Breast Lesions of Limited Metastatic Potential

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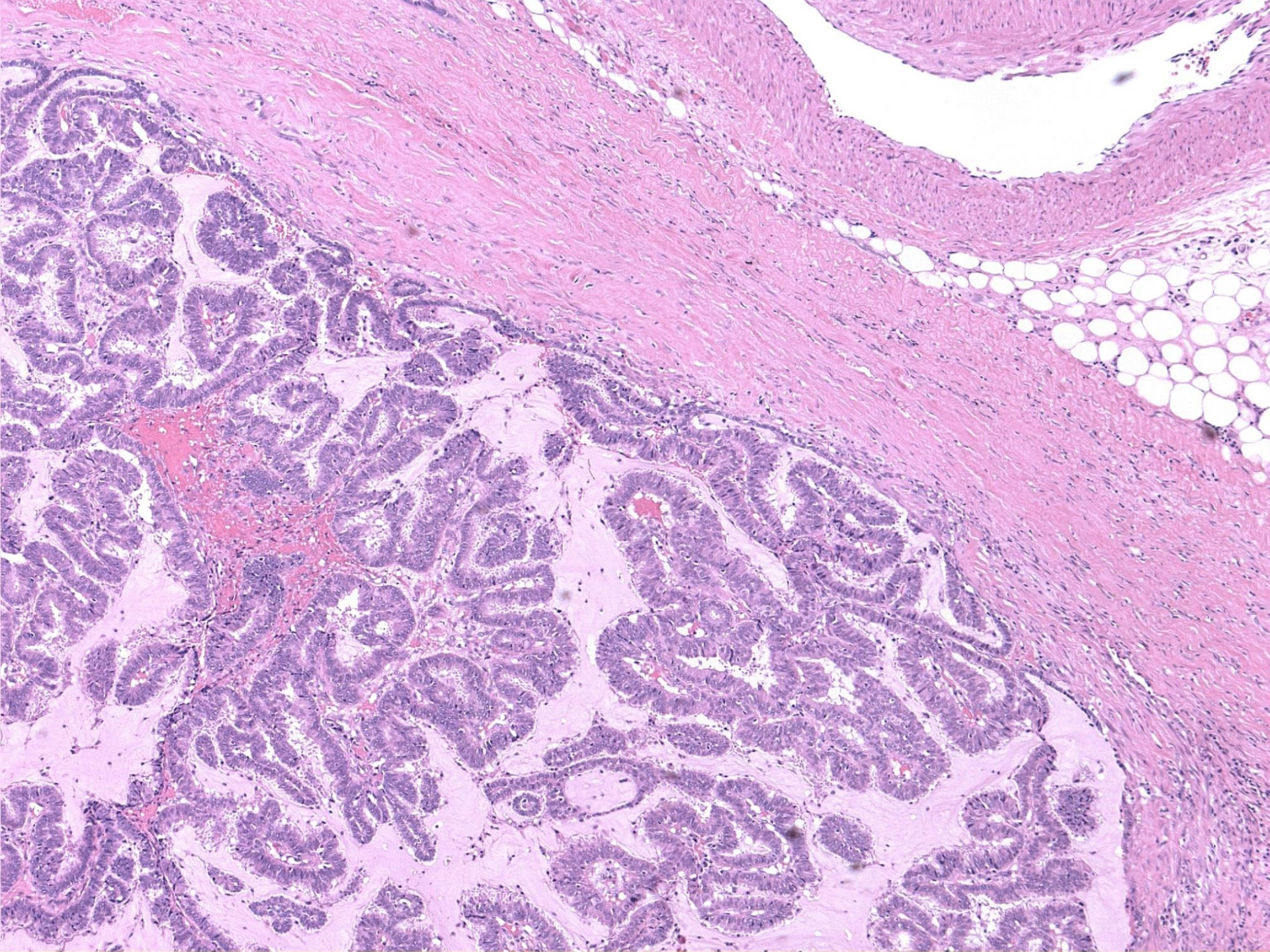
Breast lesions of uncertain malignant nature and limited metastatic potential: Proposals to improve their recognition and clinical management

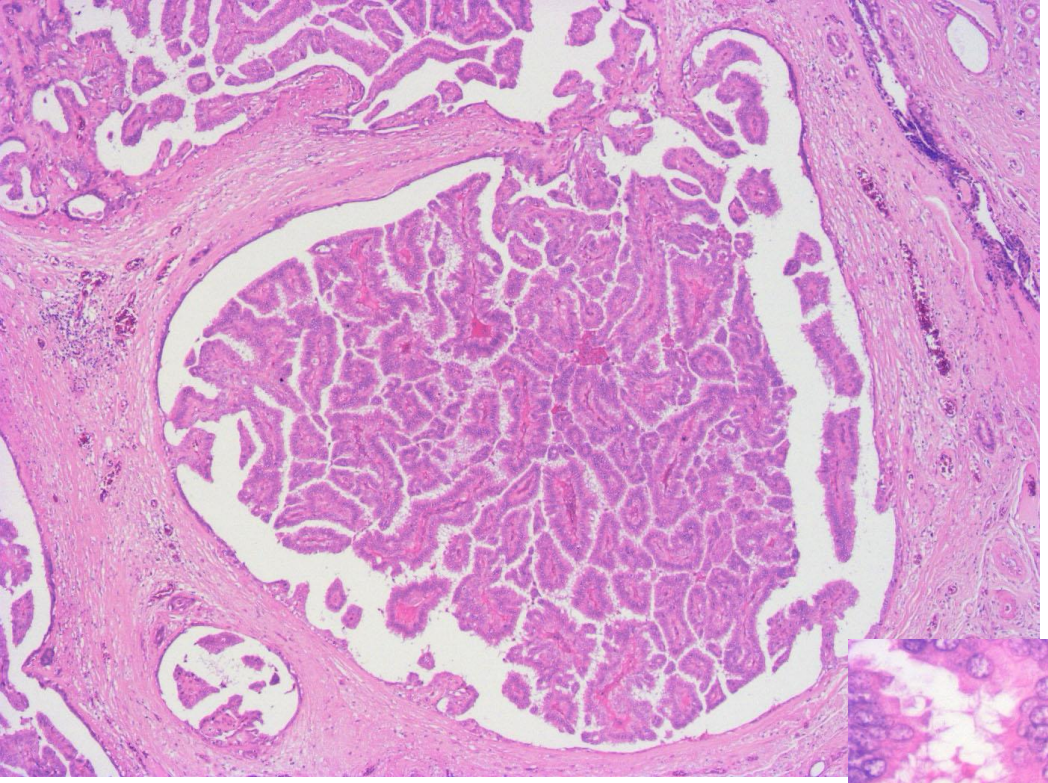
Emad A. Rakha[1], Sunil Badve[2], Vincenzo Eusebi[3], Jorge S. Reis-Filho[4], Stephen B. Fox[5], David J. Dabbs[6], Thomas Decker[7], Zsolt Hodi[1], Shu Ichihara[8], Andrew HS. Lee[1], José Palacios[9], Andrea L. Richardson[10], Anne Vincent-Salomon[11], Fernando C. Schmitt[12], Puay-Hoon Tan[13], Gary M. Tse[14], and Ian O. Ellis[1]

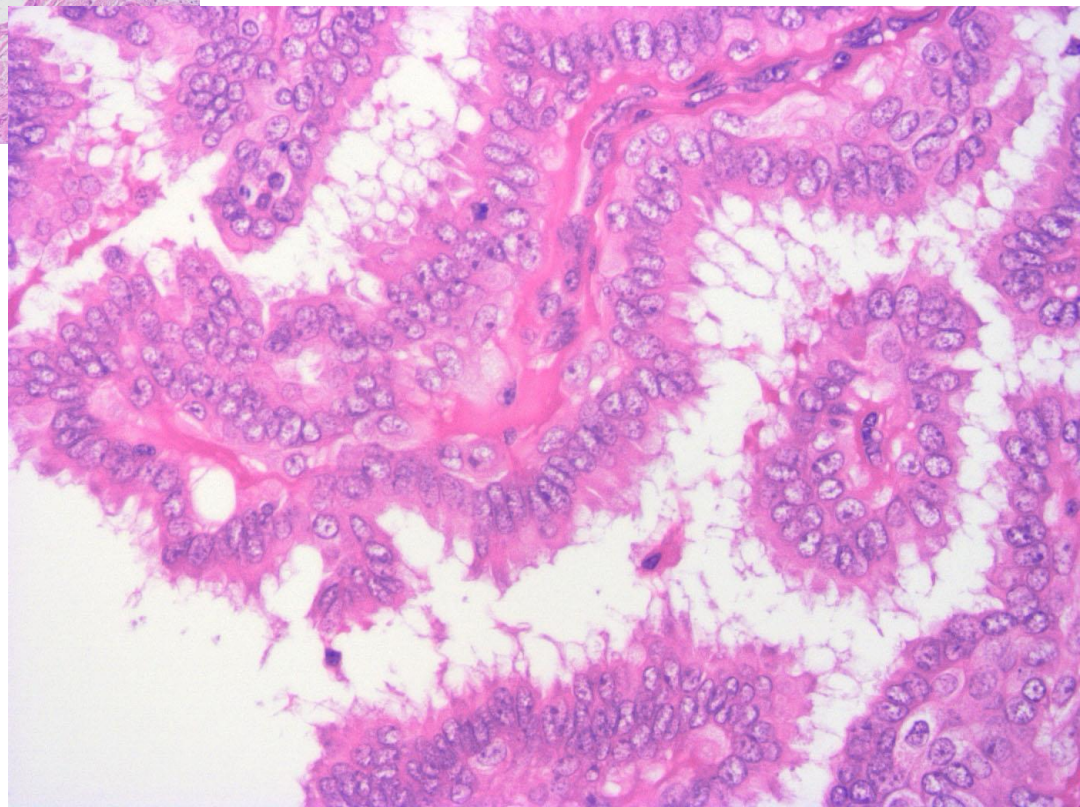
Breast Lesions of Limited Metastatic Potential

Lesions that show biological and/or histological evidence of invasive malignancy, but are associated with negligible or very low incidence of metastasis.

- Encapsulated Papillary Carcinoma
- Solid Papillary Carcinoma
- Low Grade Adenosquamous carcinoma
- Low Grade Fibromatosis Like Carcinoma
- Borderline Phyllodes Tumour
- Atypical Adenomyoepithelioma







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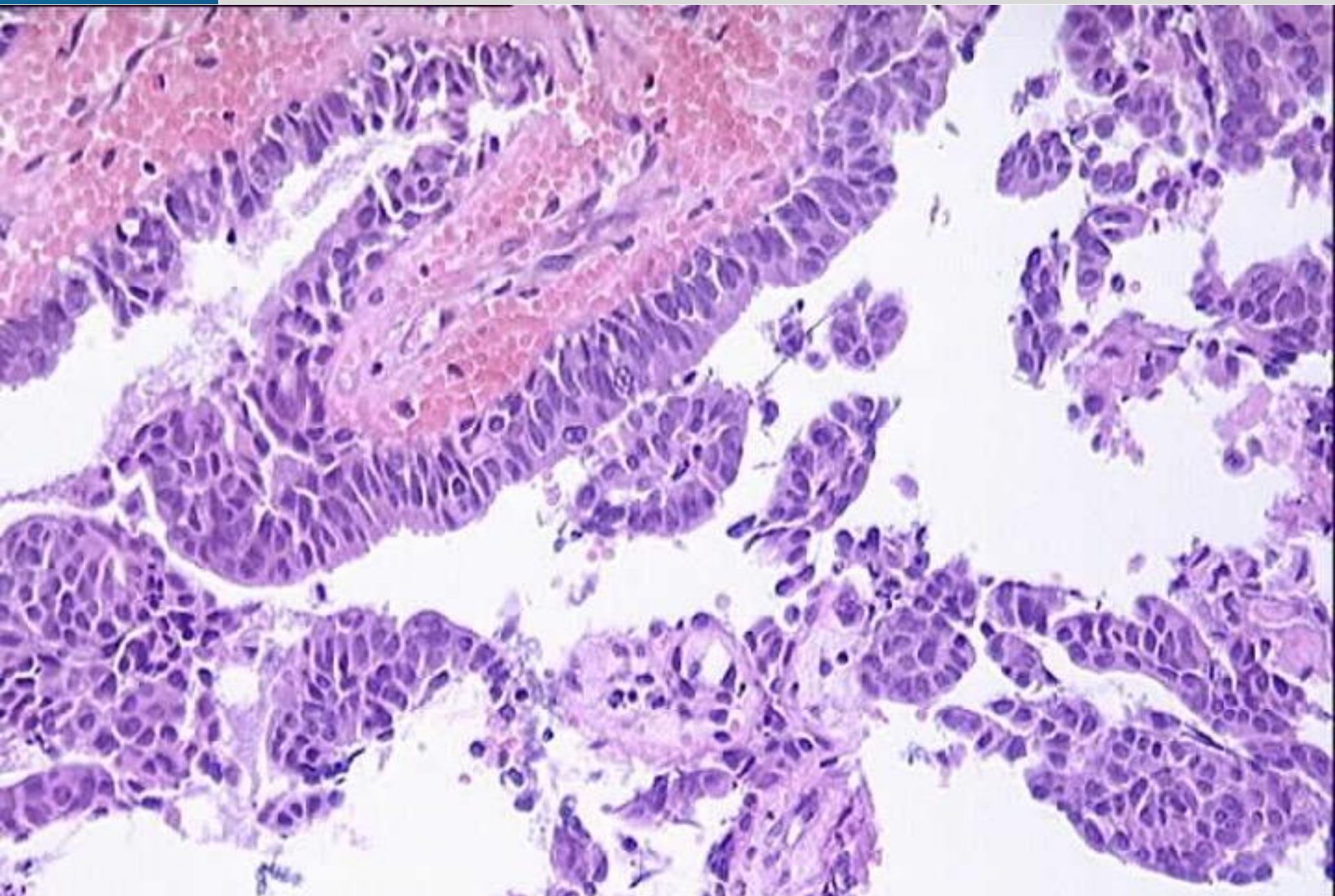
Papillary lesions of the breast



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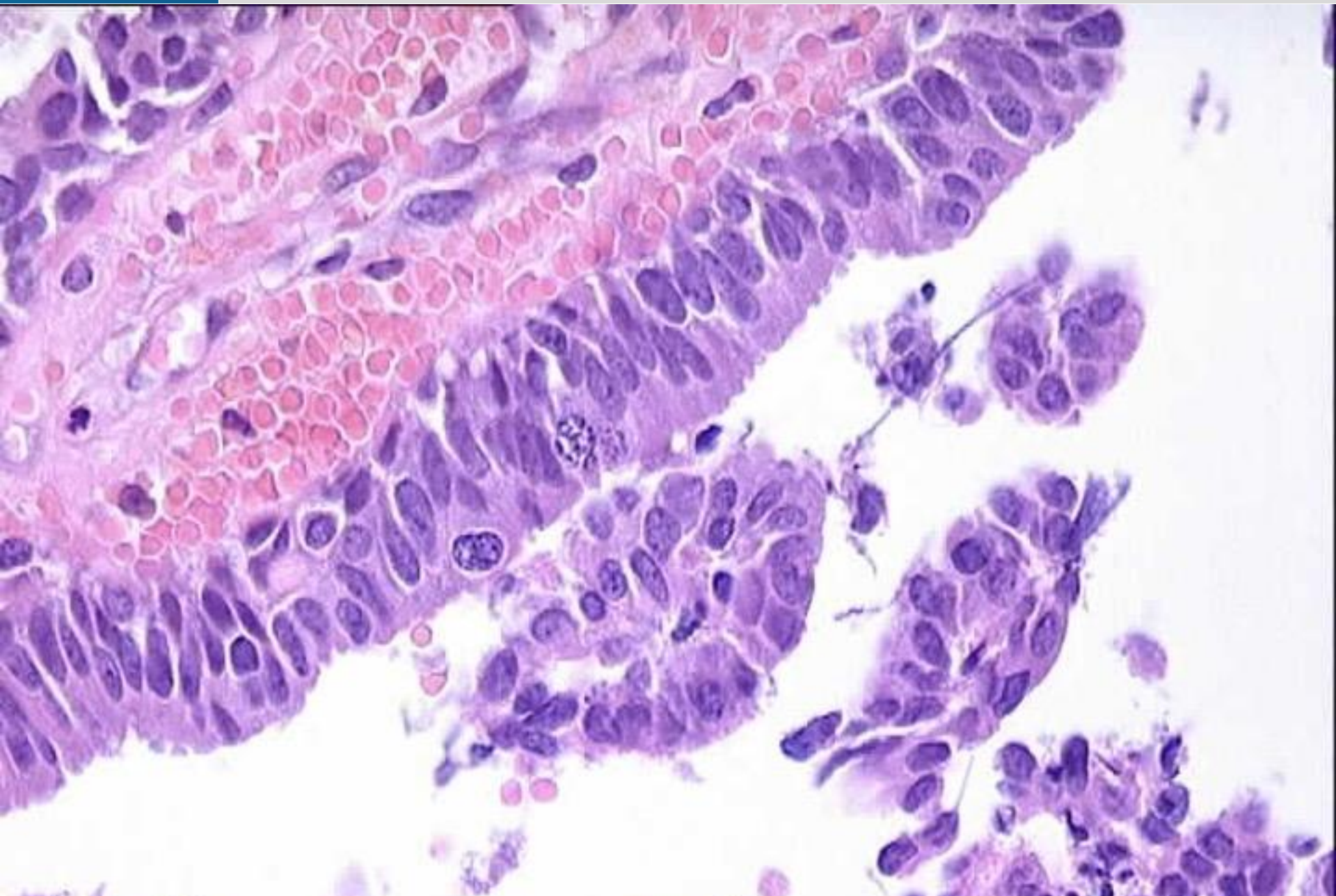
Papillary lesions of the breast



Papillary lesions of the breast

Intracystic papillary carcinoma of the breast after mastectomy, radiotherapy or excisional biopsy alone.

