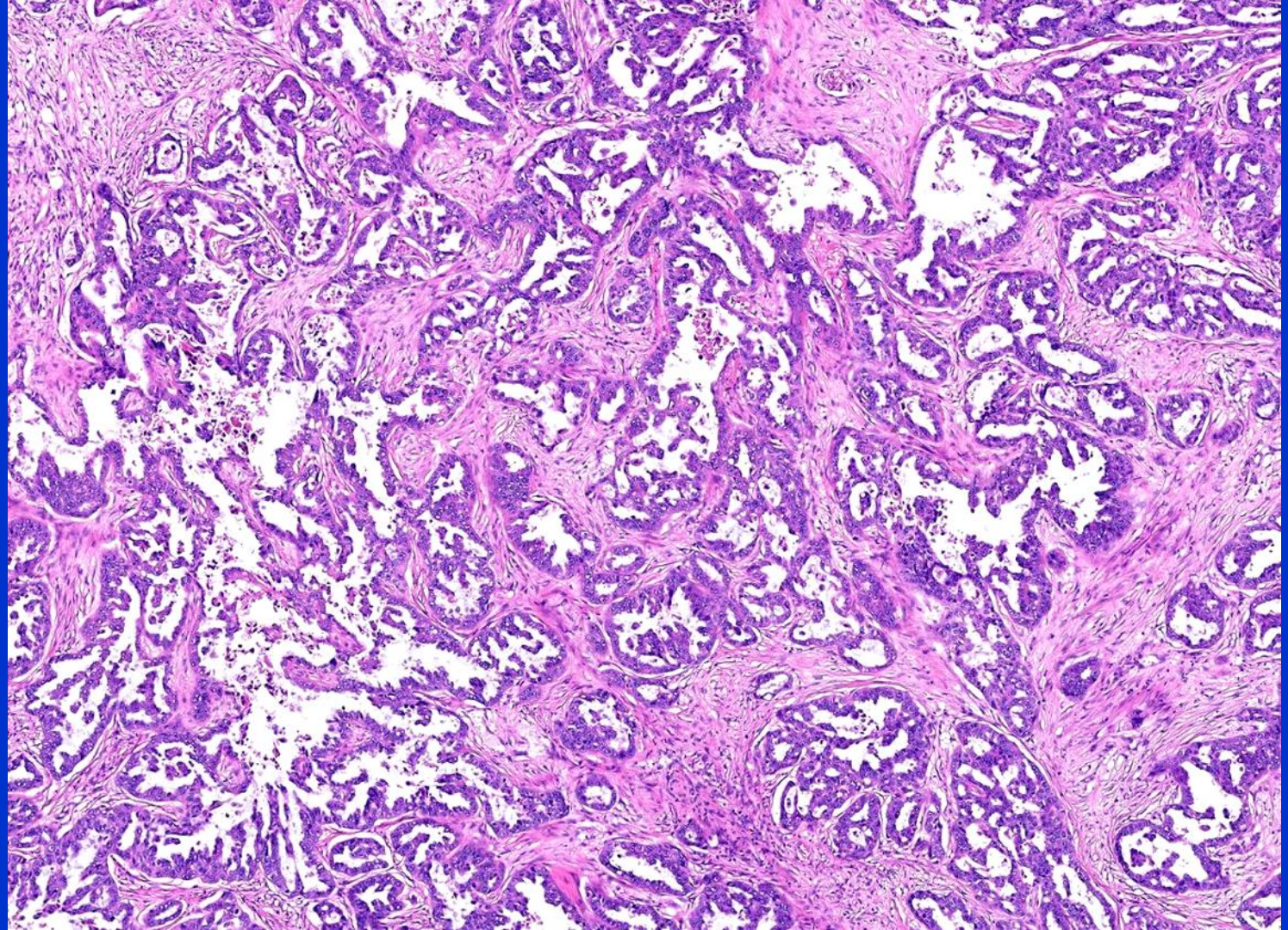
Pure invasive PC is extremely rare

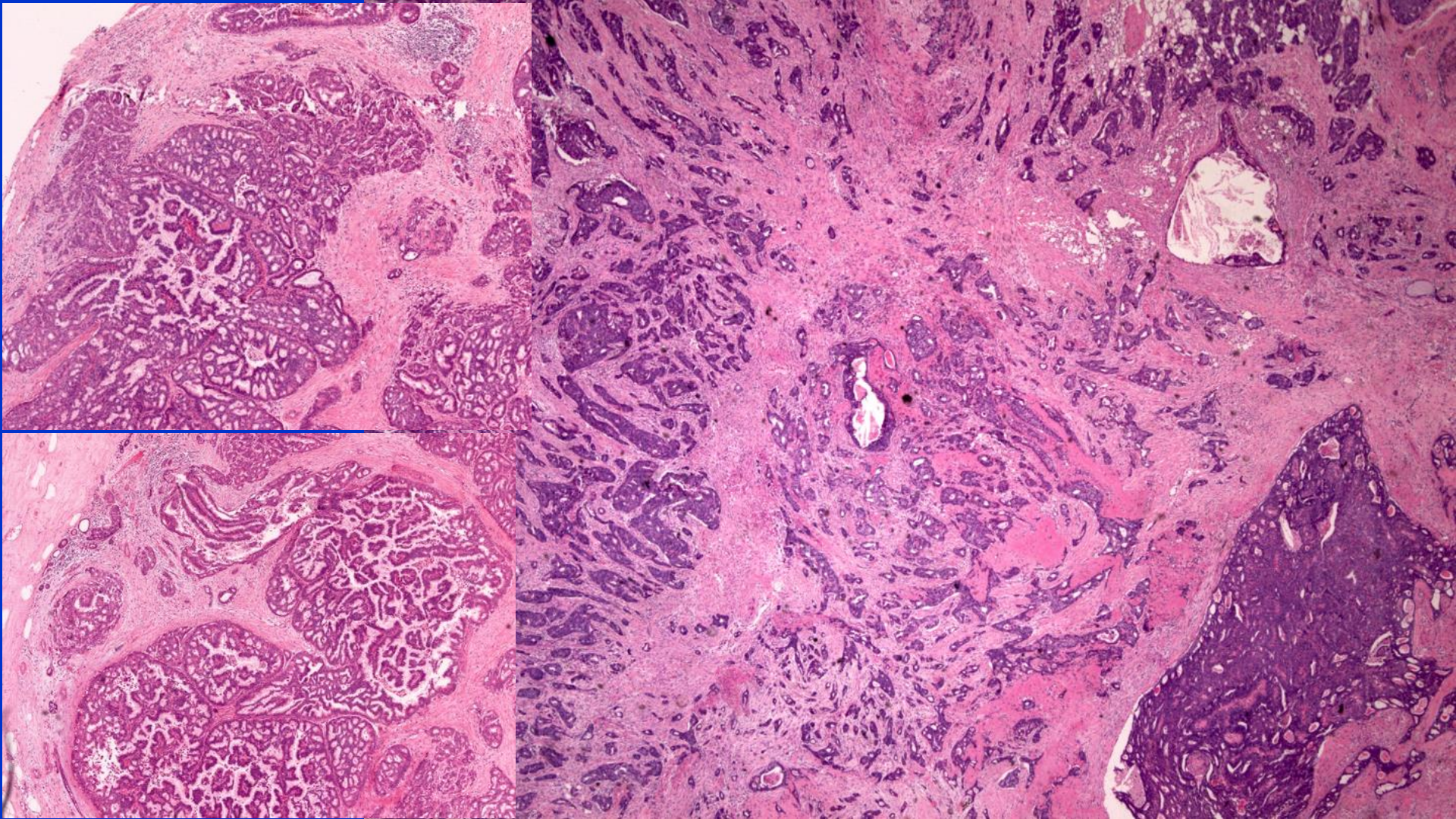
- **Papillary architecture (>90%)**
- **Infiltrating outlines**
- **Complete absence of ME cells**