Recurrence after mastecomy: 0/29 (mean follow up 59m)

Recurrence after excision biopsy

- Papillary carcinoma + DCIS: 3/4
- Papillary carcinoma alone: 0/7
- No deaths

Carter et al. Cancer 1983;52:14

Papillary lesions of the breast

Papillary Carcinoma In Situ (Encapsulated papillary carcinoma) Prognosis

- Overall long term survival is excellent
- Mastectomy is curative
- Conservation therapy gives good results if no DCIS is present in adjacent breast tissue (approx. 80% cases)
- Local recurrence (in situ and invasive) may occur in cases with adjacent DCIS, especially if excision is incomplete

Papillary lesions of the breast

Immunohistochemical analysis of benign and malignant papillary lesions of the breast

Value of actin immunohistochemistry

Benign papillomas:

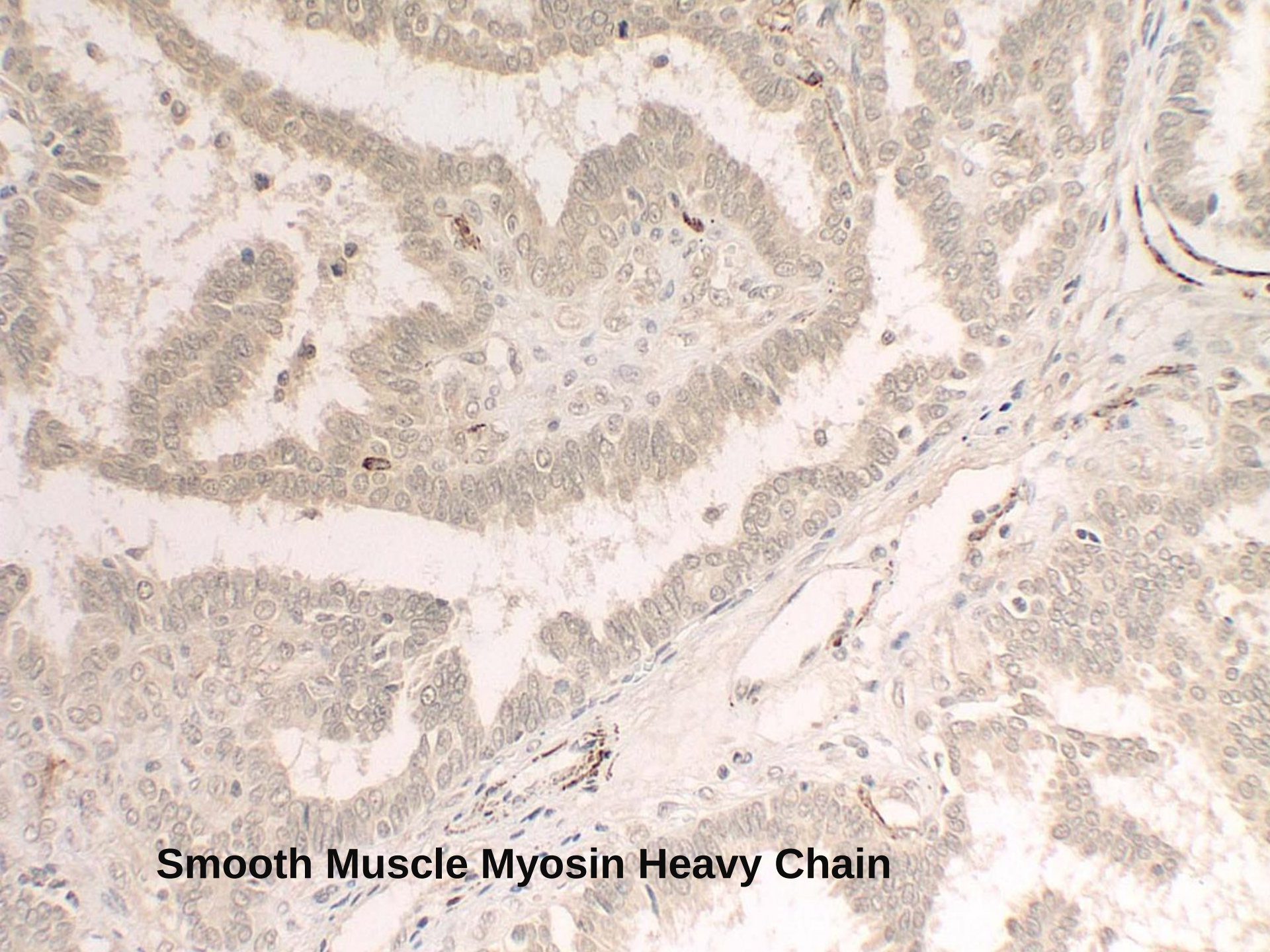
layer of myoepithelial cells

Papillary carcinomas:

loss of myoepithelium or

partial retention of myoepithelial layer

Papiotti et al Am J Surg Pathol 1983;7:451


Smooth Muscle Myosin Heavy Chain

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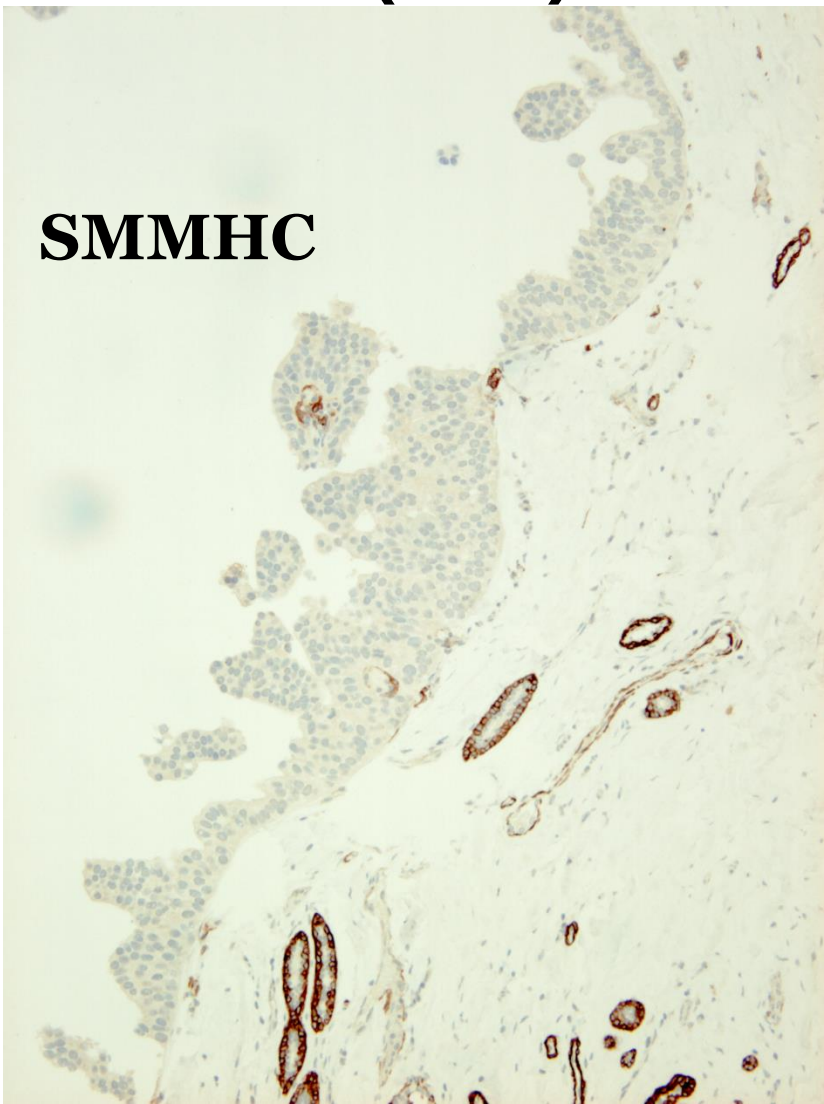
Papillary lesions of the breast

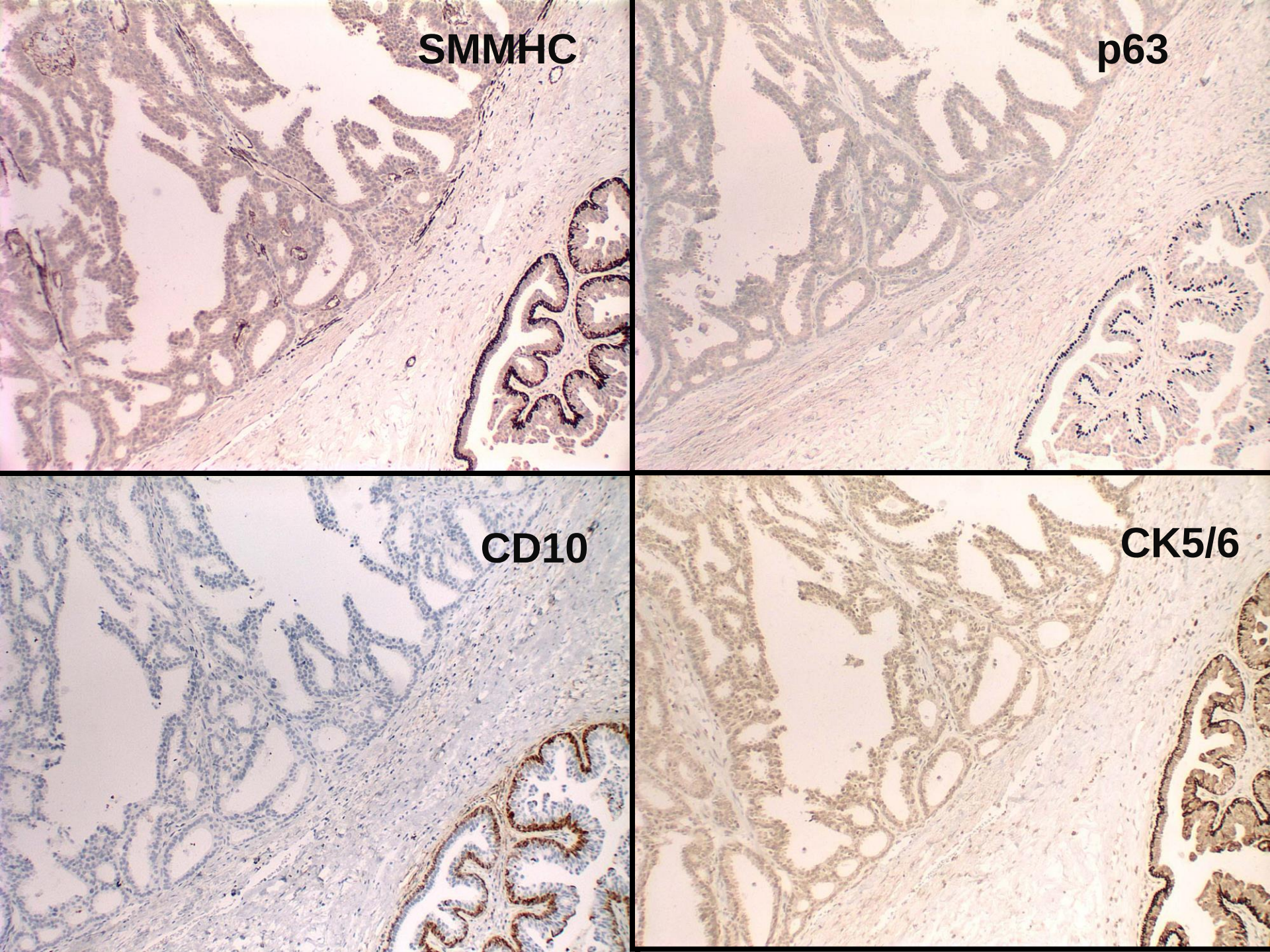
Myoepithelial Cells at Periphery of Encysted Papillary Carcinoma (EPC)

	EPC (n=22)	Papilloma (n=15)
Calponin	0/22	15/15*
SMMHC	0/22	15/15*
CK5/6	0/22	15/15*
CD10	0/22	15/15*
p63	0/22	15/15*

**including those of comparable size*

Collins LC et al.
Am J Surg Pathol. 2006; 30:1002-7




SMMHC
p63
CD10
CK5/6

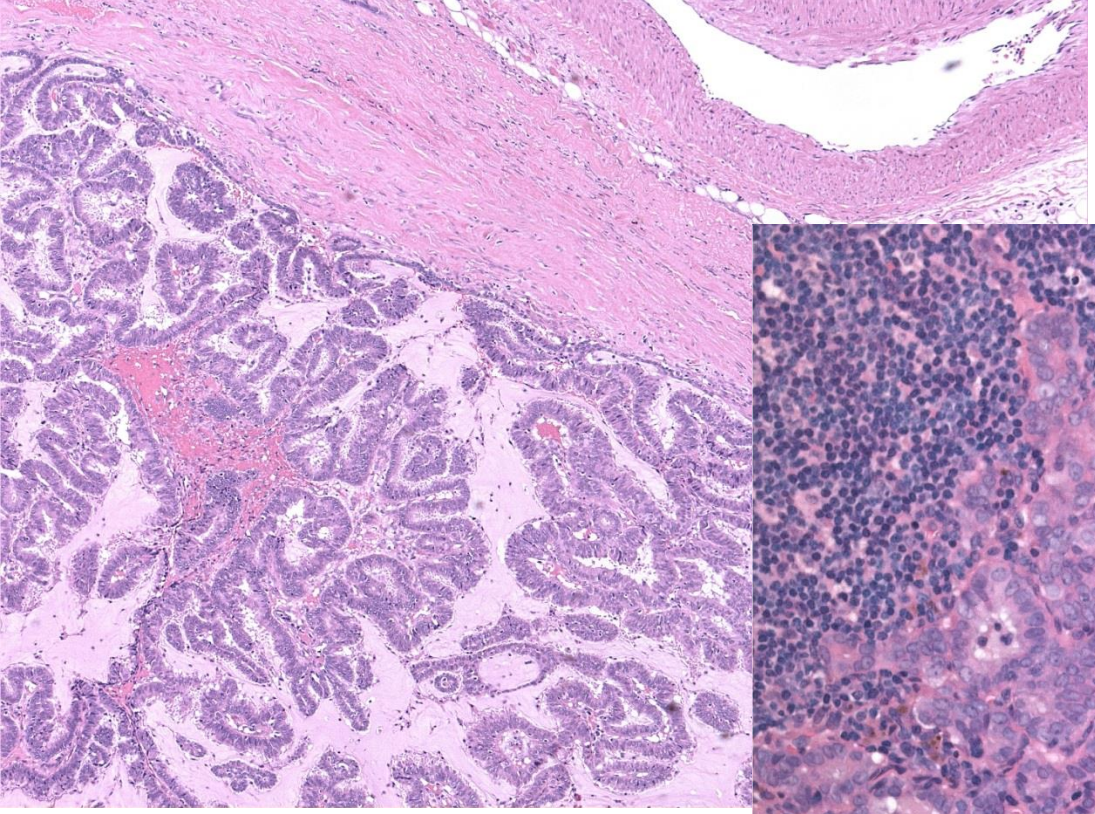
Papillary lesions of the breast

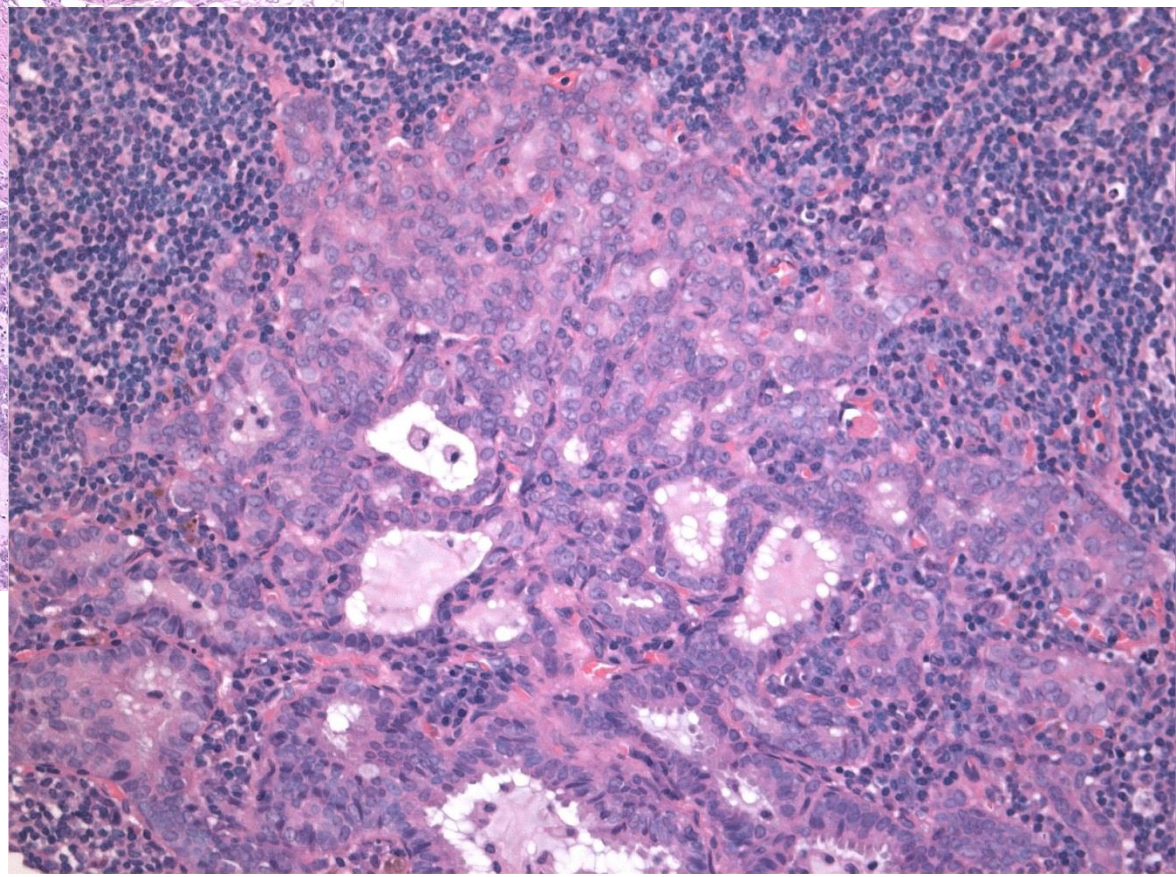
Collagen IV in Encysted Papillary Carcinoma

- Collagen type IV IHC
- 21 pure EPC & 6 with adjacent invasive carcinoma
- Moderate to intense collagen IV expression in all EPCs & absent or decreased in all invasive foci
- 1 of 21 pure EPC had a micrometastasis

"EPCs are in situ carcinomas with an excellent prognosis and can be managed with local therapy with or without sentinel lymph node biopsy"

Esposito et al. Am J Clin Pathol. 2009;131:228-42





From the literature, 1.2% (1/83) have positive axillary LN
Sentinel lymph node biopsy?
Overall, prognosis excellent with adequate local therapy alone (akin to DCIS)

Papillary lesions of the breast

Pure PC (IPC and SPC) have long been regarded as a form of *in-situ* (intraductal) carcinoma based on

A- Circumscription with lack of infiltrative pattern typical of invasive carcinoma

B- Presence of peripheral fibrous capsule akin to intact basement membrane of DCIS.

C- Indolent behaviour with lack of evidence of metastasis

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From a biological aspect: absence of peripheral ME cells has led to the proposal that Pure PC (IPC and SPC) are, in fact, invasive carcinomas with an expansile growth pattern

This concept is supported by:

A- Reporting of cases with axillary nodal or distant metastases following a diagnosis of pure PC lacking conventional morphologic forms of invasion

B- ME cells are preserved around benign papillomas of comparable size and absent around small nodules of PC

C- The capsule is often focally deficient and may be present around invasive tumour foci

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Therefore, PC remains as a controversial entity with respect to:

A- Classification: *In-situ* or Invasive

B- Definition of invasion within PC

C- Whether the behaviour of SPC is similar to the more common IPC

D- What is the so called “invasive PC”

E- What is best management of pure PC

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We aimed to study a large series of pure PC and review the outcome and behaviour of all published pure PC series to:

A) Assess the nature of pure PC (*in-situ* or invasive) based on outcome with biological consideration

B) Compare SPC and IPC

C) Identify the appropriate management of pure PC

Rakha et al Am J Surg Pathol. 2011, 35:1093-103

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Papillary lesions of the breast

Results

476 pure IPC (207 in this study + 269 published)

97 pure SPC (30 in this study + 67 published)

•Median age 63 to 75 years (average 70 for IPC and 73 for SPC)

•Median size of PC was 20 mm (12 - 35 mm)

•Majority are low to intermediate grade with 0 – 14% being high grade.

•The vast majority are ER+, PR+ and HER2-

Rakha et al Am J Surg Pathol. 2011, 35:1093-103

Papillary lesions of the breast

Results

Vascular invasion

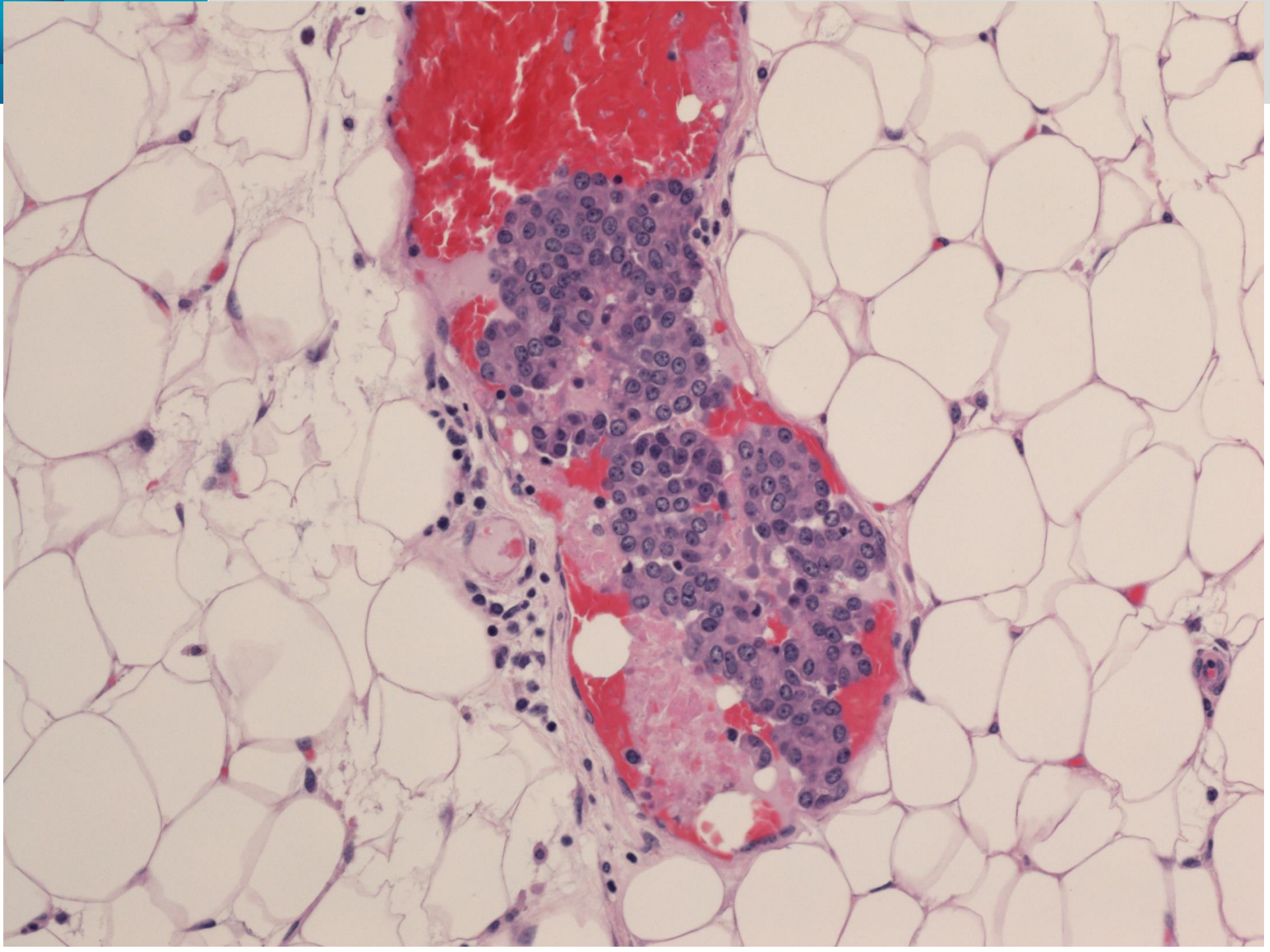
VI was identified in 5 cases (4/169 IPC and 1/20 SPC all local cases)

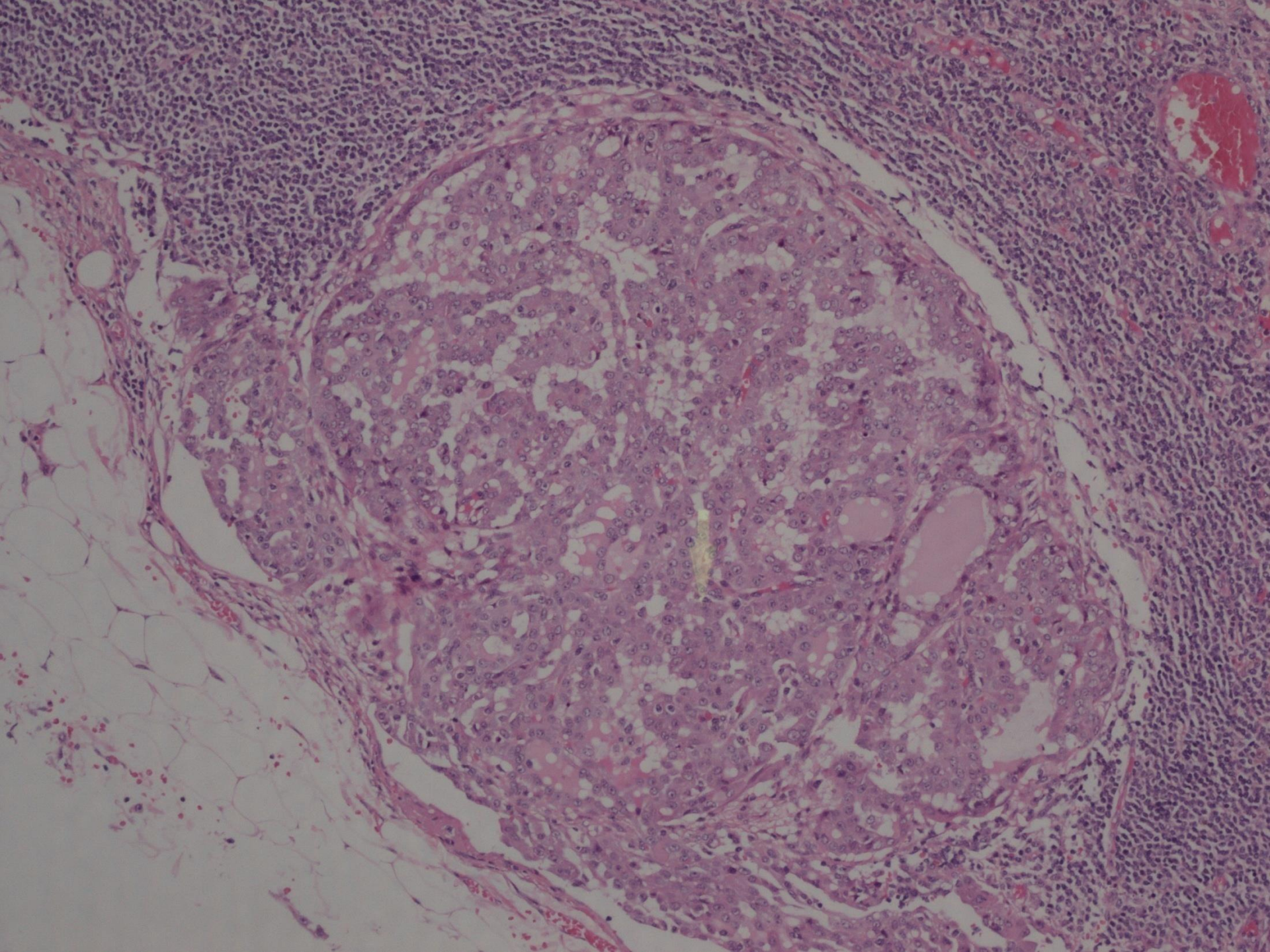
LN metastasis

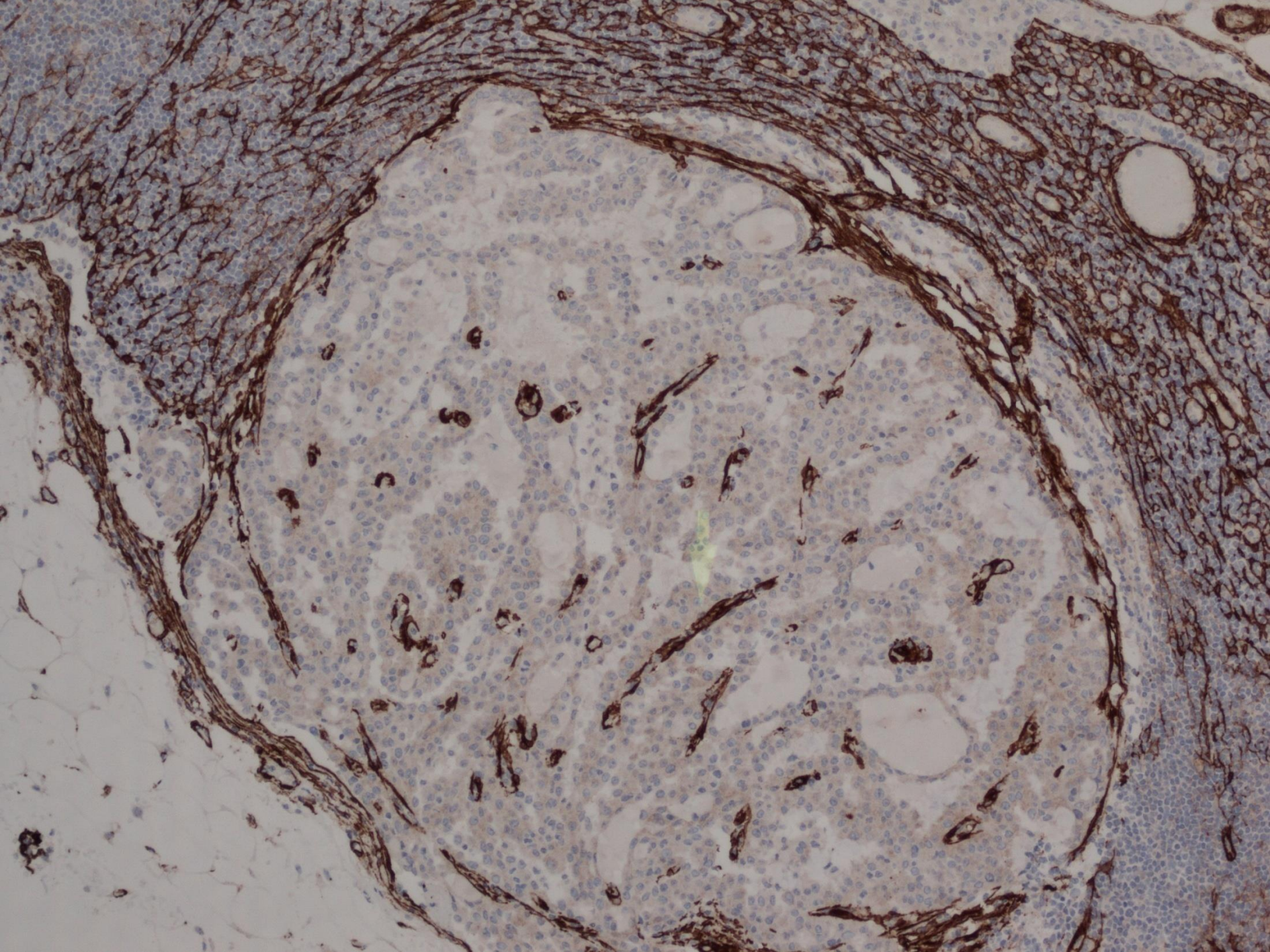
8 cases (out of 239; 3%) showed positive LN in addition to 3 patients published as case reports (2 IPC and 1 SPC); total 11 cases reported with positive nodes

Nodal metastasis in pure PC is always in the form of micrometastases involving only 1 or 2 nodes and none of these cases with follow-up data developed subsequent regional recurrence or DM

Rakha et al Am J Surg Pathol. 2011, 35:1093-103







Papillary lesions of the breast

Local recurrences & local infiltration

Local in-breast / chest wall recurrences were reported in 20 cases (18 [7%] of IPC and 2 [4%] of SPC that had follow-up):

- 4 as pure PC* and 7 as infiltrating PC
- 6 as invasive non-papillary carcinomas and
- 3 cases in which recurrence was not characterised.

In addition to a case reports of

1 case that recurred as pure IPC in the axilla (originally LN negative)

2 recurrences following (IPC and SPC) as pure PC in muscles

* 1 case was papillary DCIS but IHC showed absence of ME cells in both primary and recurrent papillary DCIS like lesions