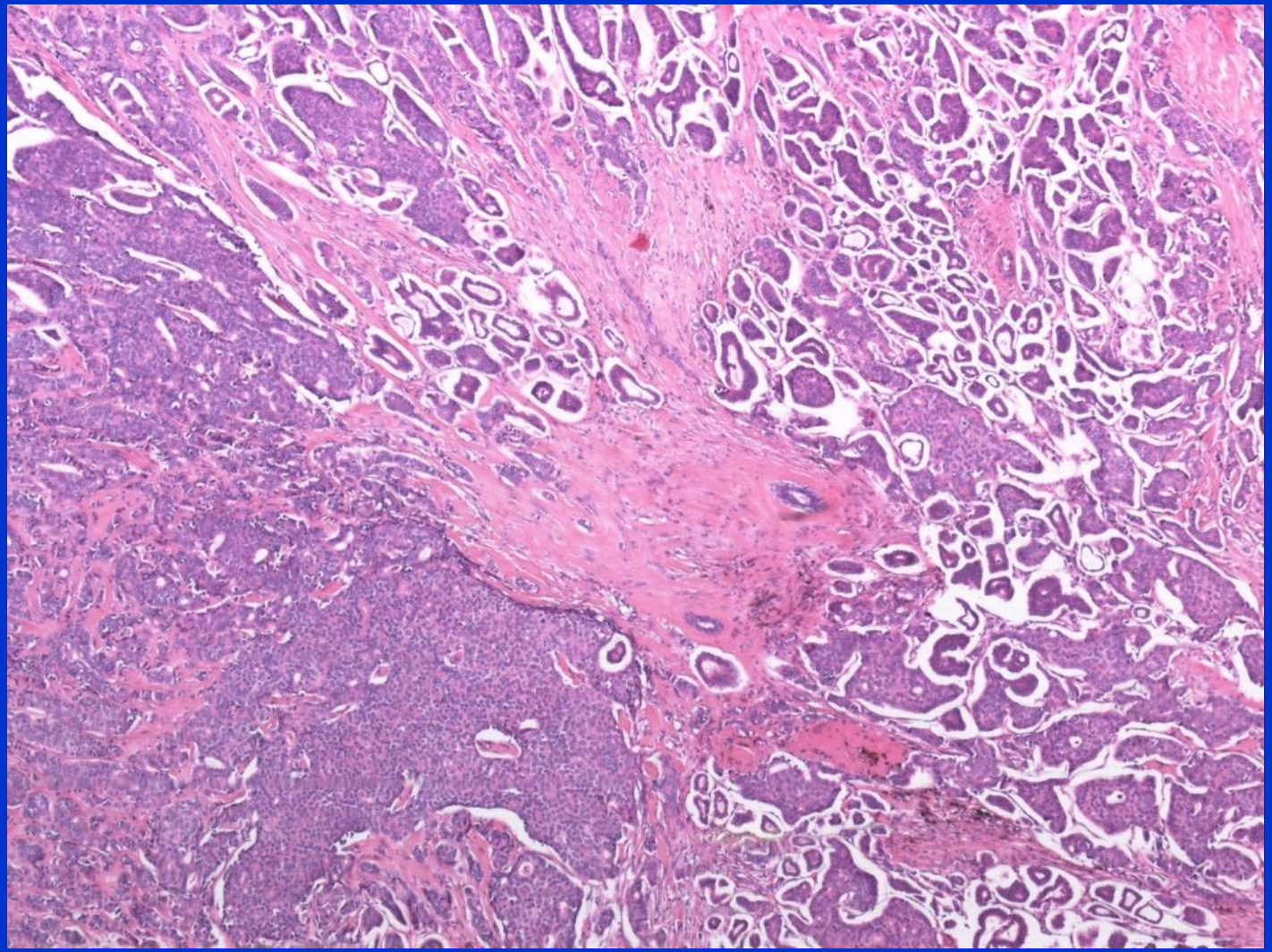
Often low/intermediate grade



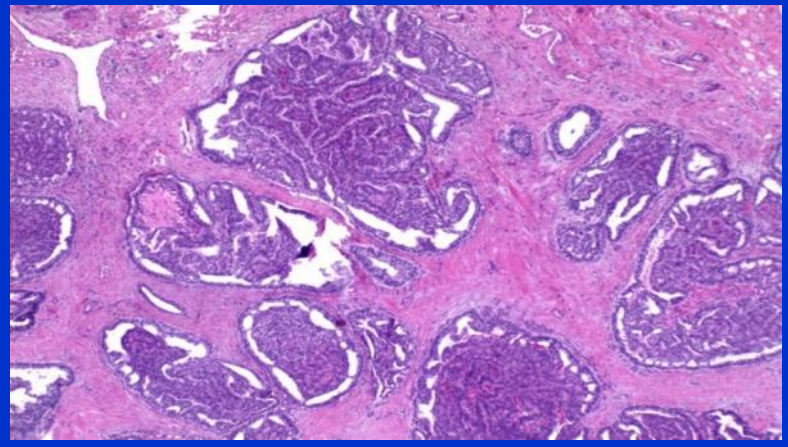


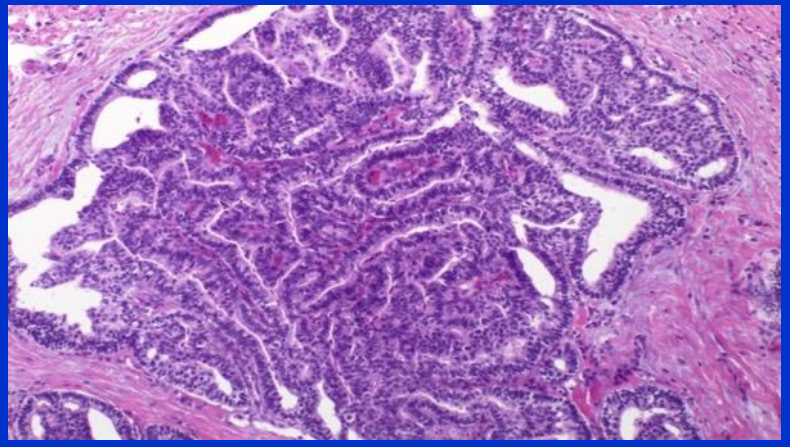


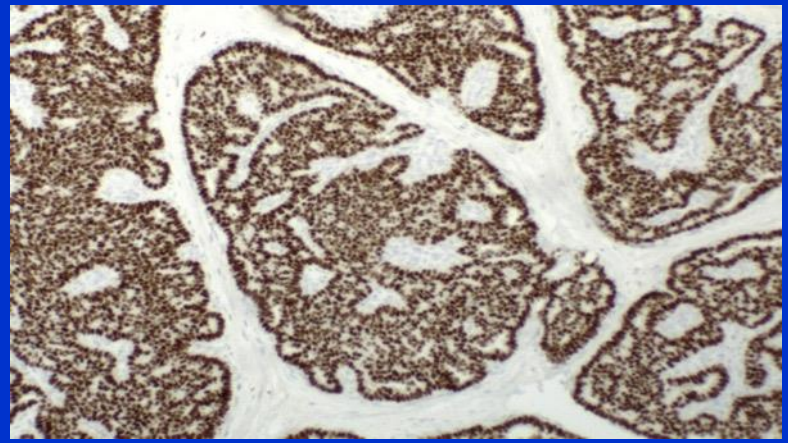


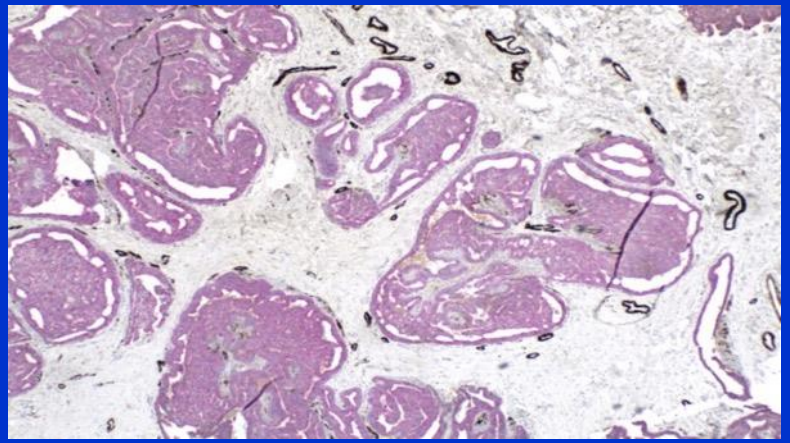


IHC – Invasive Papillary Ca









5th edition of the WHO book

2.4: Papillary neoplasms: Introduction

- 2.4.1: Intraductal papilloma
- 2.4.5: Papillary ductal carcinoma in situ
- 2.4.2: Encapsulated papillary carcinoma
- 2.4.3: Solid papillary carcinoma (in situ and invasive)
- 2.4.4: Invasive papillary carcinoma

Papillary neoplasms

5th edition of the WHO book

	Intraductal Papilloma	Papilloma with ADH or DCIS	Papillary DCIS	Encapsulated Papillary carcinoma	Solid Papillary Carcinoma	Invasive Papillary Carcinoma
Presentation	Single (central papilloma) or multiple lesions (peripheral papillomas)	Single (central papilloma) or multiple lesions (peripheral papillomas)	Multiple lesions	Single lesion	Single or multiple lesions	Single lesion
Papillary Architecture	Generally broad, blunt fronds	Generally broad, blunt fronds	Slender fronds, sometimes branching	Numerous Slender fronds, sometimes branching. Peripheral, typically well-developed, fibrous capsule	Solid with inconspicuous delicate fibrovascular septa	Dilated duct-type structures and microcysts with internal papillae