Papillary lesions of the breast

Local recurrences & local infiltration

In our local cases

7/8 cases with local fat/skeletal muscle infiltration

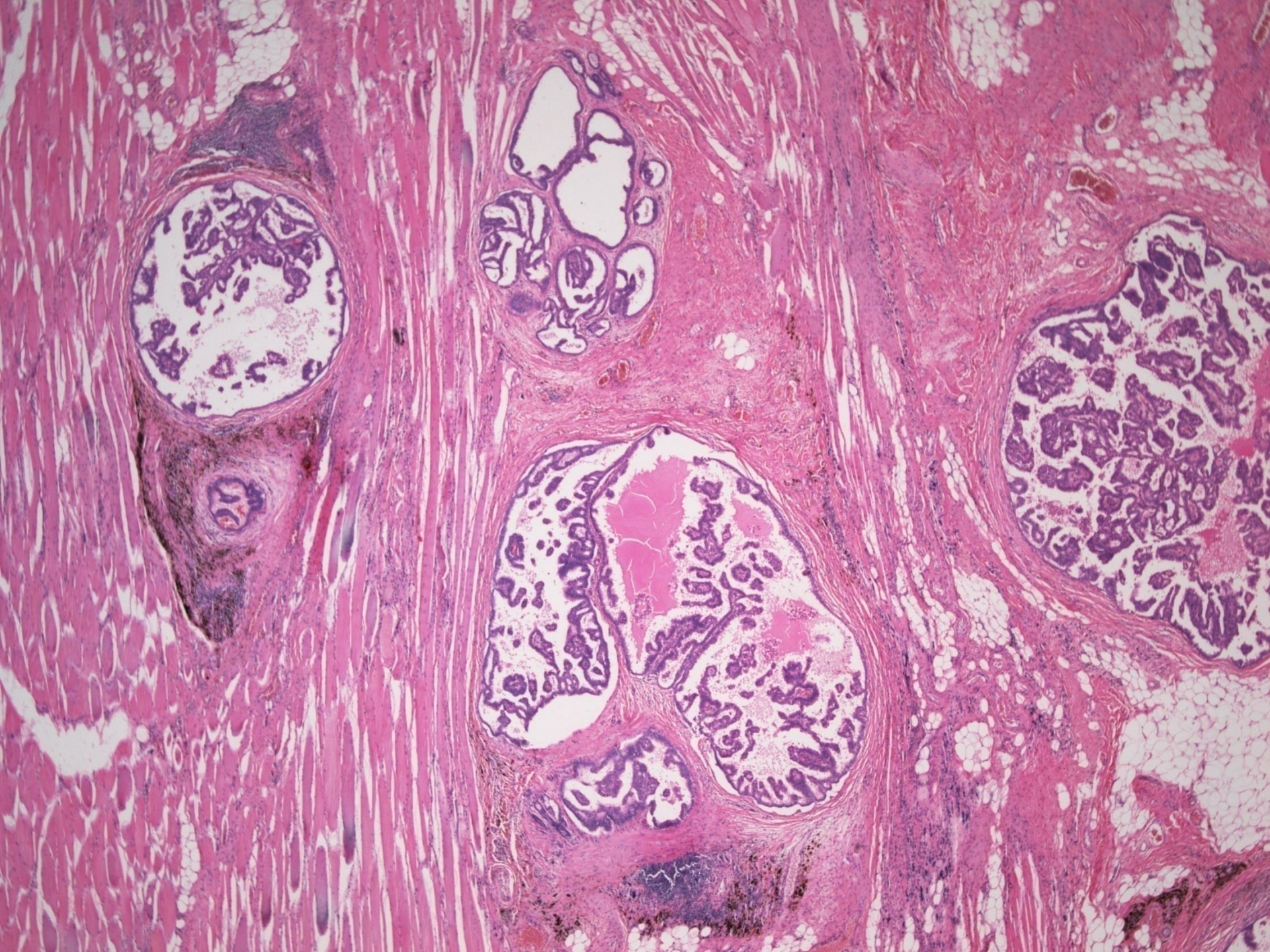
2/4 cases with LN metastasis and

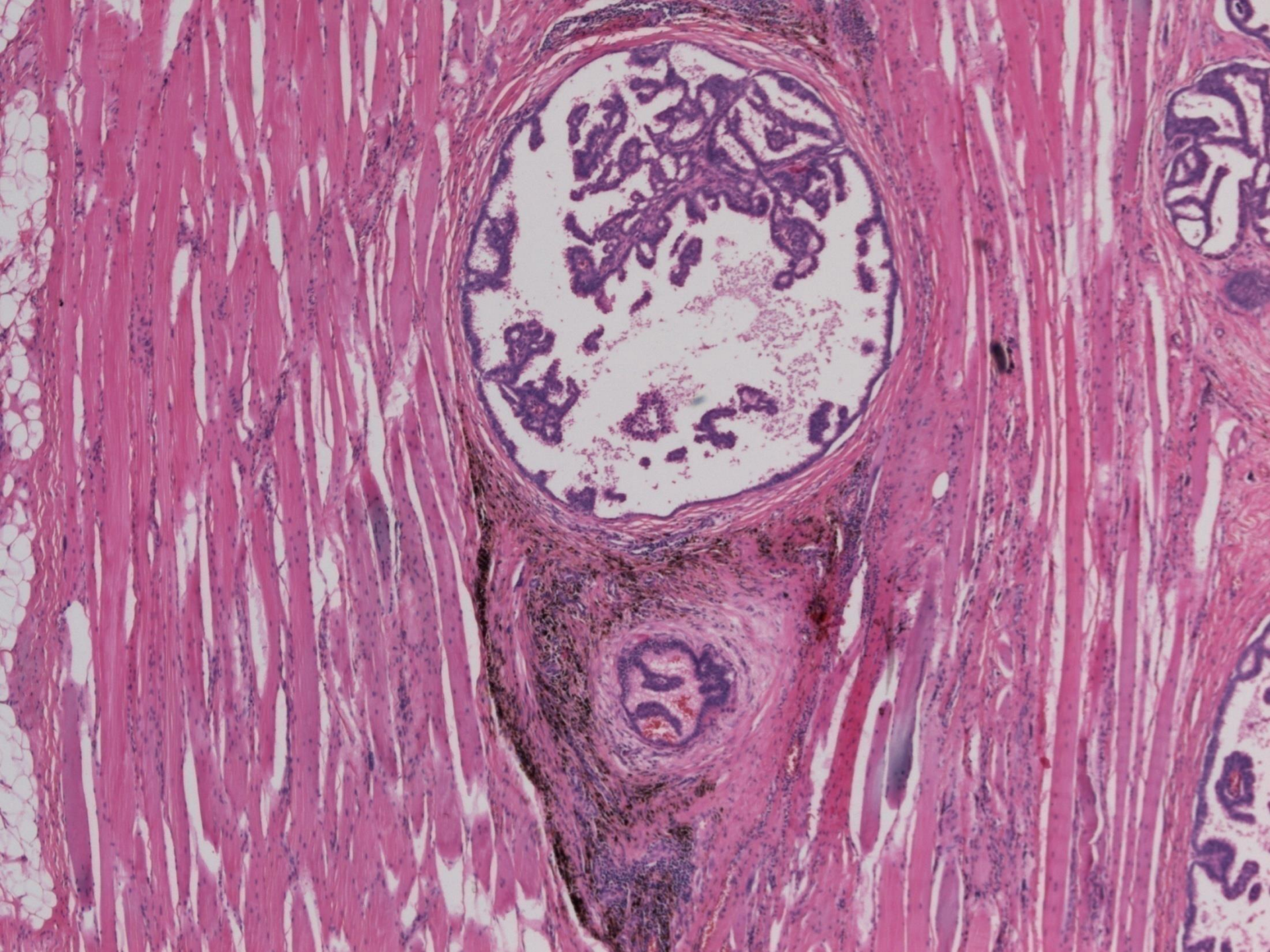
3/5 cases with VI

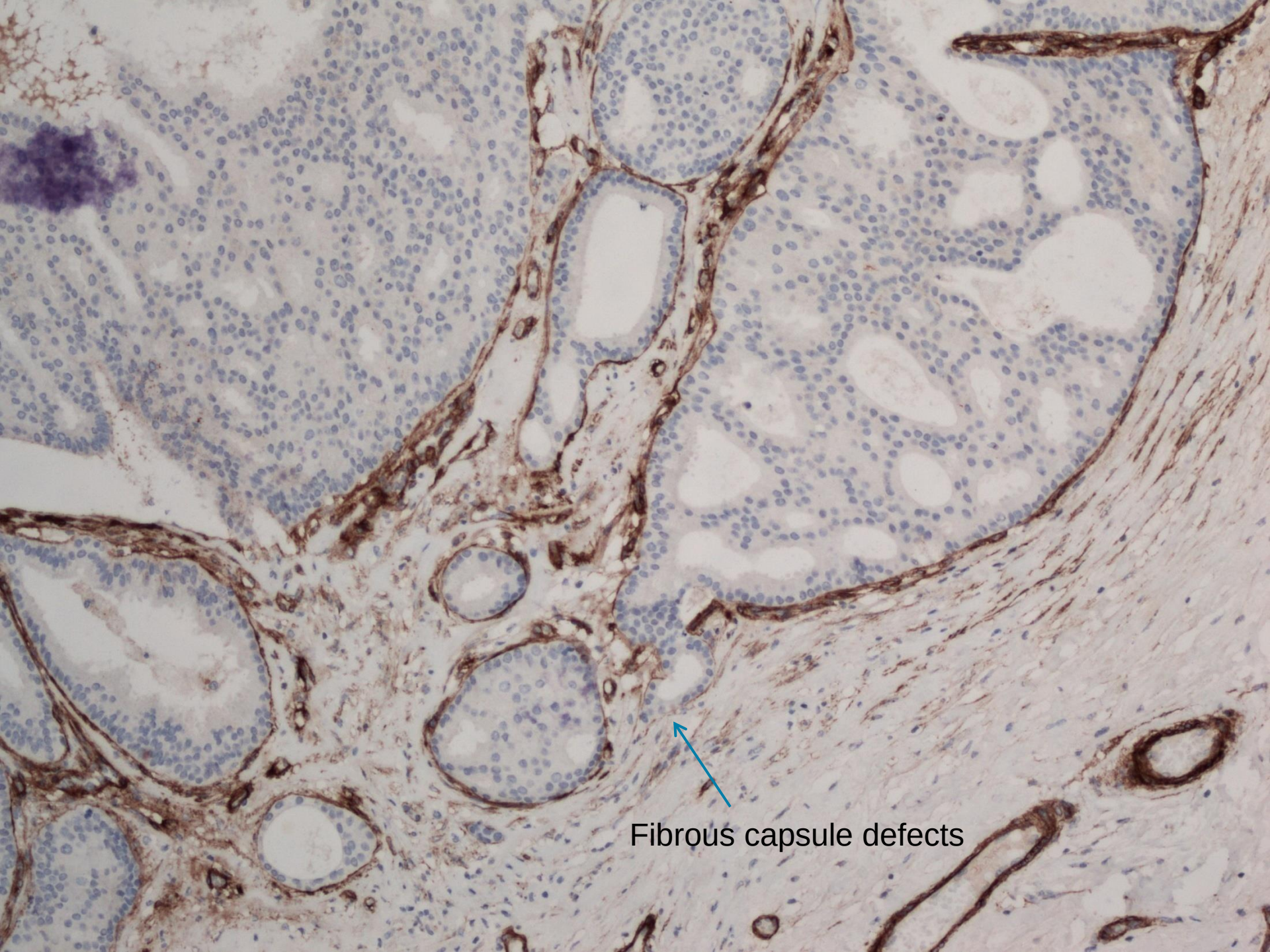
All were recurrent PC and all showed complete absence of ME cells (both within and around PC)

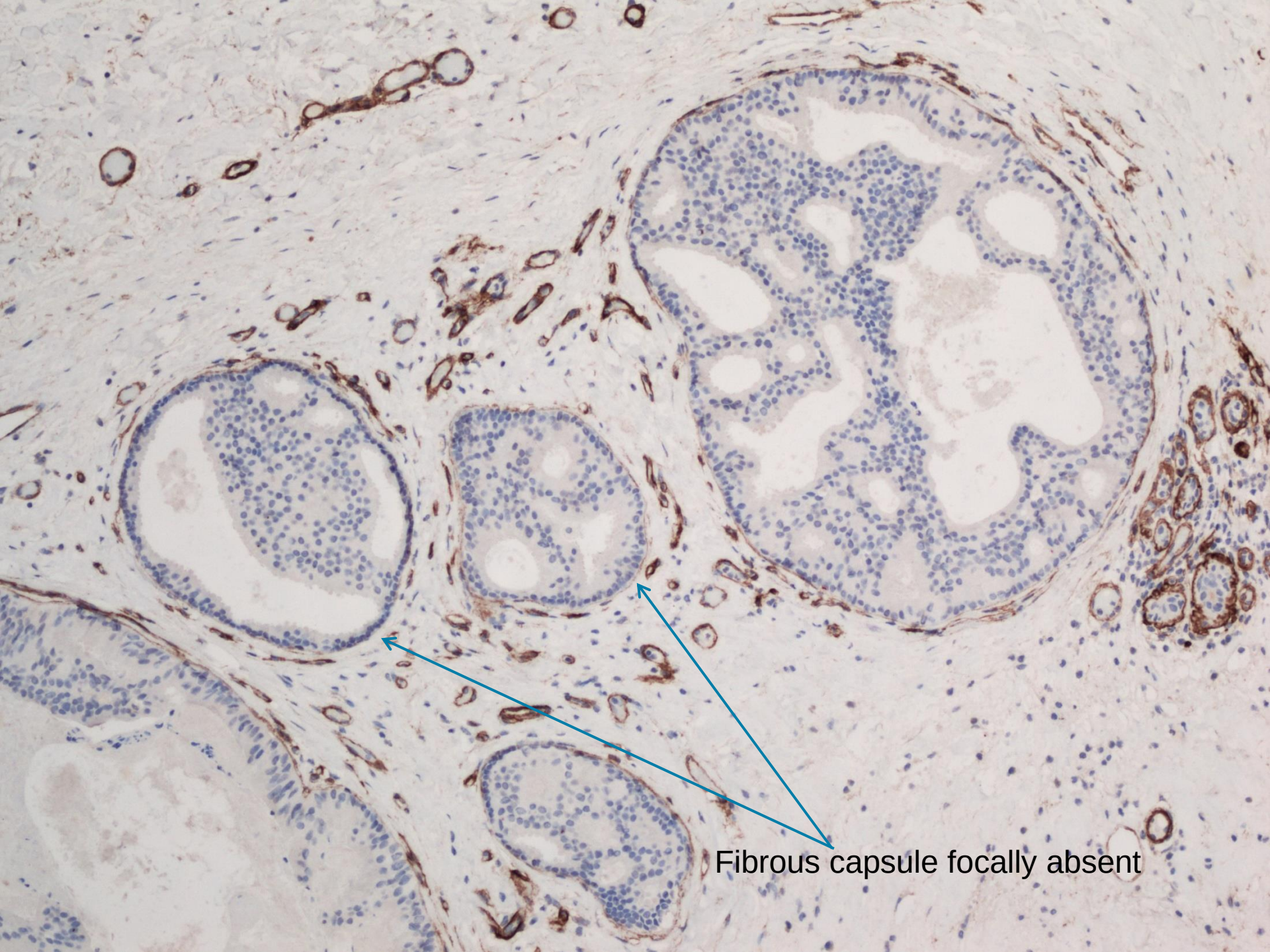
The only published 2 cases of PC (1 IPC and 1 SPC) in the skeletal muscles were recurrent (Chung et al ., APLMed 2004;10: 1157-60)

:- ? Recurrence is associated with more aggressive / invasive behaviour






Fibrous capsule defects


Fibrous capsule focally absent

Papillary lesions of the breast

Distant Metastasis

6 (out of 366) patients with Pure IPC (without coexisting conventional invasive carcinoma) developed DM (bone, lung and brain) however,

- 1 showed intervening recurrence as NST
- 1 received adjuvant systemic therapy indicating that primary PC was invasive
- 3 recurred but histology of recurrence was not mentioned
- 1 DM but recurrence was not mentioned
- But the papillary nature of the metastatic lesion was confirmed histologically in 2 patient

1 (out of 93) SPC developed DM.

It was SPC with signet-ring cell morphology and developed metastatic signet-ring cell tumor after 10 years and it was presumed to be breast primary. This patient was the only one reported to die after a diagnosis of pure SPC

Papillary lesions of the breast

IPC Vs SPC

Association with coexisting invasive carcinoma:

13% to 32% of IPC was associated with invasion (average of 27%)

45% to 80% of SPC (average of 63%)

This difference is statistically significant ($p<0.001$).

Rakha et al Am J Surg Pathol. 2011, 35:1093-103

Papillary lesions of the breast

Management

5 elderly patients (> 70 years) with pure PC diagnosed solely on needle core biopsy and treated with hormone therapy alone without surgery (in Nottingham).

None of these 5 elderly patients showed disease progression during the follow-up period (median 48 months [range 39 to 77])

= ? successful endocrine therapy

Rakha et al Am J Surg Pathol. 2011, 35:1093-103

Papillary lesions of the breast

Predictors of aggressive behaviour in pure PC

The outcome of pure PC with or without associated microinvasion or suspicion of invasion is not different

Although some studies reported associated between larger tumor size, higher grade PC or presence of associated conventional DCIS and aggressive behaviour, other studies including the present study did not find such associations

Papillary lesions of the breast

Should pure PC be regarded as an *in-situ* or invasive?

***Biologically:* Invasive**

A- Absence of ME cells at peripheral tumour-stromal interface

B- Peripheral capsule is

- Often deficient, may be absent (at least focally)
- Present around foci of PC in muscles
- Similar capsule found around invasive carcinomas and in LN metastasis.

This capsule seems to be a reactive process (stromal reaction around neoplastic cells) and not a native layer.

Therefore, we support the use of the term "Encapsulated PC" akin to encapsulated PC of the thyroid to replace the words "*in-situ*" or "invasive" PC

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Should pure PC be regarded as an *in-situ* or invasive?

***Biologically:* Invasive**

C- Presence of VI, LN metastasis and local infiltration into surround tissue and skeletal muscles and the confirmed papillary nature of 2 cases with DM

Also

D- Although LN metastasis and DM is reported in pure DCIS, these metastatic foci show morphology of invasive carcinoma (e.g., NST) and not as DCIS thus representing undetected foci of invasion and not representing a biological phenomenon

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Should pure PC be regarded as an *in-situ* or invasive?

***Clinically*: Indolent disease**

A- Although absence of ME cells suggests an invasive phenotype, it is only one step of the metastatic cascade

B- Indolent behaviour and excellent clinical outcome similar to DCIS:

- Very low % of LN micromets (low volume low number) with excellent outcome even when LN positive

- Reported events are few and no reported cancer related deaths; only 1 case of unusual metastatic signet ring-cell SPC

Therefore pure PC can be managed in the same way as DCIS.
Identification of microinvasion/suspicion of invasion seems to be of no clinical significance

Papillary lesions of the breast

Summary

Encapsulated PC is a clinically indolent disease with behaviour similar to DCIS therefore, the local management and the approach to LN sampling should be the same as for conventional DCIS

Papillary lesions of the breast

Intracystic / encapsulated papillary carcinoma

WHO and consensus pathologist view 2019

Best classified as pTis unless there is frank conventional invasive carcinoma present.


Captain, this may be invasion
but not as we know it

5th edition of the WHO Blue book 2019

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.

EPC/SPC with frank conventional-type invasion

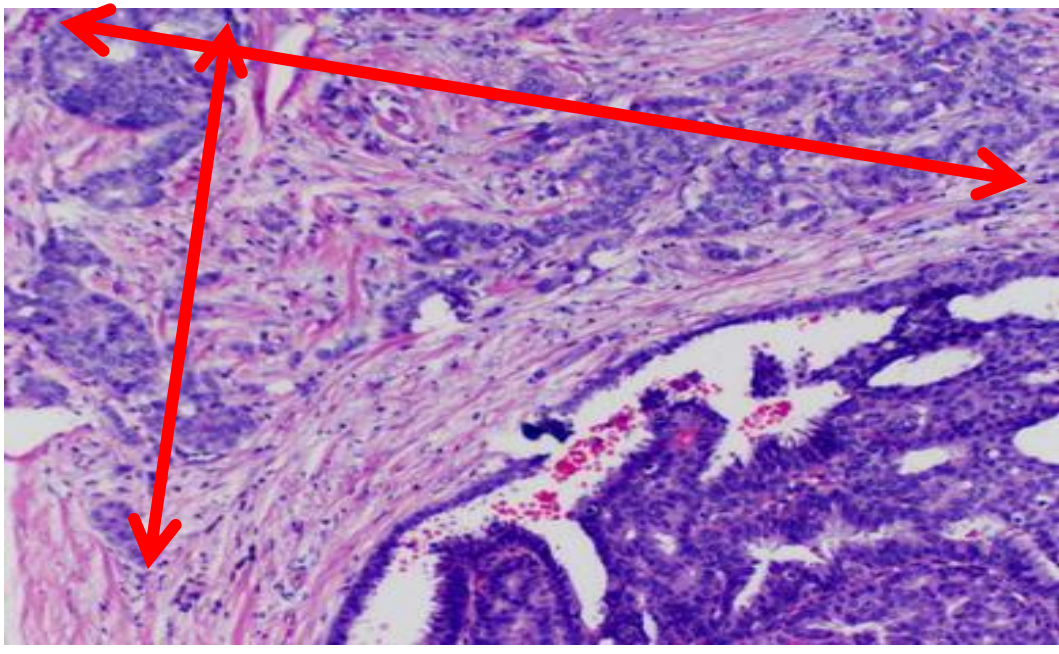
It is usually easy to identify frank invasion associated with PC (e.g., usually conventional carcinoma such as mucinous, NST or cribriform)

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

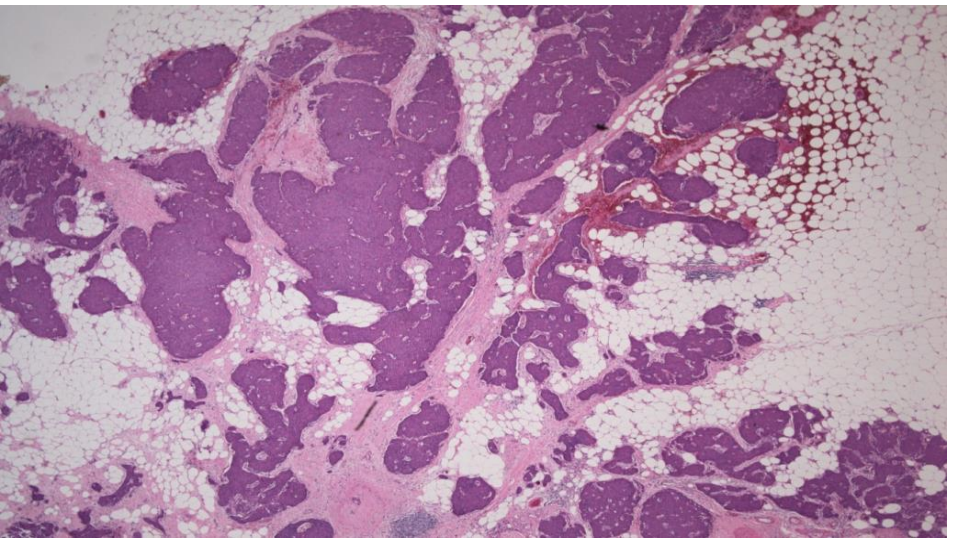
Many scattered foci, measure the whole area and mention this in the text