Epithelial Cells	Heterogeneous non-neoplastic cell population: -Luminal cells, -Usual ductal hyperplasia, -Apocrine metaplasia and hyperplasia	-Focal areas of cells with architectural and cytological features of ADH or DCIS (usually low grade) -Background of heterogeneous non-neoplastic cell population	Entire lesion occupied by a cell population with architectural and cytological features of DCIS of low, intermediate or rarely high nuclear grade. Can grow as a single layer along thin fibrovascular stalks.	Entire lesion occupied by a cell population with architectural and cytological features of DCIS of low or intermediate grade. Can grow as a single layer along thin fibrovascular stalks. Cribriform, micropapillary, and solid patterns may be present with fusion of adjacent papillae.	Entire lesion occupied by a cell population with cytological features of low or intermediate nuclear grade, growing predominately in a solid manner Spindle cell component Neuroendocrine and mucinous differentiation frequent	Low, intermediate or rarely high grade nuclear atypia
Myoepithelial cells	Present throughout and at periphery	Mostly present throughout and at periphery May be attenuated in areas of ADH/DCIS	-Absent or scant in papillae -Present in attenuated form at the periphery of ducts	Usually absent throughout and at periphery	Present or absent within the solid papillary proliferation or at the outer contours of the nodules	Absent throughout

In rare cases there are overlapping features between solid papillary carcinoma and encapsulated papillary carcinoma or between encapsulated papillary carcinoma and papillary DCIS and it may not be possible to distinguish PC subtypes in every single case

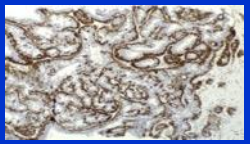
Papillary Carcinomas

	Encapsulated papillary carcinoma	Encapsulated papillary carcinoma with frank invasion	Solid papillary carcinoma in situ	Solid papillary carcinoma with invasion	Invasive solid papillary carcinoma	Invasive papillary carcinoma
Periphery of the lesion	Neoplastic cells surrounded by fibrous capsule	-Neoplastic cells with infiltrative growth beyond fibrous capsule -Invasive carcinoma NST, cribriform, tubular, mucinous carcinoma	Nodules with smooth rounded contours	Nodules with smooth rounded contours associated with an invasive component that can take the form of: -Strands and cell clusters within pools of extracellular mucin corresponding to mucinous carcinoma -Invasive carcinoma NST, cribriform, tubular	Nodules with ragged contours creating a geographical jigsaw pattern within a desmoplastic stroma.	invasive mammary carcinoma with predominantly papillary morphology (> 90%) and infiltrative growth pattern
Myoepithelial cell layer	Absent Occasionally present	Absent in frankly invasive component	Absent or present	Absent in the invasive component	Absent	Absent
Tumor grading	Lesion should be graded according to nuclear grade	Frankly invasive component should be graded according to Nottingham grading system	Lesion should be graded according to nuclear grade	Invasive component should be graded according to Nottingham grading system	Invasive component should be graded according to Nottingham grading system	Lesion should be graded according to Nottingham grading system
Tumor staging	pTis(DCIS)	pT according to size of frankly invasive component	pTis(DCIS)	pT according to size of invasive component	pT according to size of invasive component	pT according to size of lesion
Immunophenotypic characteristics	**For diagnostic purposes**: ER strongly and diffusely positive, PR variable, Her2 negative **For theranostic purposes**: receptor and Her2 status not needed	**For diagnostic purposes**: ER strongly and diffusely positive, PR variable, Her2 negative **For theranostic purposes**: ER, PR, and Her2 status should be assessed on the frankly invasive component	**For diagnostic purposes**: ER strongly and diffusely positive, PR variable, Her2 negative **For theranostic purposes**: receptor and Her2 status not needed	**For diagnostic purposes**: ER strongly and diffusely positive, PR variable, Her2 negative **For theranostic purposes**: receptor and Her2 status should be assessed on the invasive component only.	**For diagnostic purposes**: ER strongly and diffusely positive, PR variable, Her2 negative **For theranostic purposes**: receptor and Her2 status should be assessed on the invasive component only.	**For diagnostic purposes:** exclude metastatic carcinoma **For theranostic purposes**: ER, PR, and Her2 status should be assessed on the entire lesion.

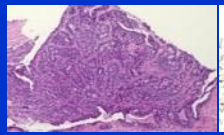
Core biopsy

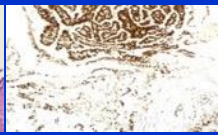
- **Benign papilloma: B3 (without atypia)**

Basal/ME markers

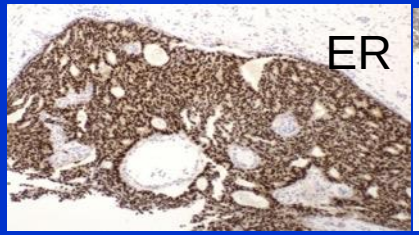


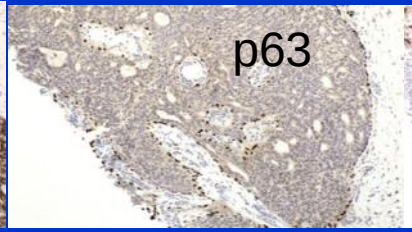
- **Benign papillary lesion with Atypia: B3 (with atypia)**



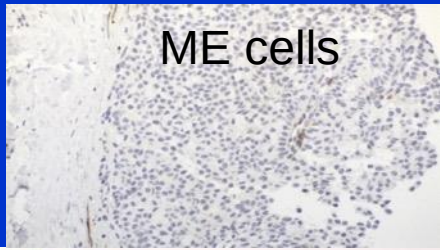


- **Papillary lesion with extensive atypia (?DCIS): Unless it is sufficient for the diagnosis of DCIS (ie high grade or definitely large size) (B5a) otherwise B3 with comments that it is likely to represent DCIS on excision to be considered in the management**





Core biopsy

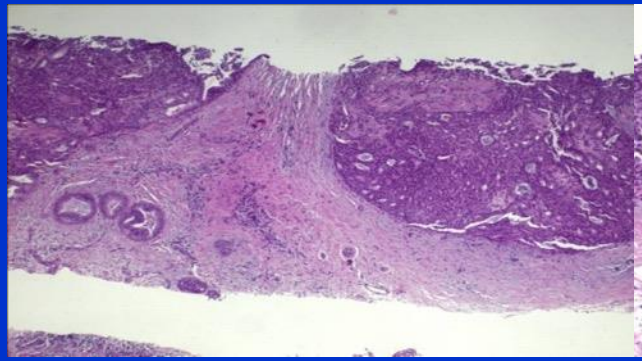


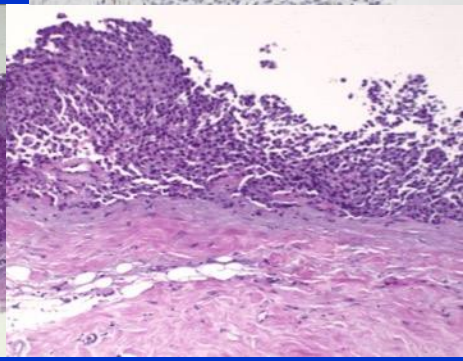
EPC/SPC: B5a

-Well-defined margin,

-Surrounded by capsule

- No evidence of invasion





EPC with suspicious area/not sure about invasion: B5 ?