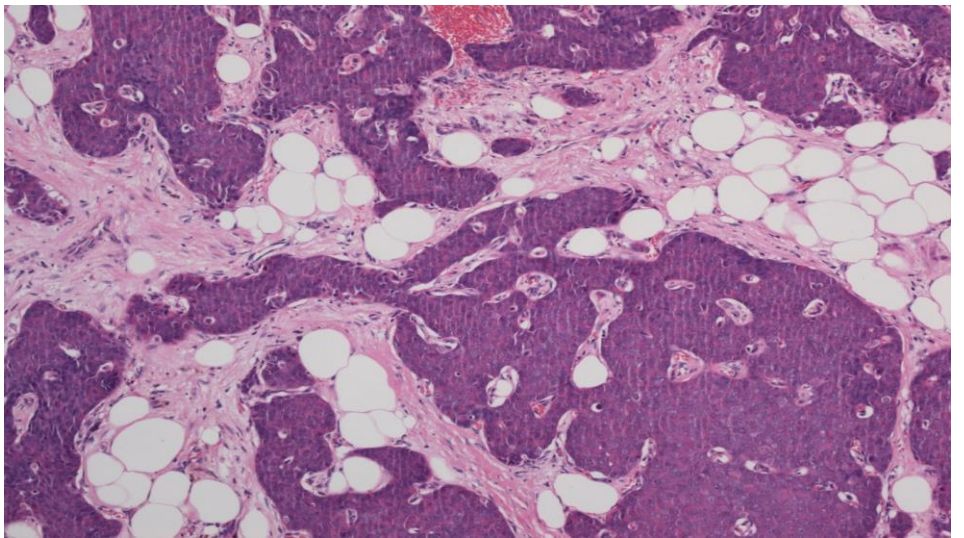


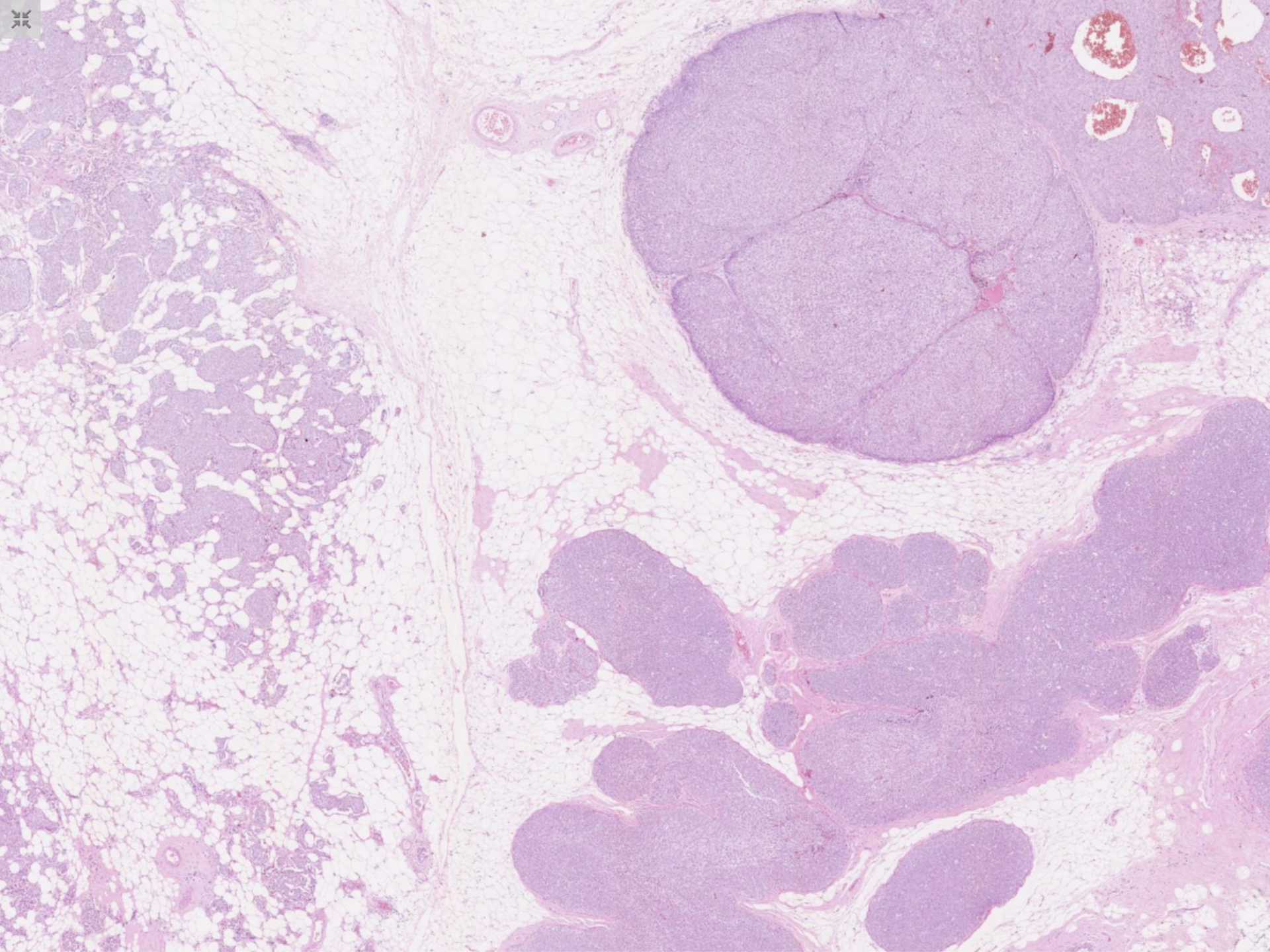
Invasive solid PC

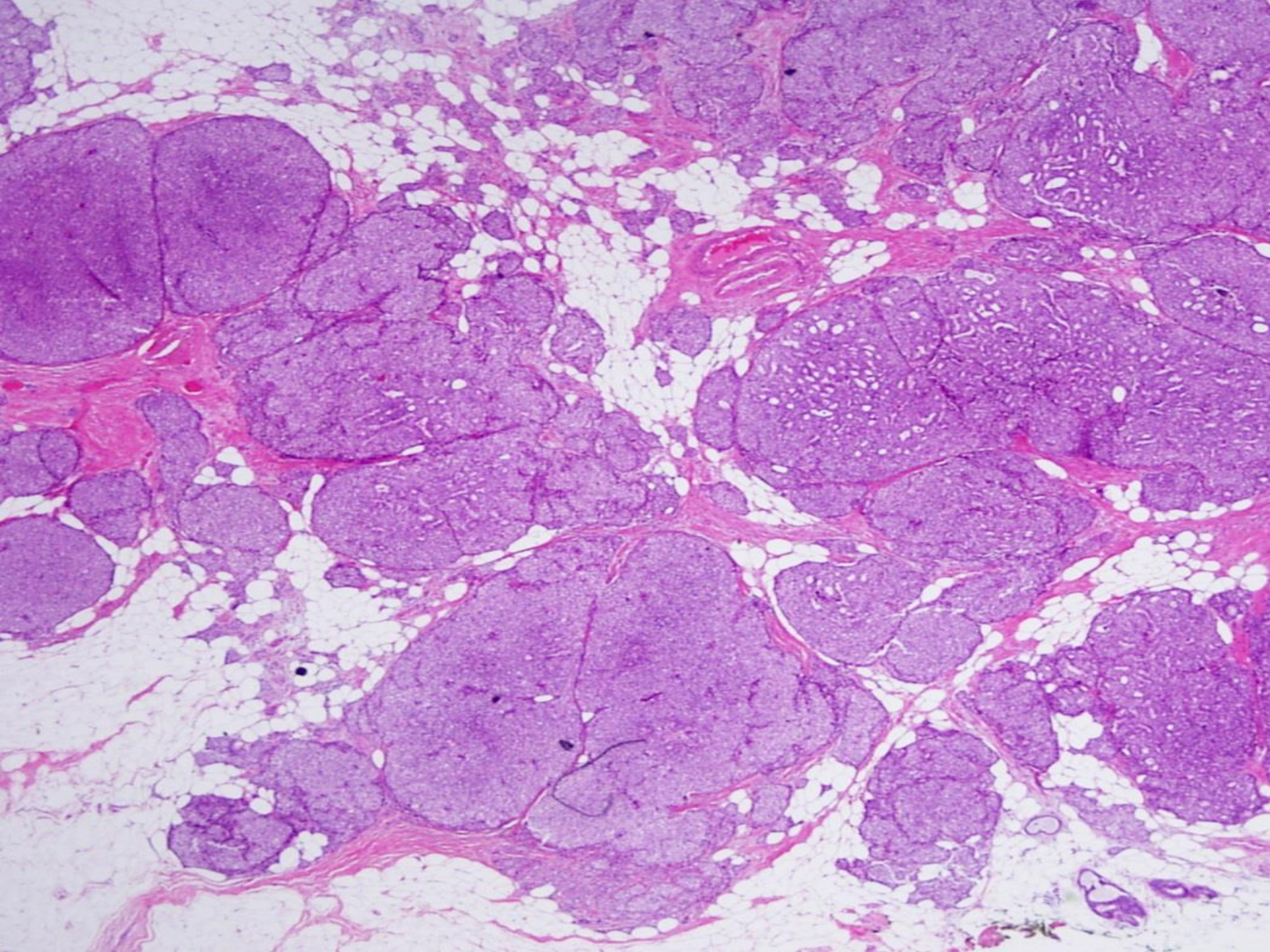
WHO definition of invasion in SPC:

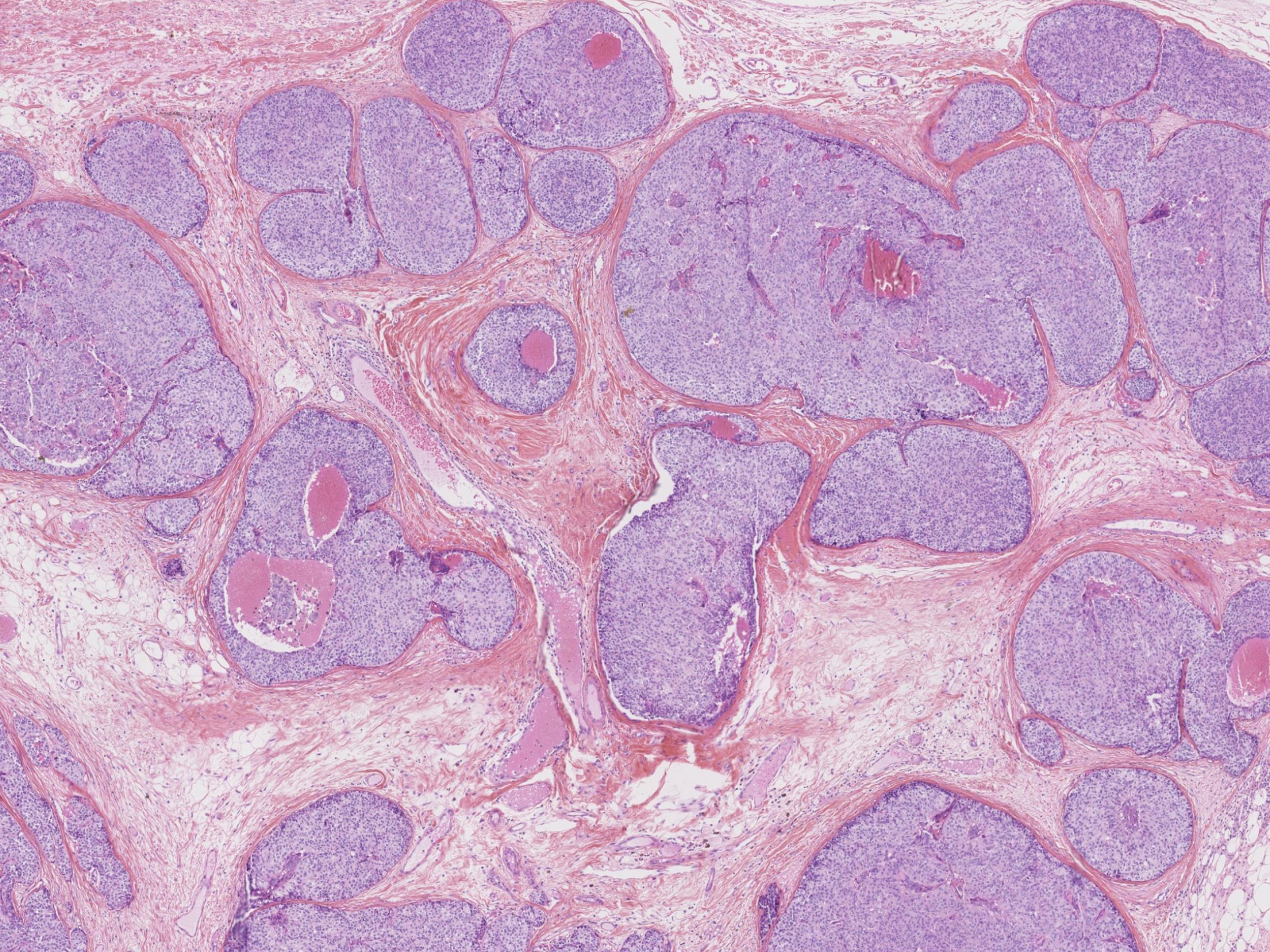
Geographic jigsaw pattern with ragged and irregular margins, + absence of ME cells +/- infiltrating fat