Papillary with invasion: B5b

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REVIEW: 50TH ANNIVERSARY ISSUE

Diagnostic challenges in papillary lesions of the breast

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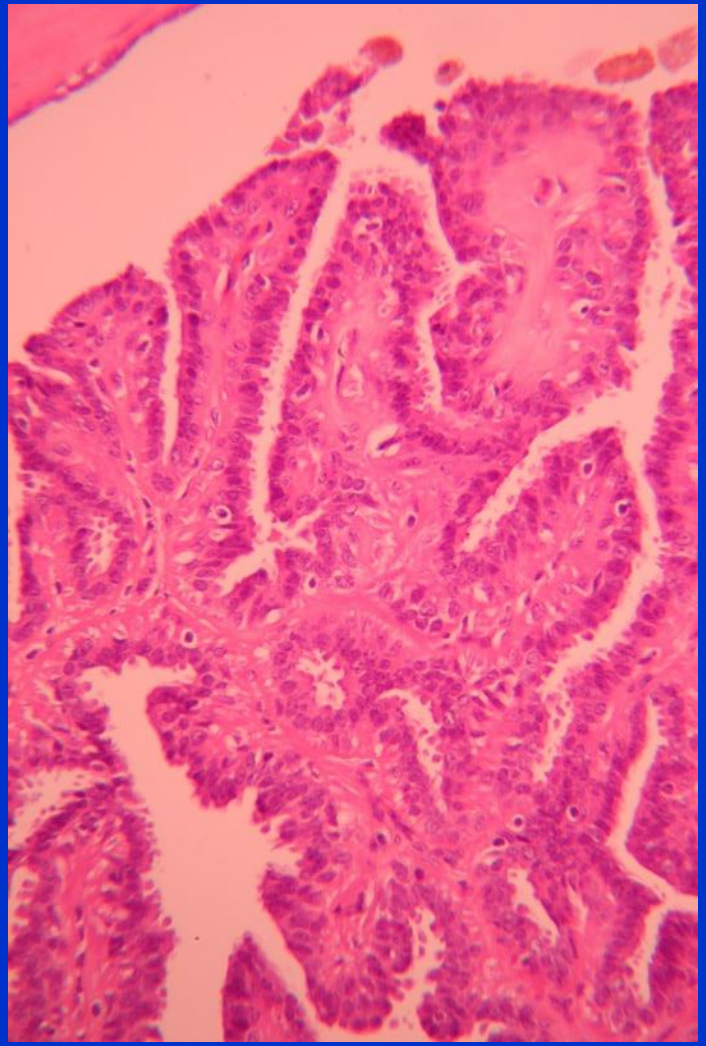
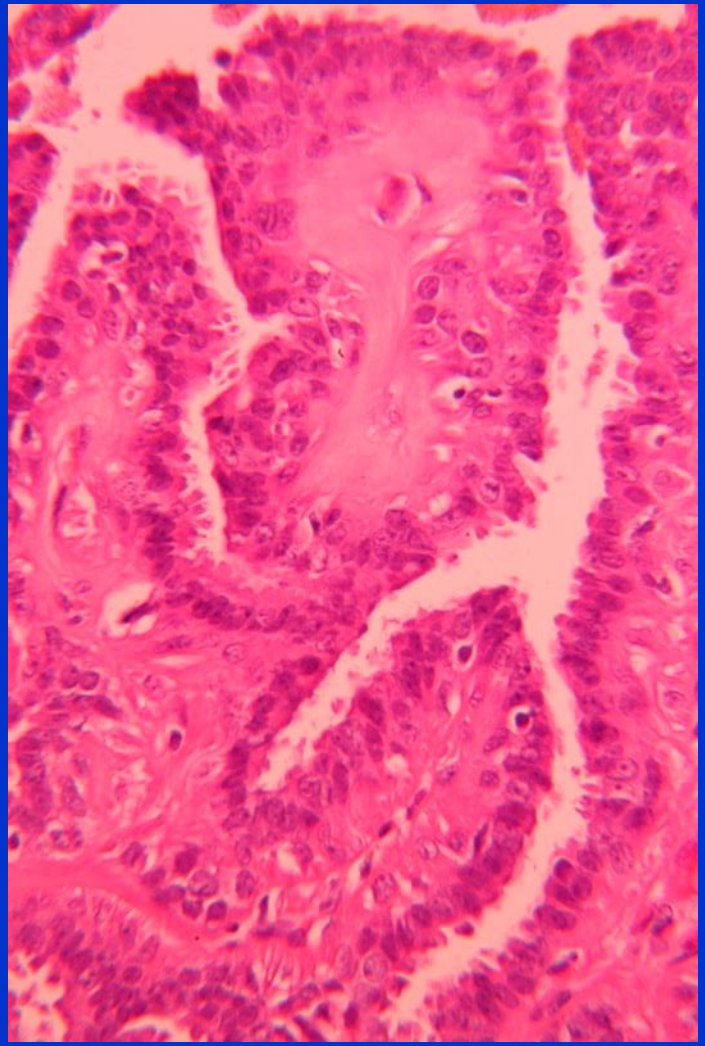
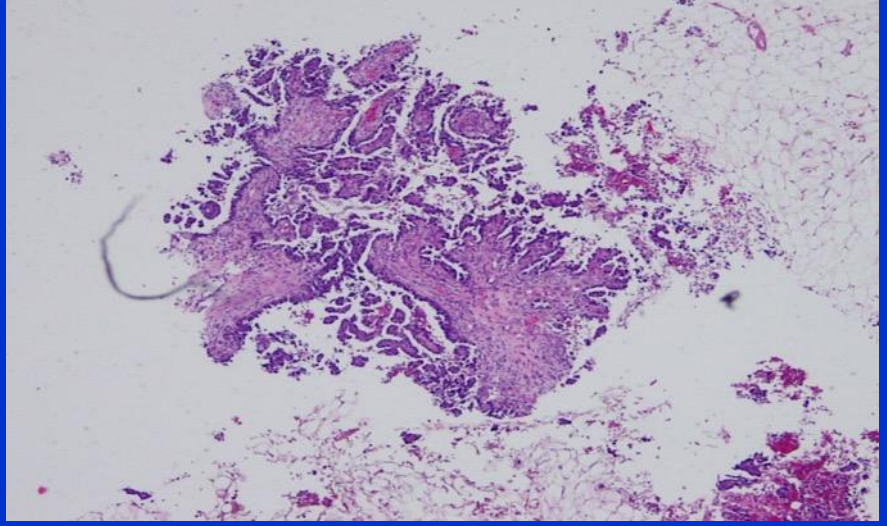
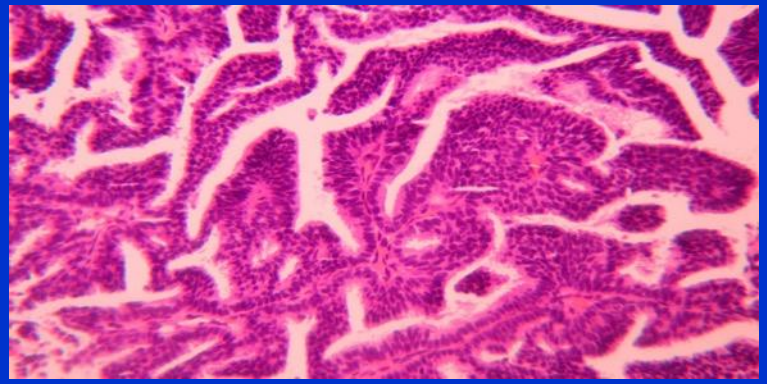


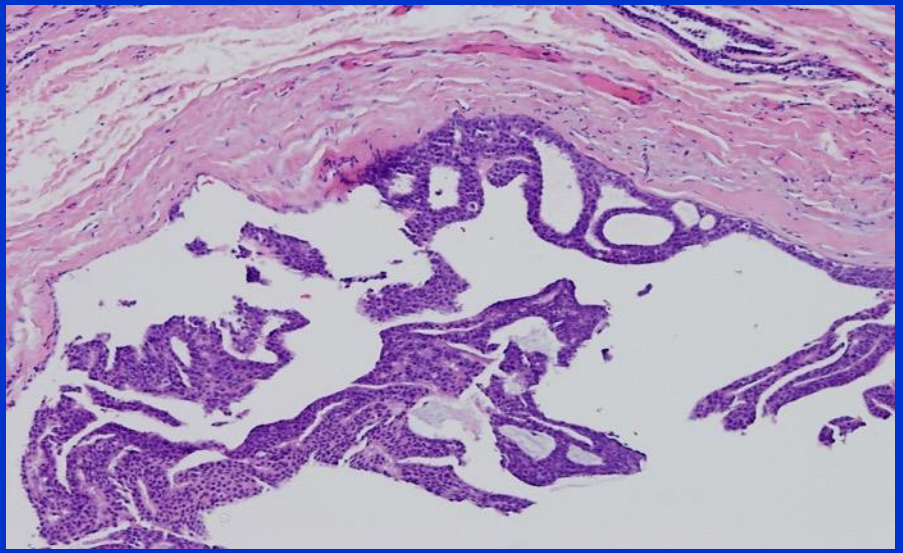


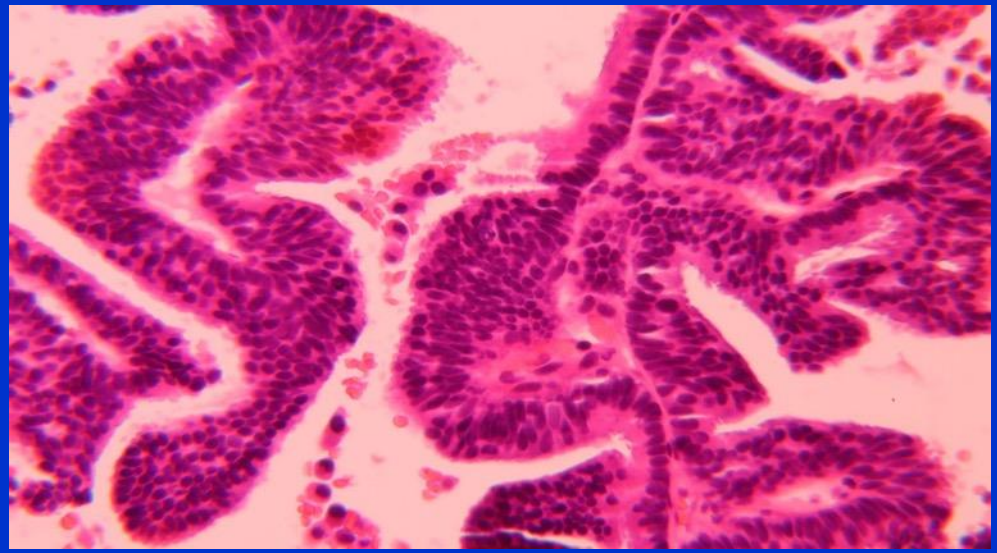
B3

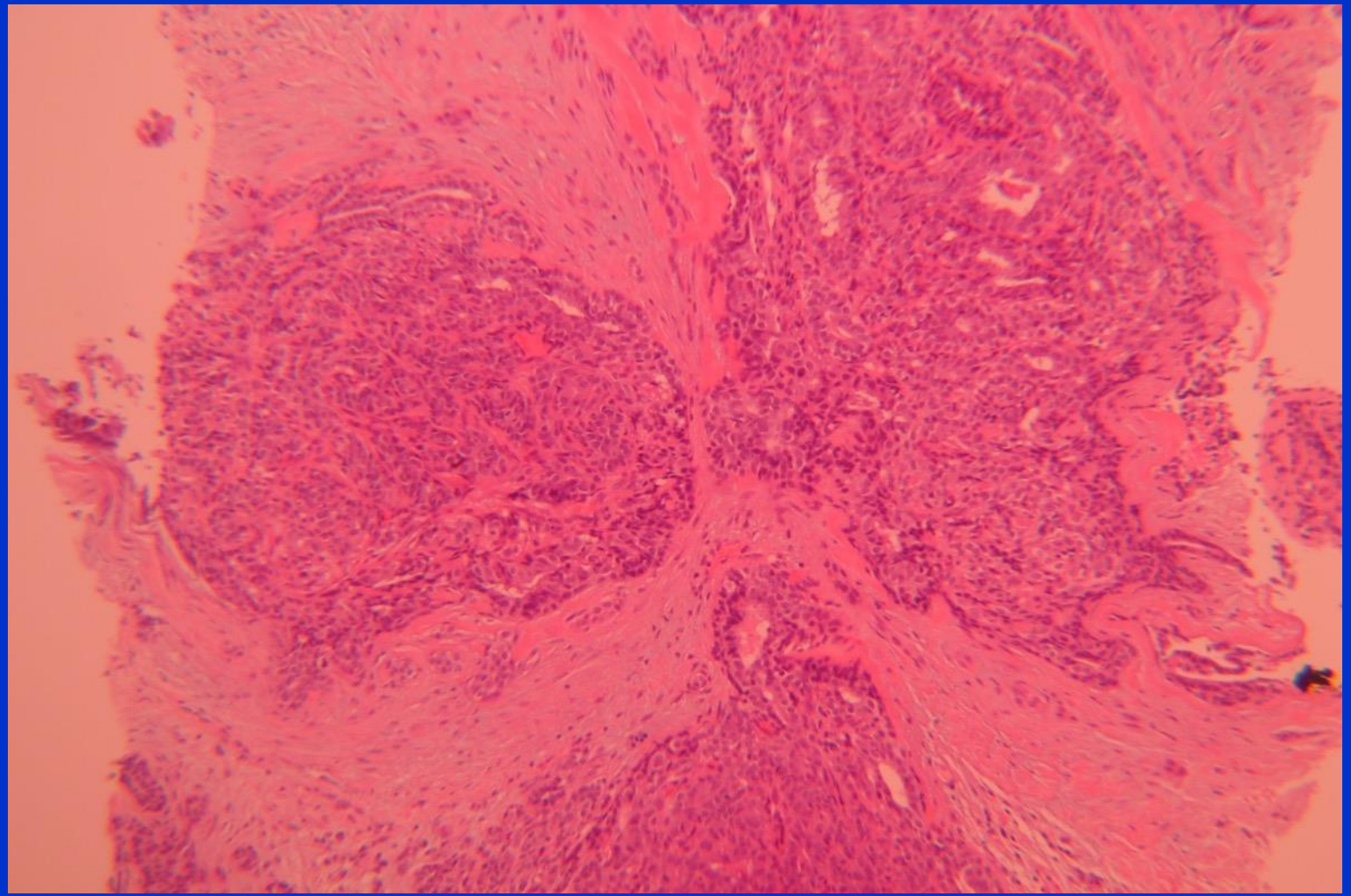
B5a