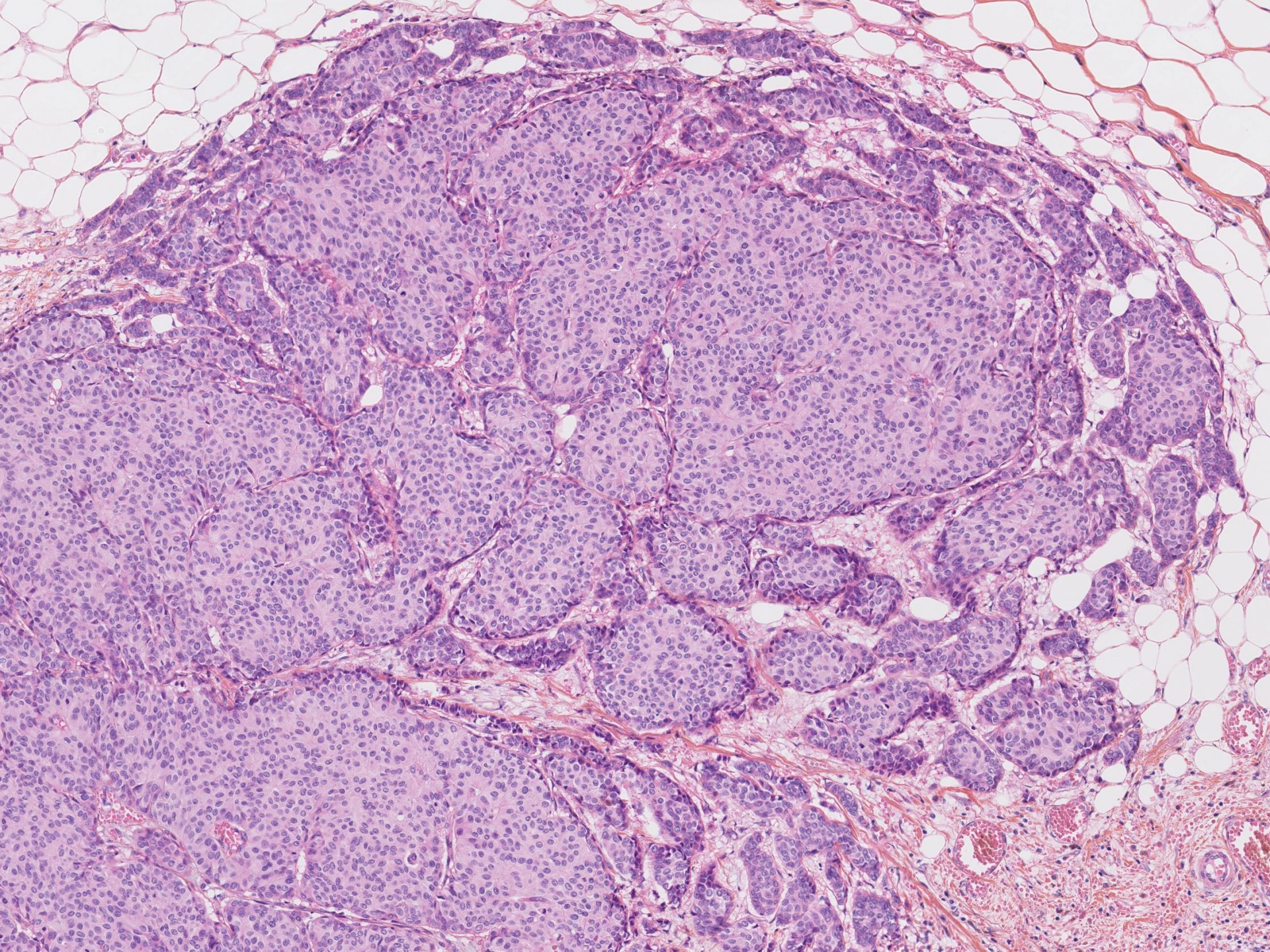






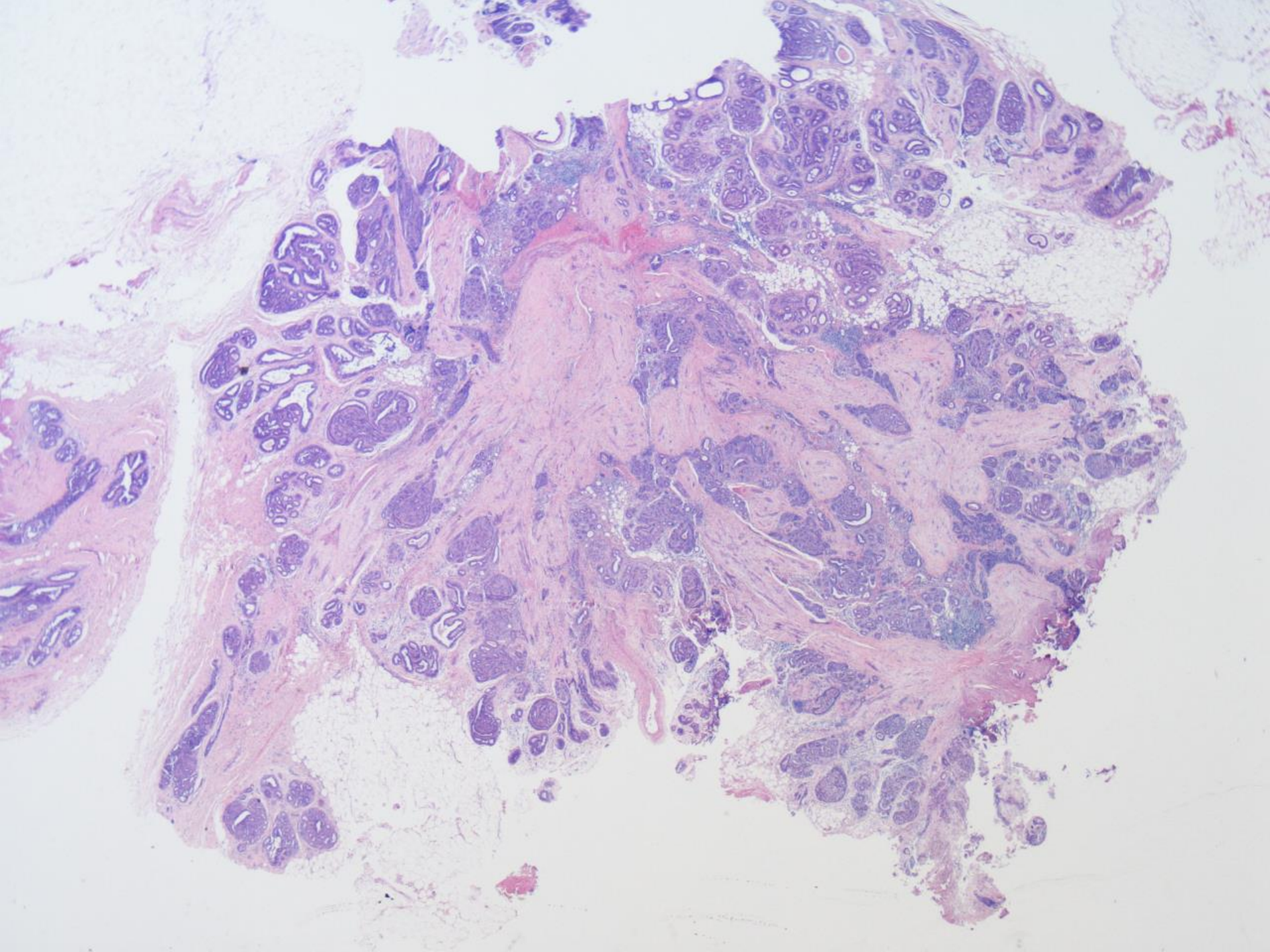


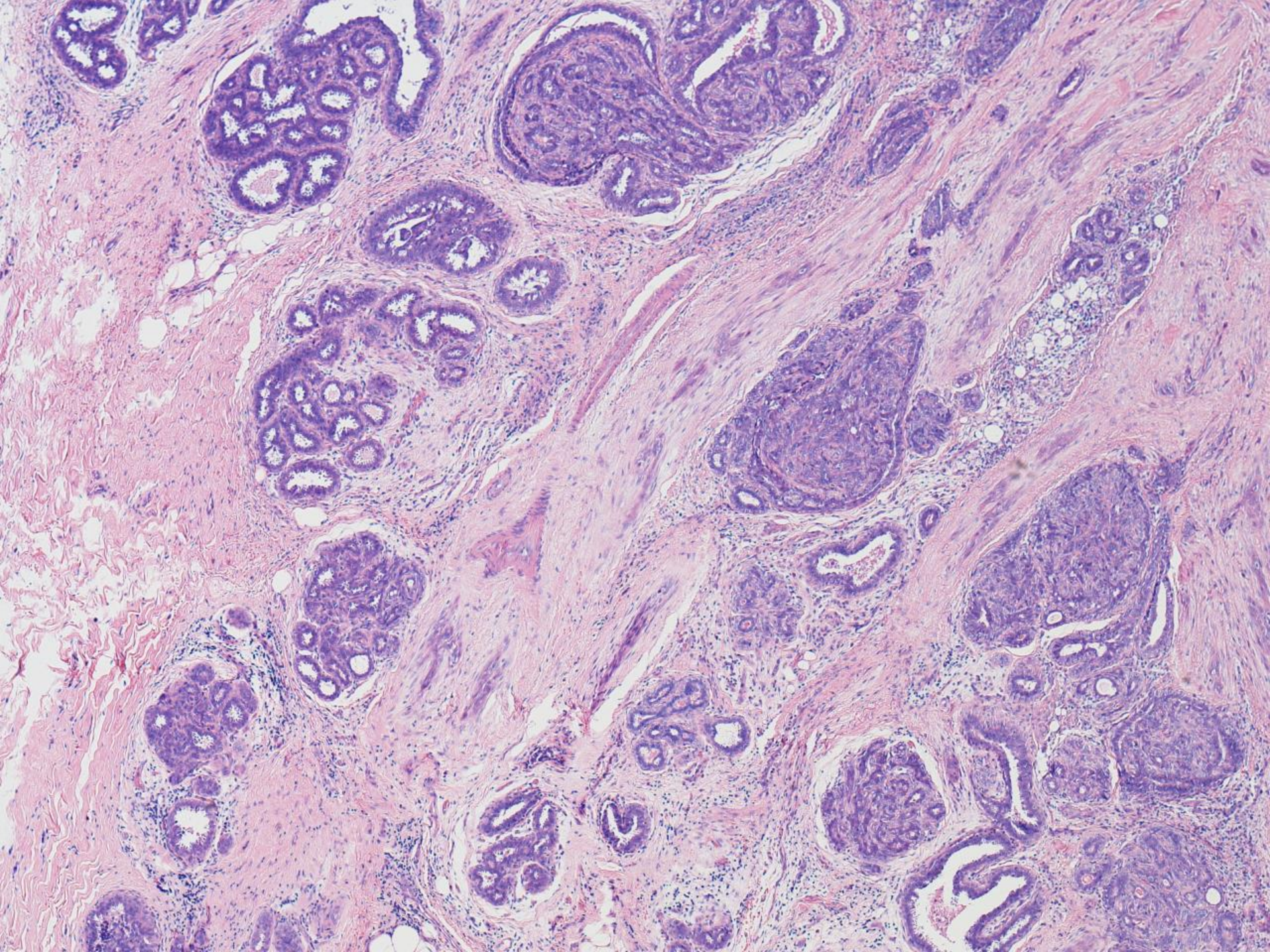




Low-grade Adenosquamous Carcinoma

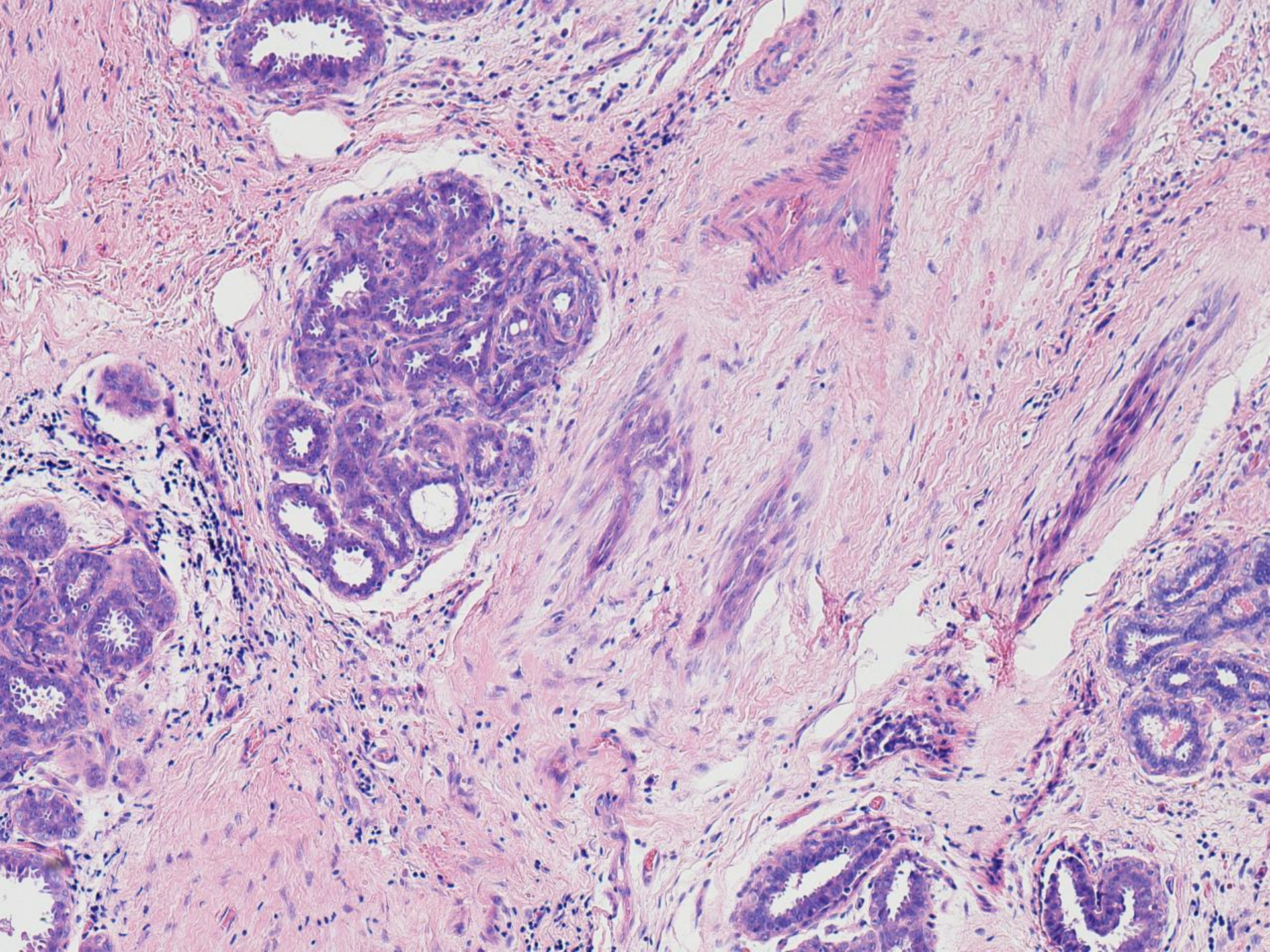
- Originally described by Rosen in 1987, Am J Surg Path
- Small round to oval glandular and tubule structures and solid cords admixed with solid nest of squamous epithelium within the desmoplastic stromal component
* Stroma typically desmoplastic / spindle-cell "fibromatosis-like" but can be more hyalinised and collagenous
- Epithelial component extends beyond lesion and infiltrates normal breast tissue
- Tendency to grow between and around ducts and lobules

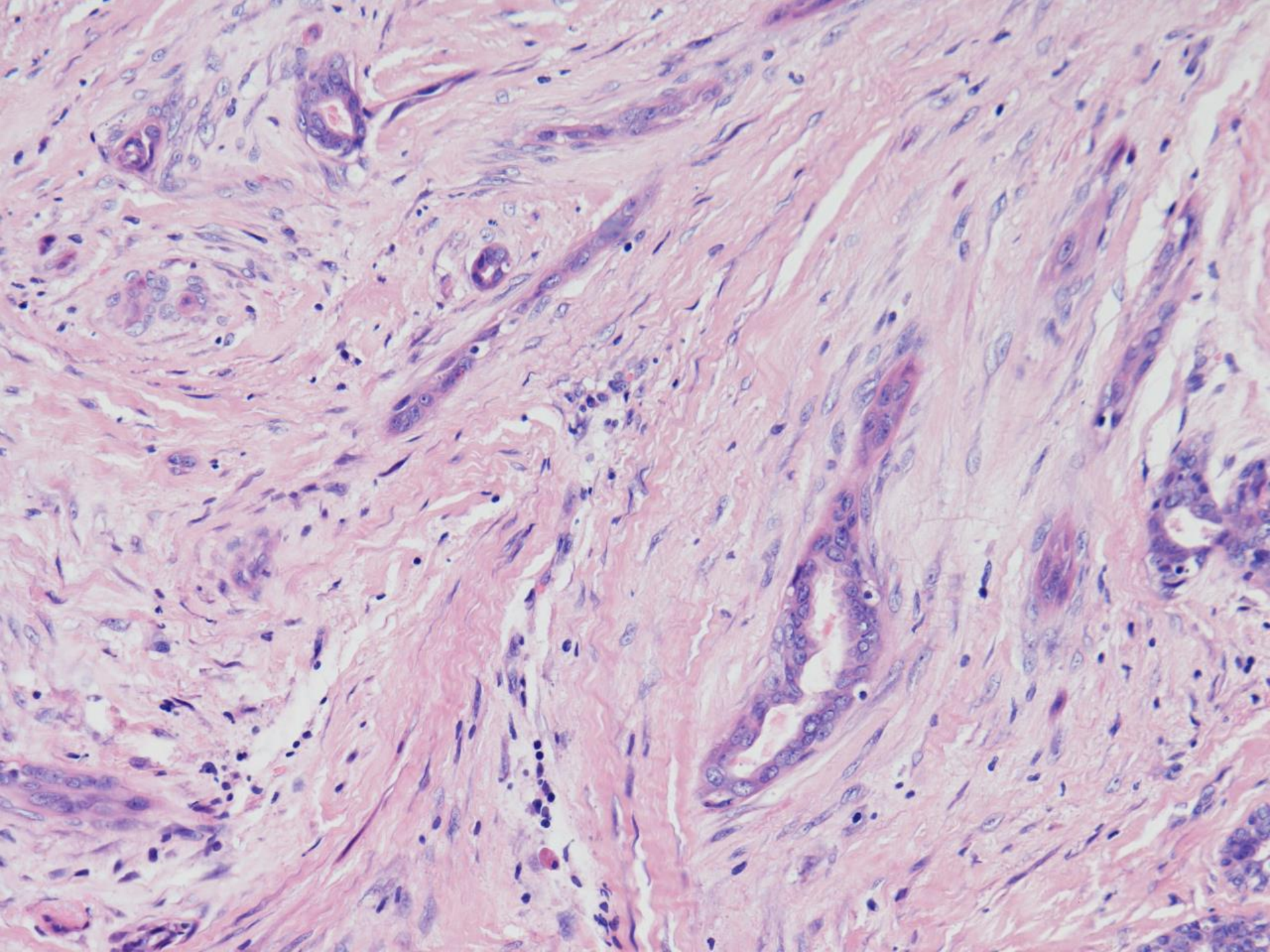




Low-grade Adenosquamous Carcinoma

- Solid nests may contain squamous cells, pearls or cysts
- Squamous component 5-80%
- Can have spindle cell and syringomatous areas
- Frequently associated with clusters of lymphocytes usually at the periphery
- All ER/PgR negative
- Association with underlying fibrosclerotic lesions including complex sclerosing lesions, papillary lesions and nipple adenomas





Low-grade Adenosquamous Carcinoma

- Epithelial element is the neoplastic component and this shows strong diffuse basal (CK5/6, CK14) and luminal (CK7 and CK18) CKs and p63.
- Typically ER-negative
- Excellent prognosis (?locally aggressive)

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

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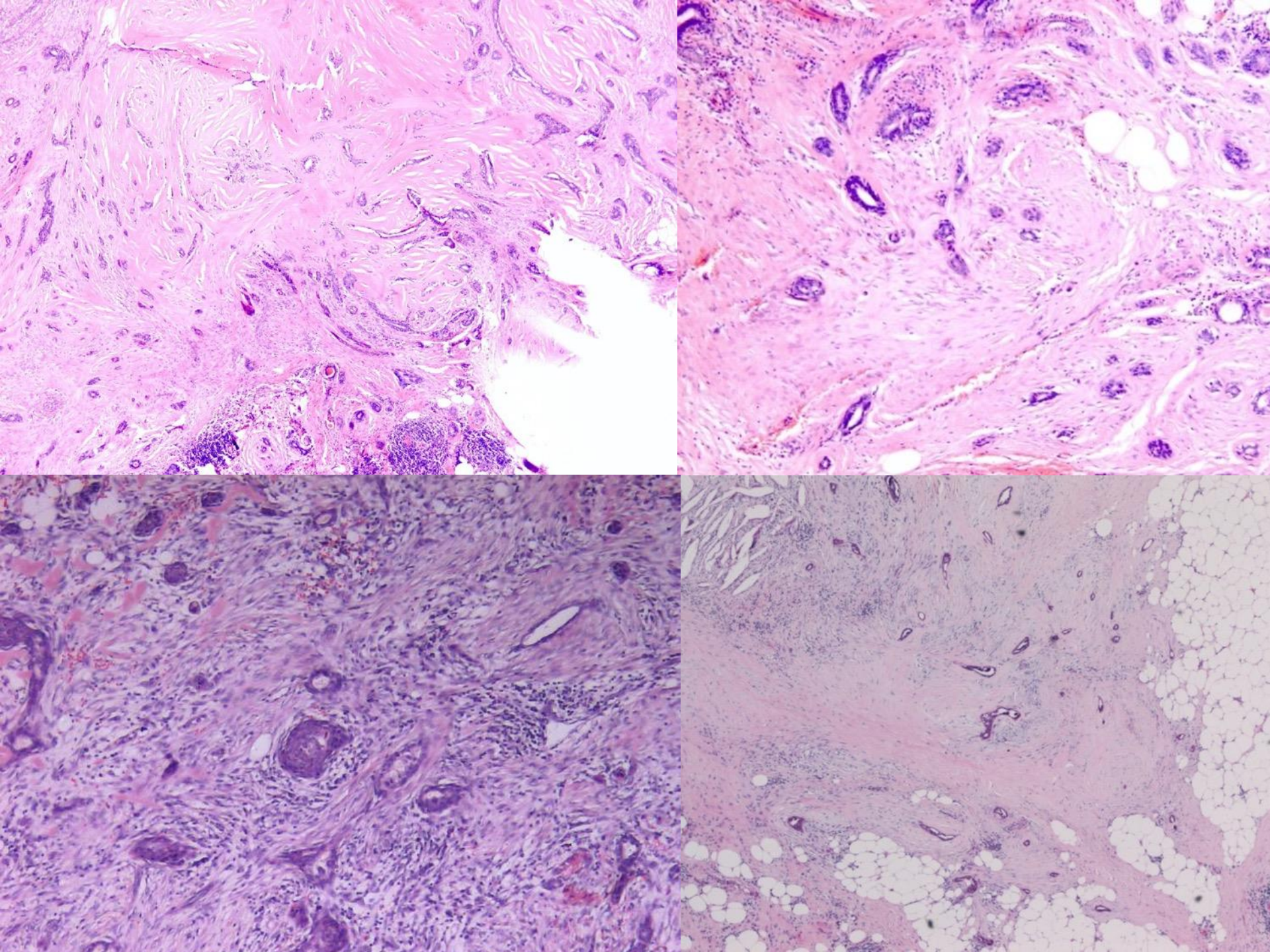
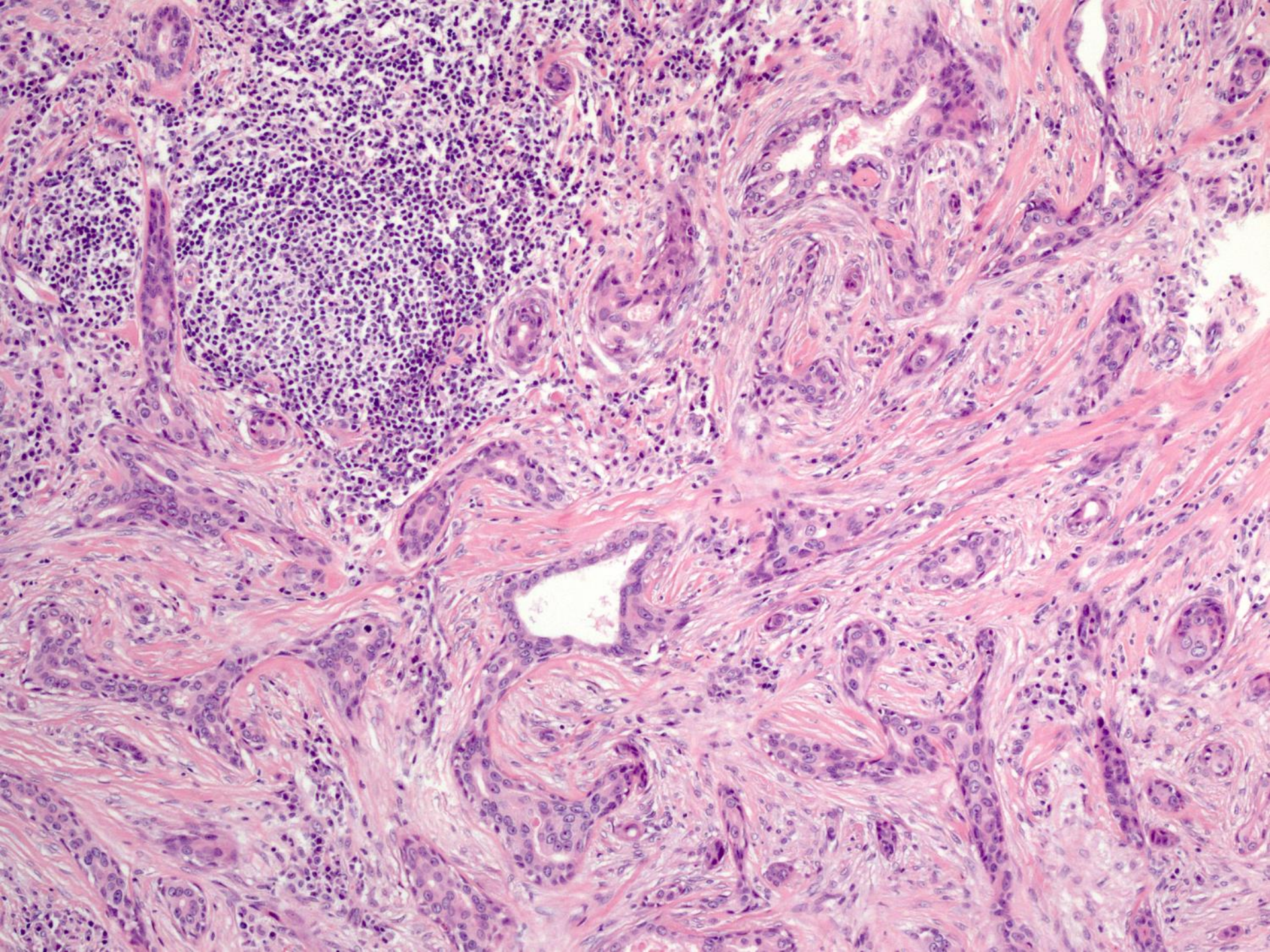
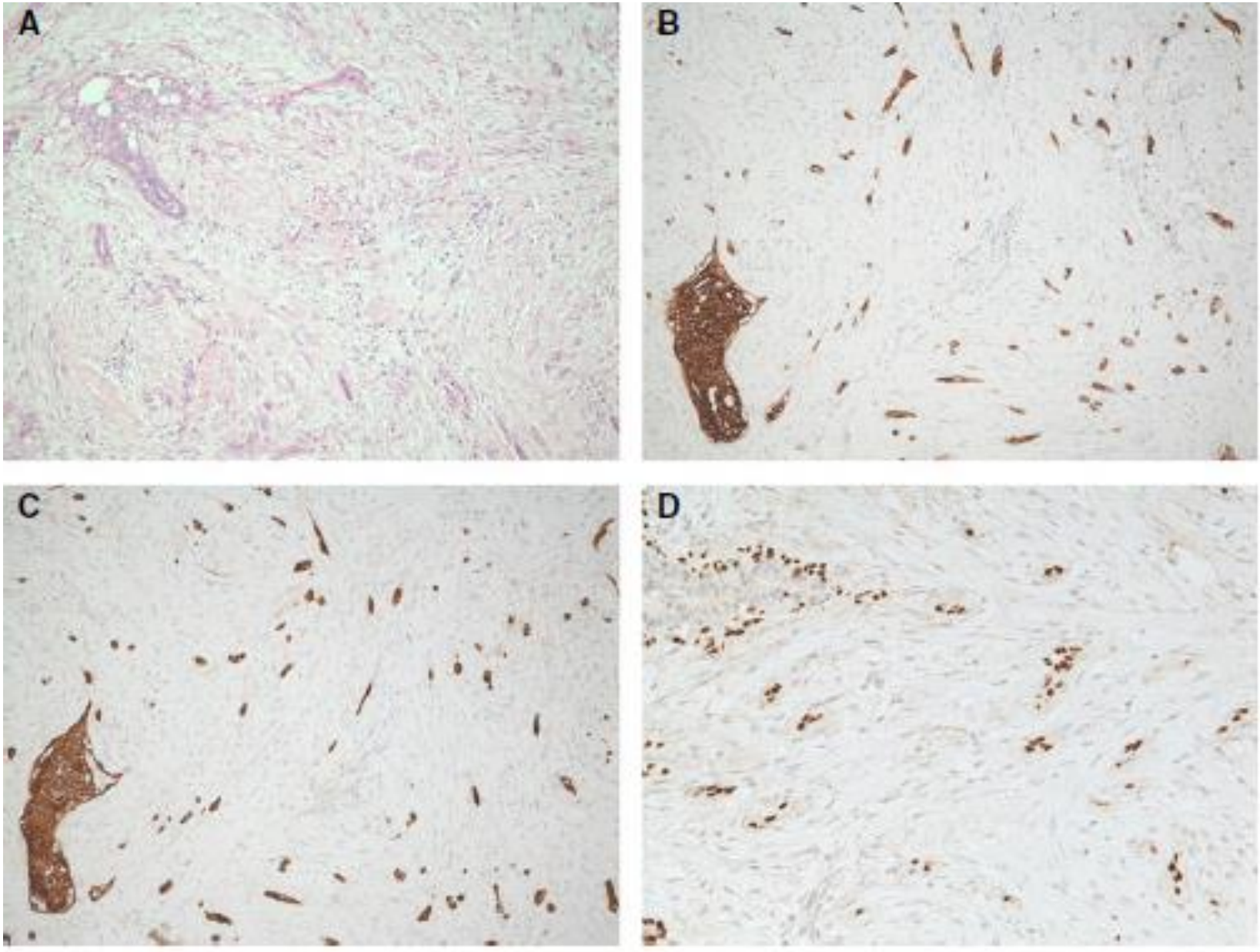




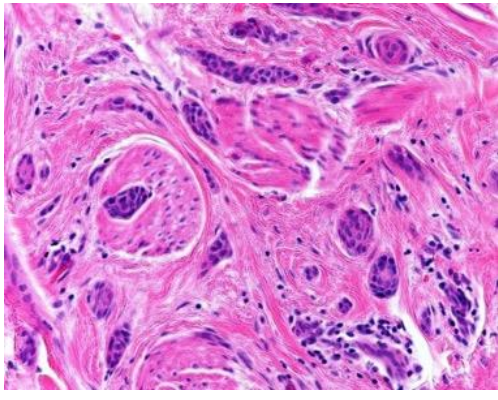


Low-grade adenosquamous carcinoma showing expression of cytokeratin 7 (CK7) (B), CK14 (C) and p63 (D).