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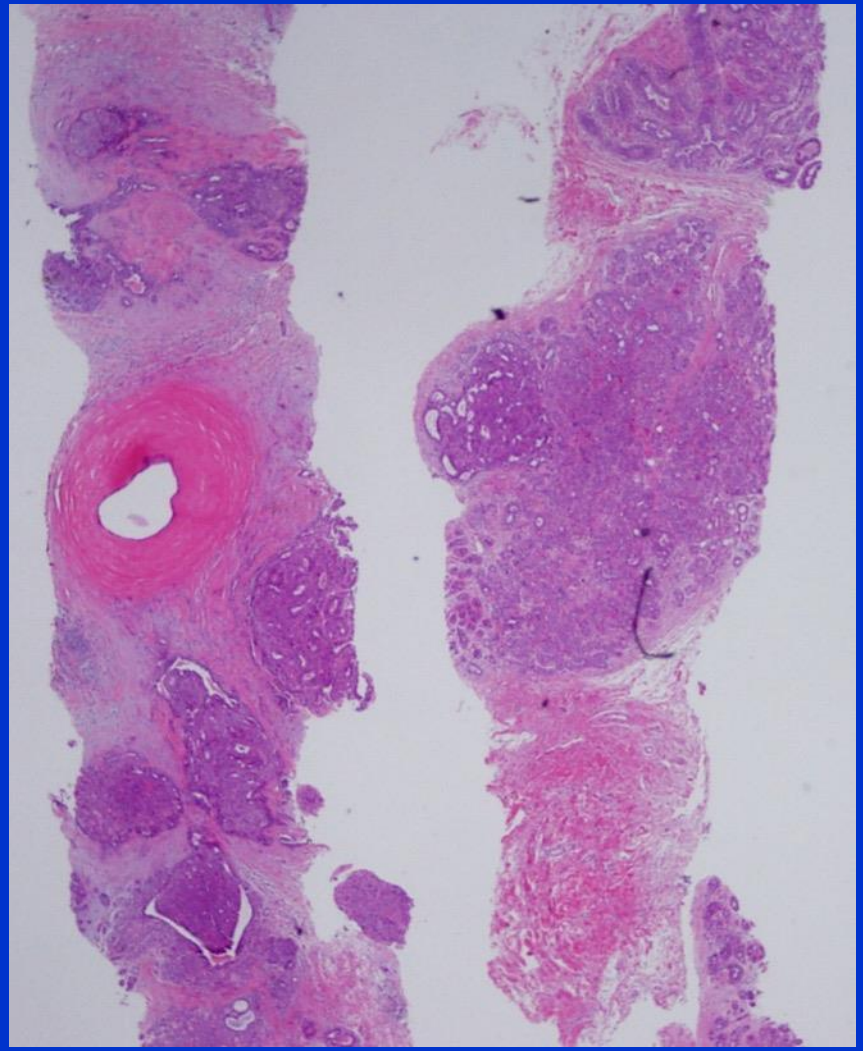

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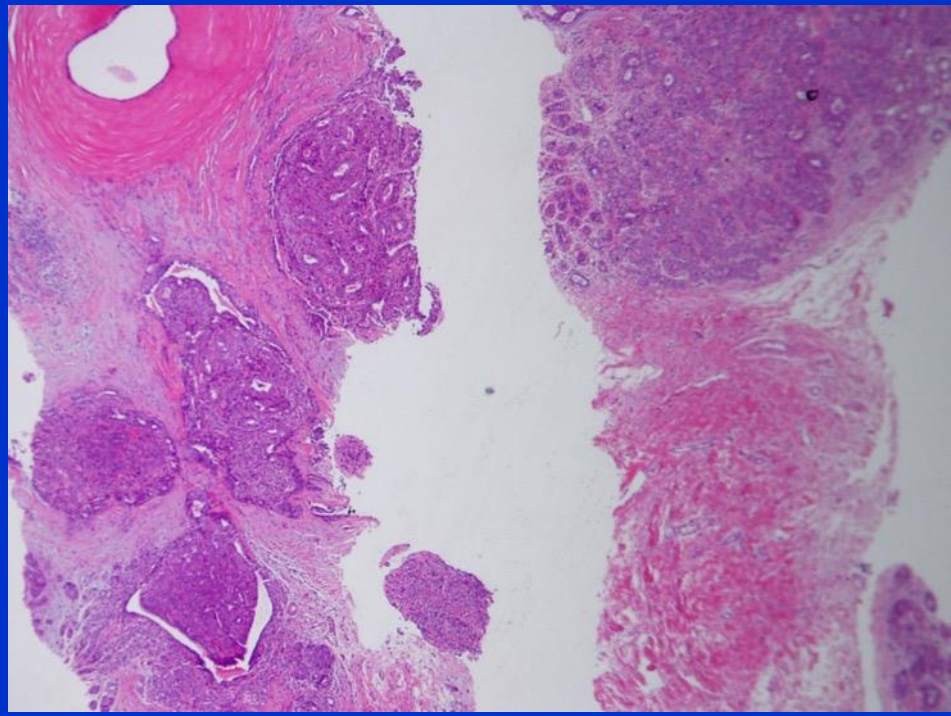

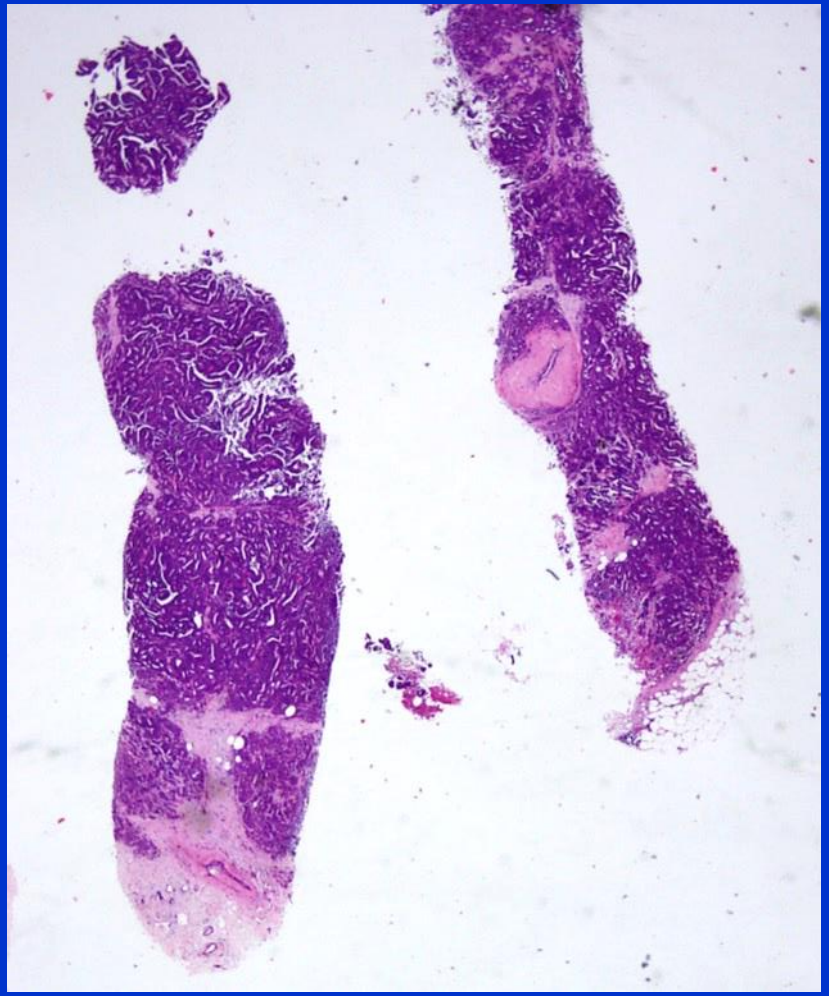

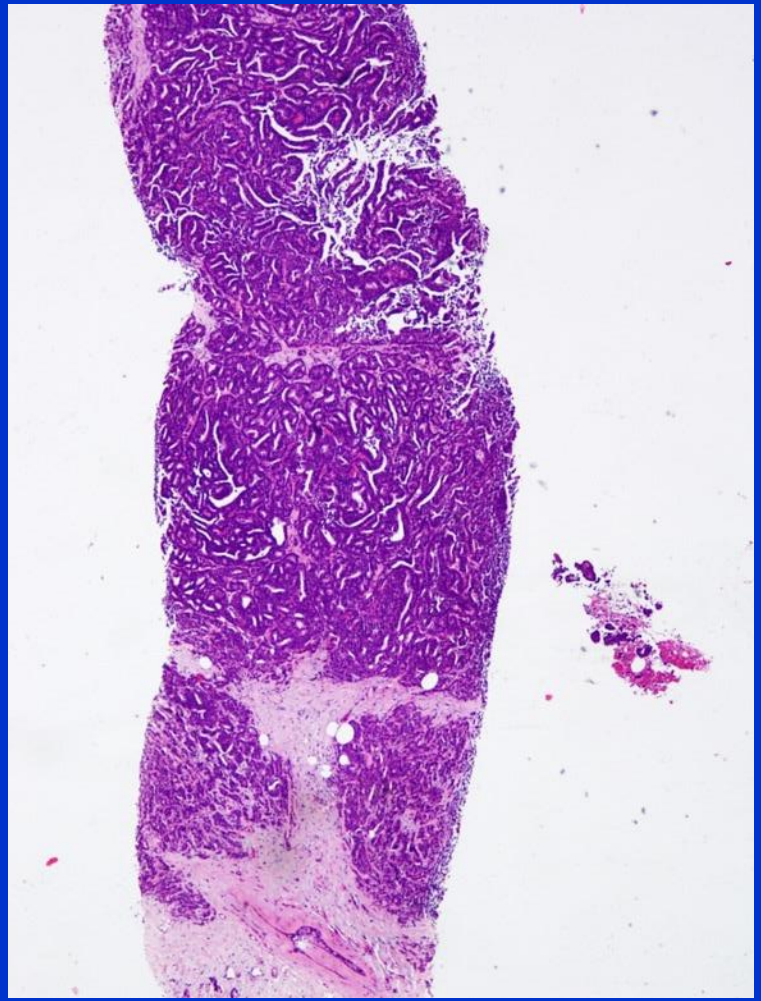

B5b

Thank you

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