Low-grade Adenosquamous Carcinoma

Pitfalls:

- Papillary lesion may show areas of fibrosis, sclerosis, entrapped epithelial islands and squamous metaplasia
- Proliferative phase of RS/CSL
  - ER heterogeneous.
  - No extension beyond desmoplastic stroma
  - Not very florid. ?? peripheral ME cells (IHC)
  - Size may be important
  - More regressive changes and lymphoid follicles
  - No DCIS in the surrounding tissue
- Histologically and molecularly similar to syringomatous adenoma of the nipple



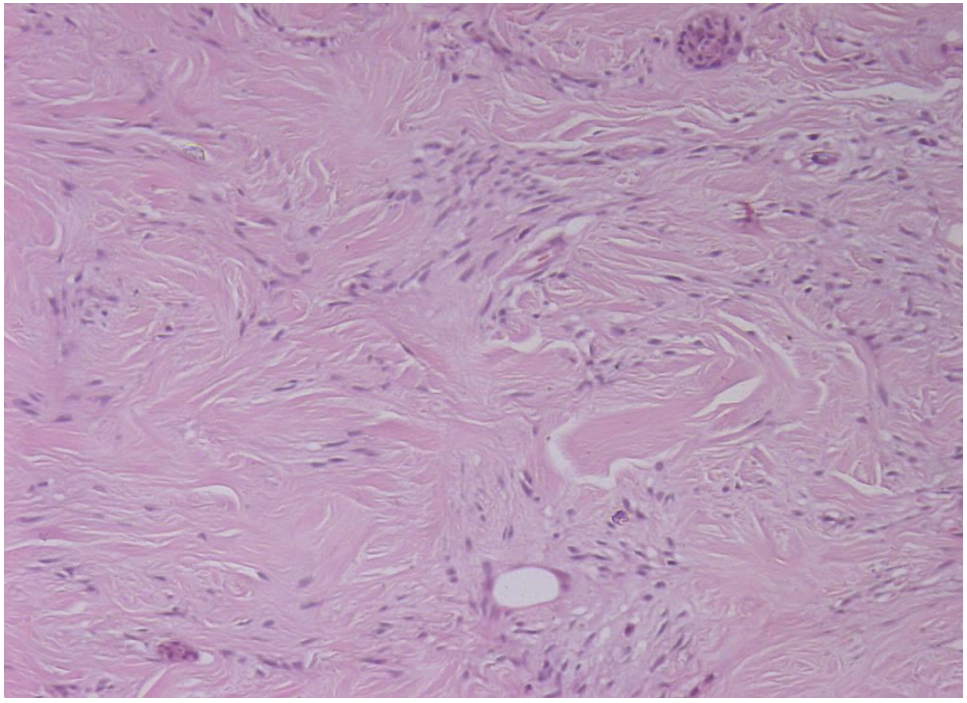
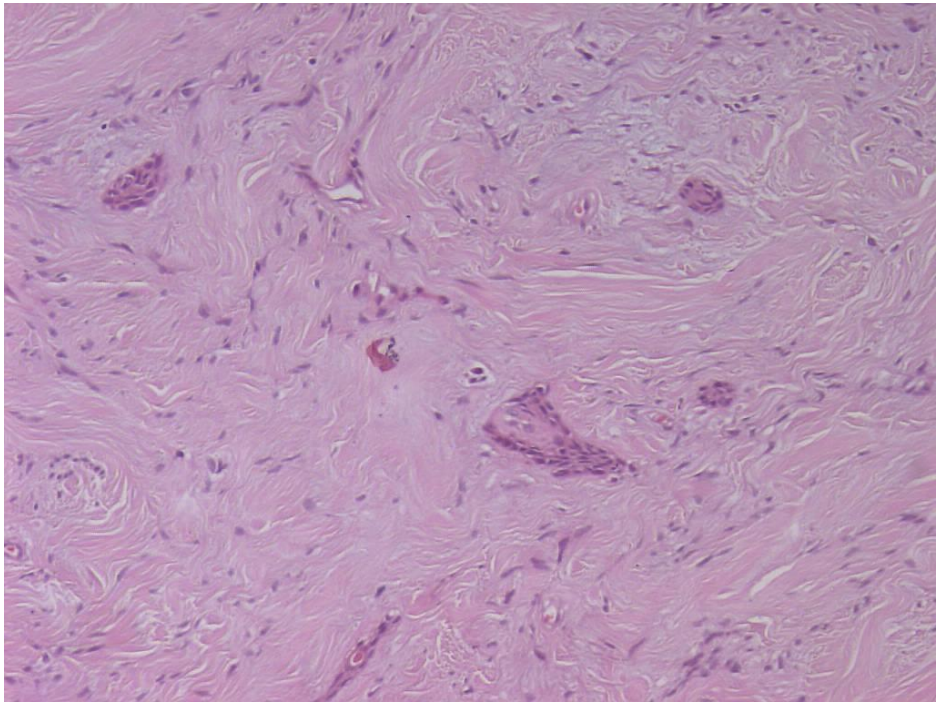
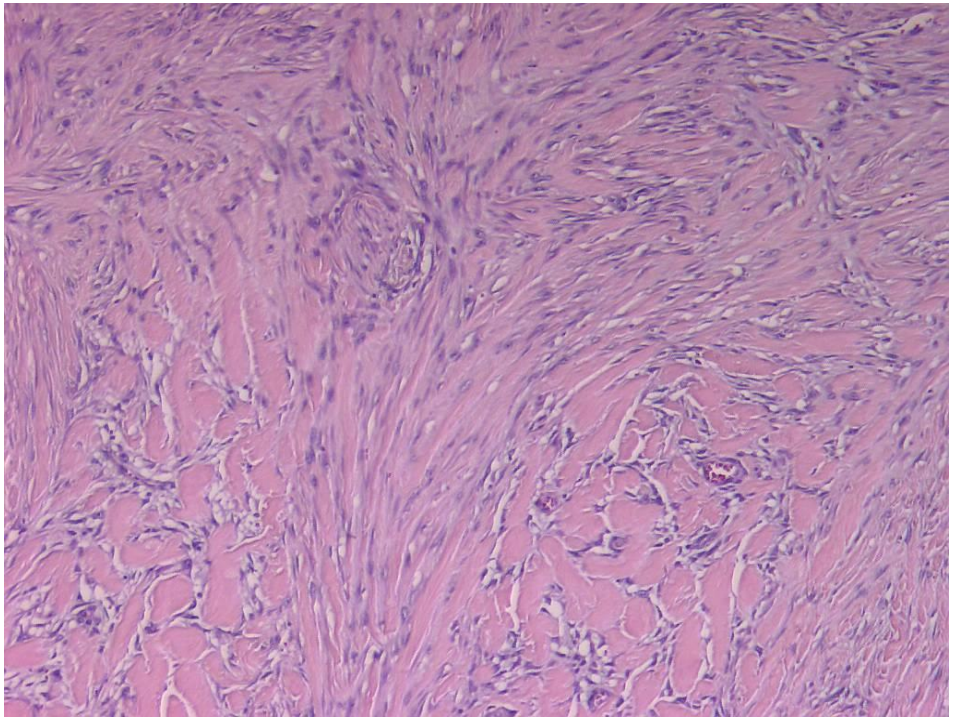
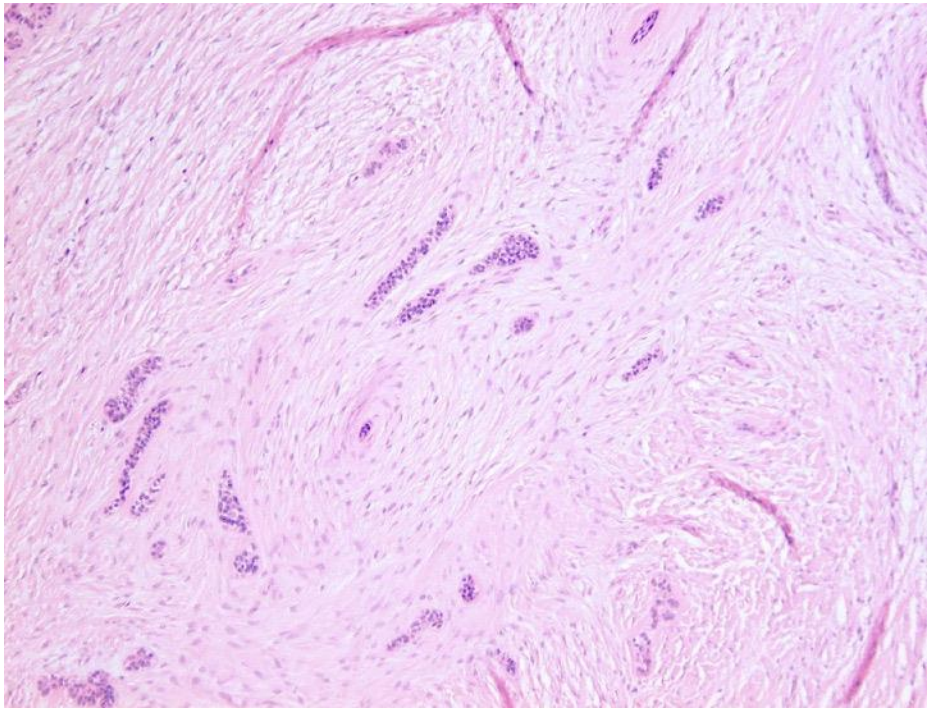
Low-grade spindle cell MBC
Fibromatosis like

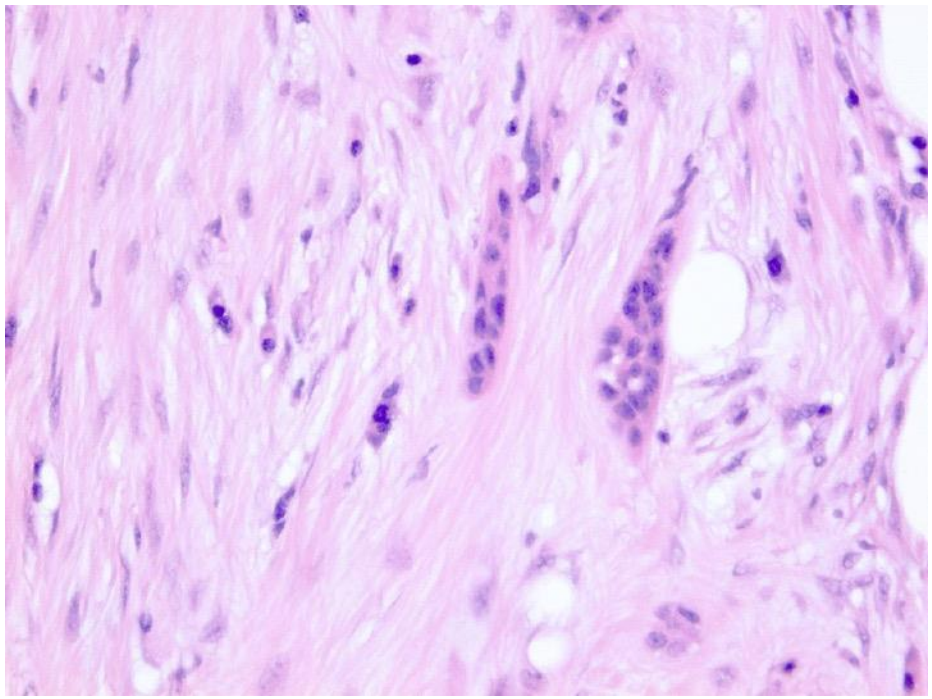
* Bland spindle cells in fascicular or storiform growth pattern infiltrating adjacent parenchyma, mimicking fibromatosis.
* Slender/wavy nuclei. Atypia mild/focal. Low mitotic activity
* Stroma usually shows regressive changes at least focally (hyalinization, myxoid degeneration and inflammatory infiltrate).
* +/- Scattered epithelioid/glandular elements (cords/clusters)
* CK5/6, CK14 and p63 are positive in the majority of cases.
* Luminal CKs are usually +ve particularly in epithelioid cells.
* Typically ER- & B-catenin negative or cytoplasmic staining

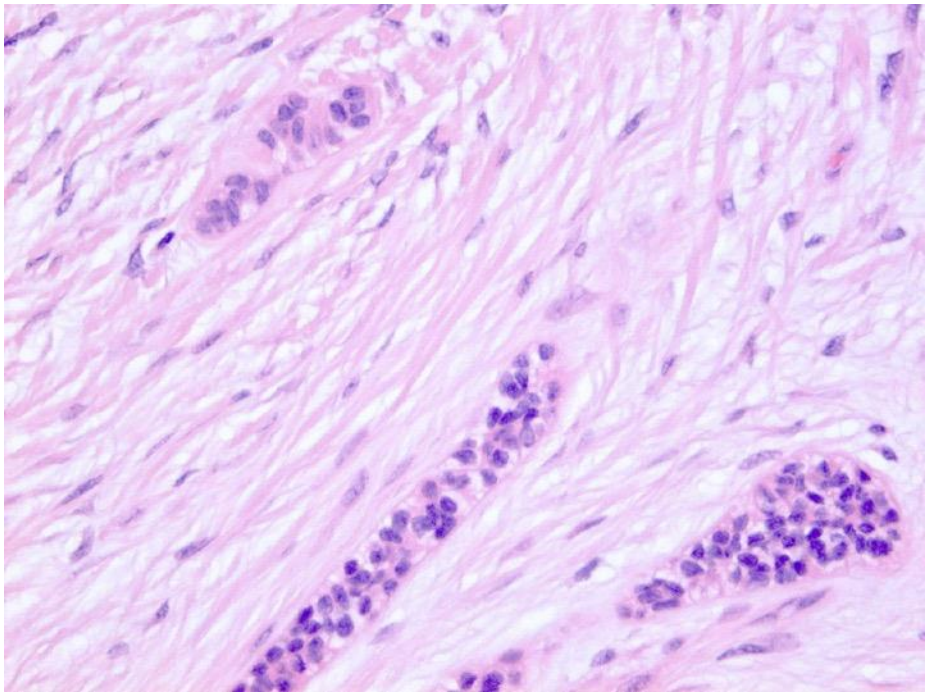
Low grade adenosquamous carcinoma

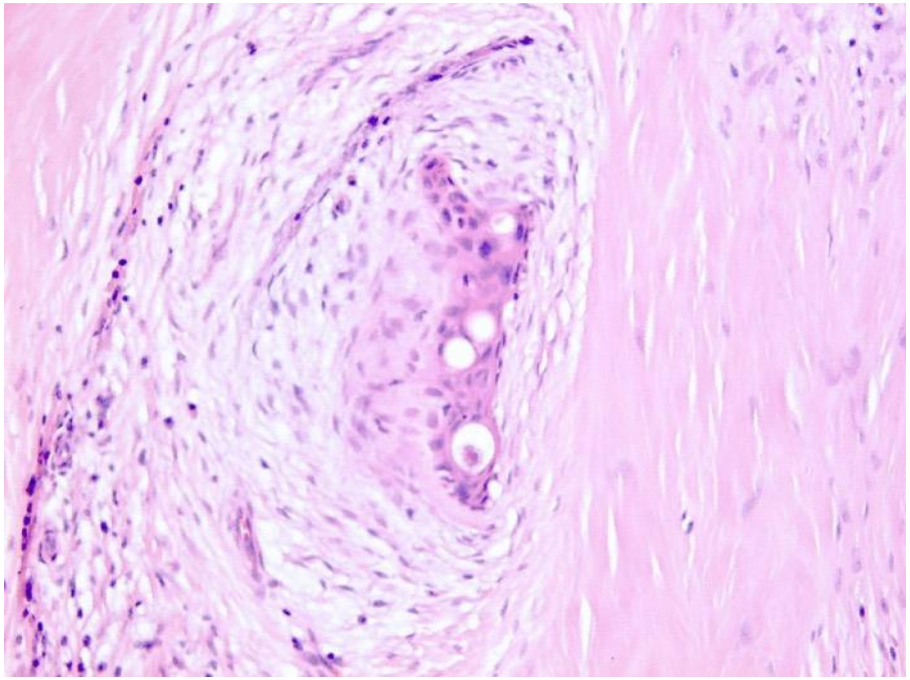
Behaviour

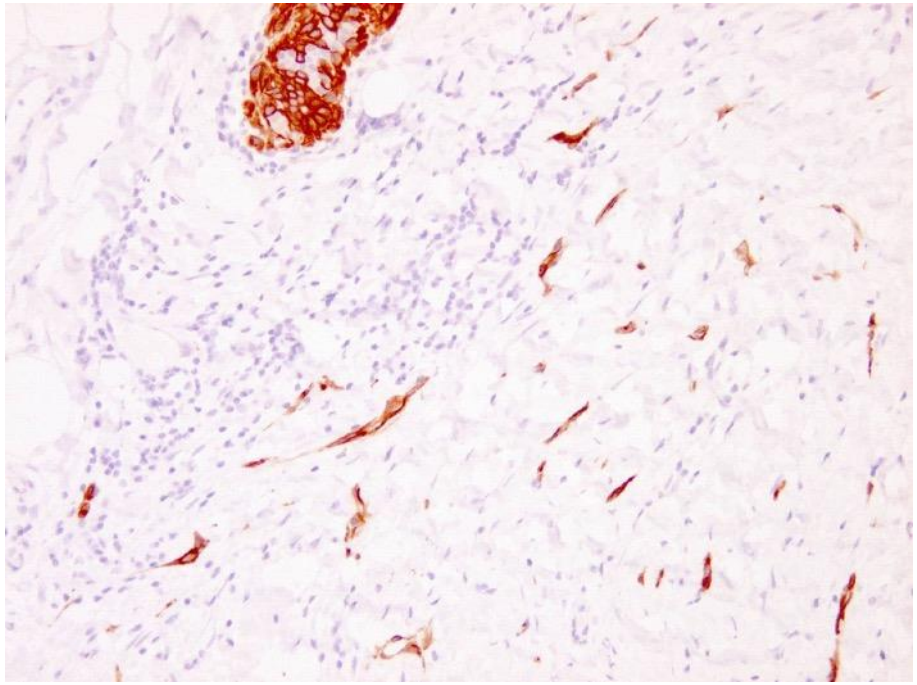
- Lymph node involvement – rare
- Metastatic disease - exceptional

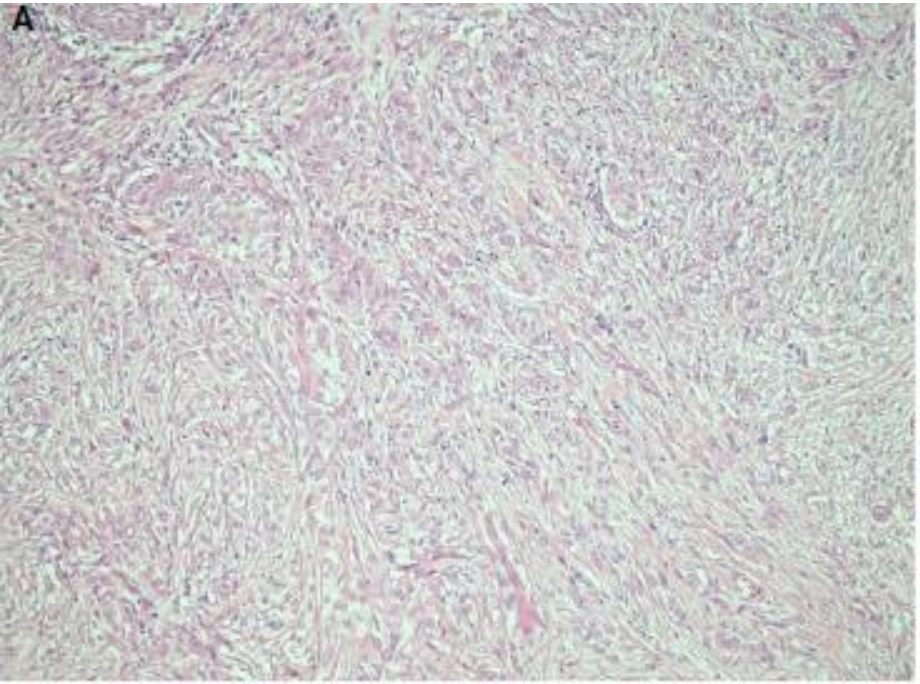





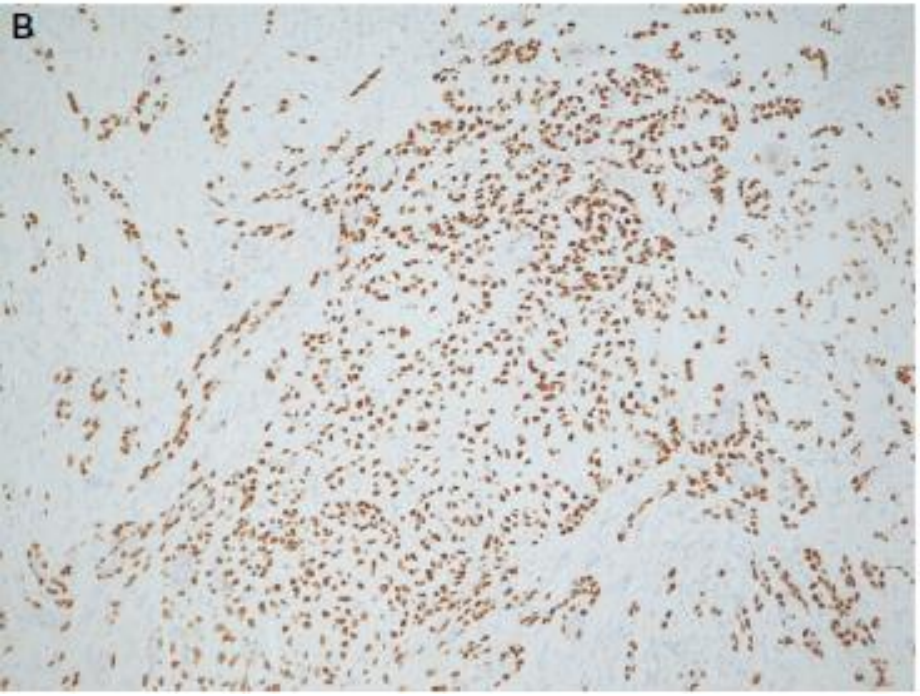












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P63

Histopathology

Histopathology 2016, **68**, 33–44. DOI: 10.1111/his.12865

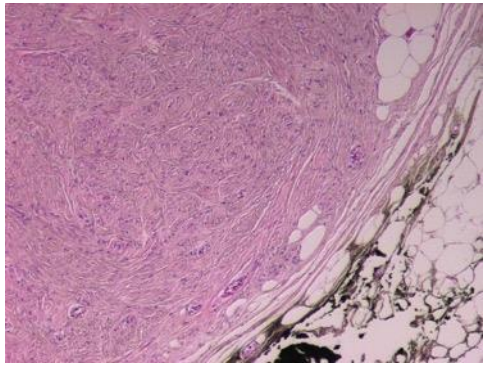
REVIEW

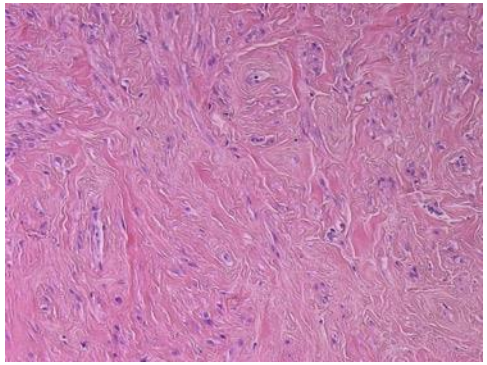
An approach to the diagnosis of spindle cell lesions of the breast

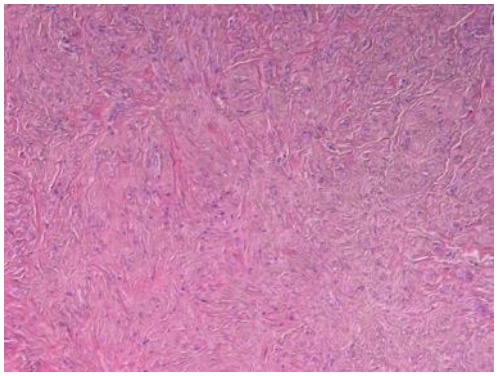
Emad A Rakha, Mohammed A Aleskandarany, Andrew H S Lee & Ian O Ellis

Low-grade Spindle Cell Carcinoma

- Remember:
- **DD**: Fibromatosis, Scar and Nodular fasciitis (CKs, CD34, SMA and Beta-catenin)
- ? Myofibroblastoma (ER+, PR+, CD34+, Desmin+)







- Pseudoangiomatous stromal hyperplasia (CD34+ve)

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

Emad A Rakha[1], Sunil Badve[2], Vincenzo Eusebi[3], Jorge S Reis-Filho[4], Stephen B Fox[5], David J Dabbs[6], Thomas Decker[7], Zsolt Hodi[1], Shu Ichihara[8], Andrew HS Lee[1], José Palacios[9], Andrea L. Richardson[10], Anne Vincent-Salomon[11], Fernando C Schmitt[12], Puay-Hoon Tan[13], Gary M Tse[14], and Ian O Ellis[1]

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REVIEW

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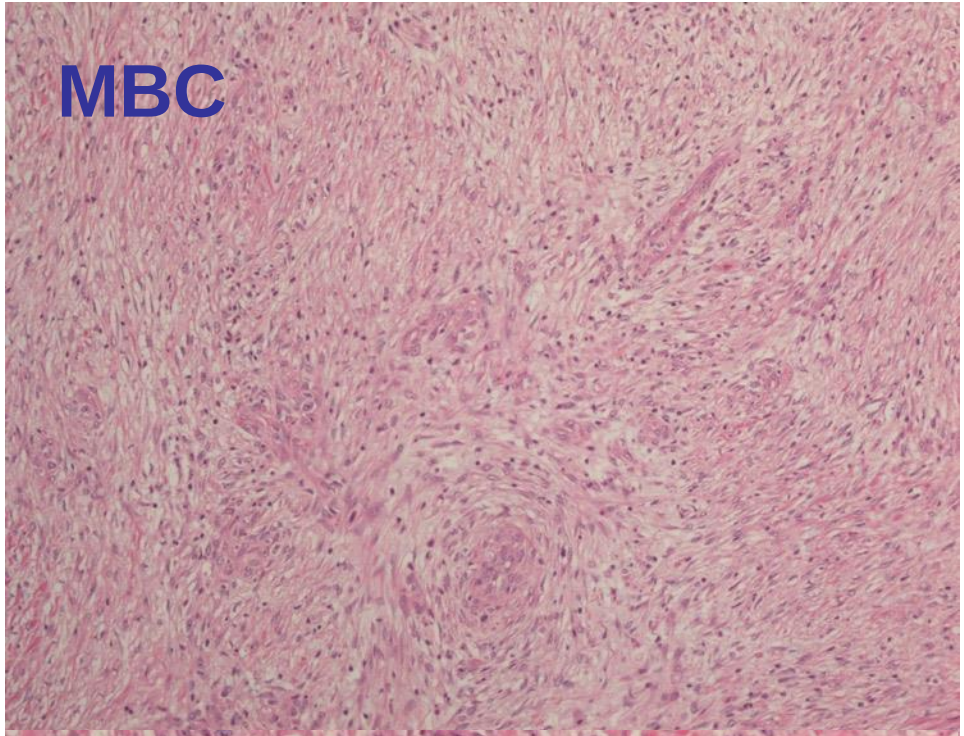
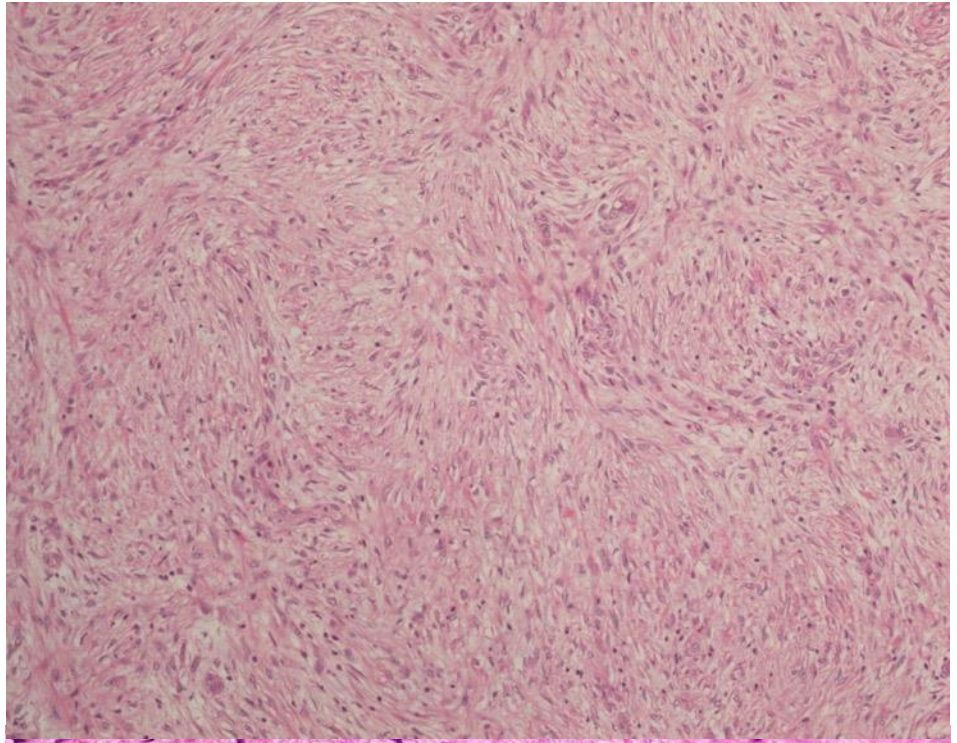
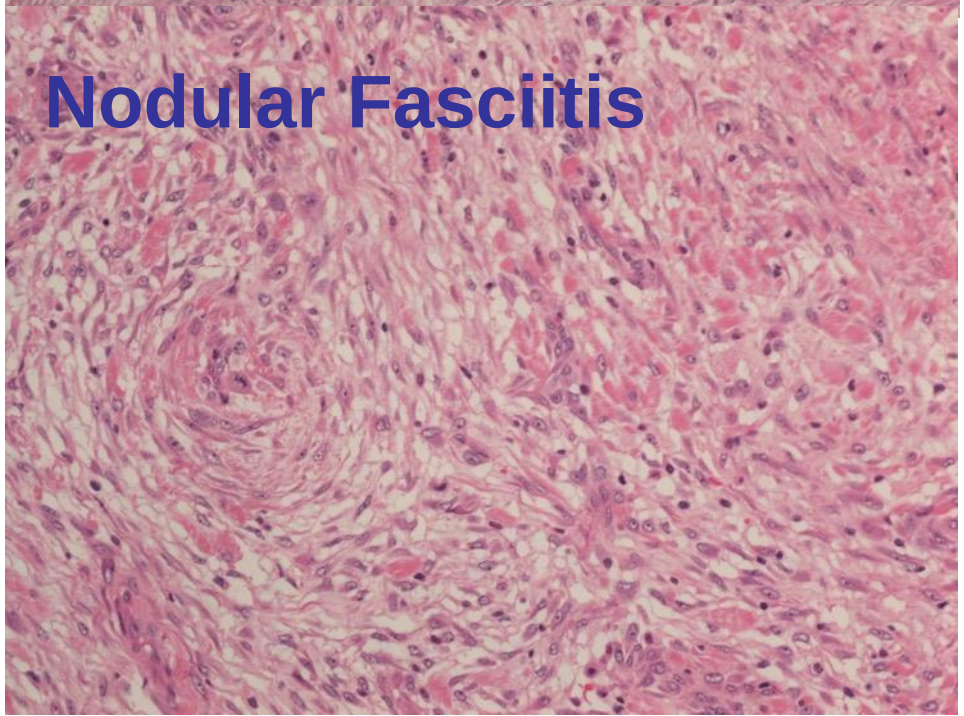
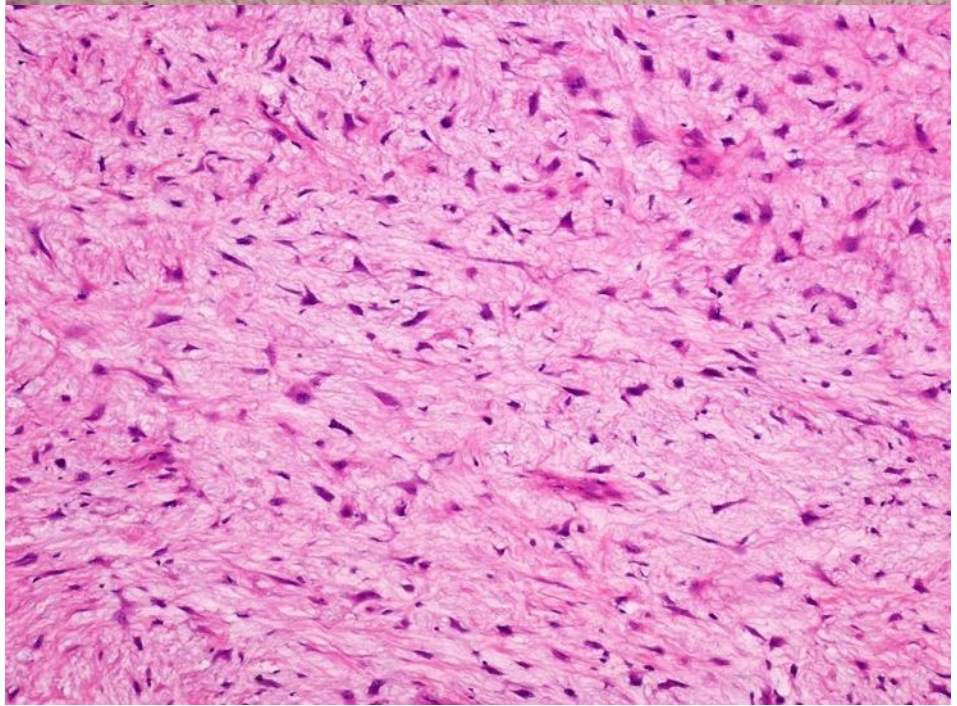

MBC




Nodular Fasciitis



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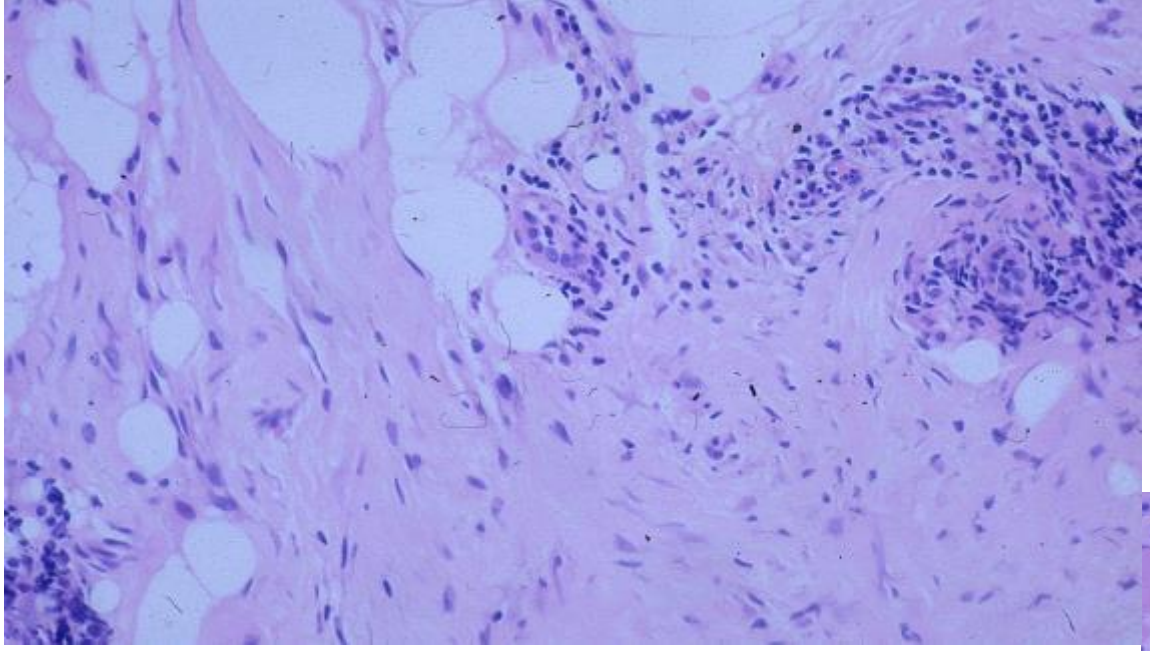
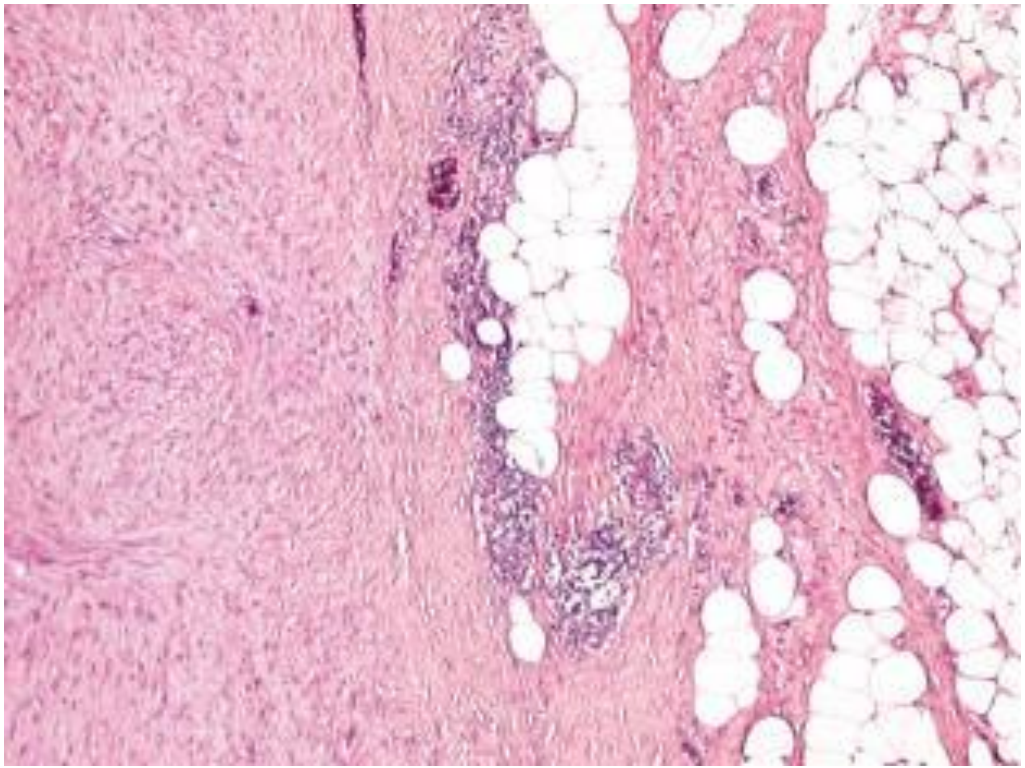
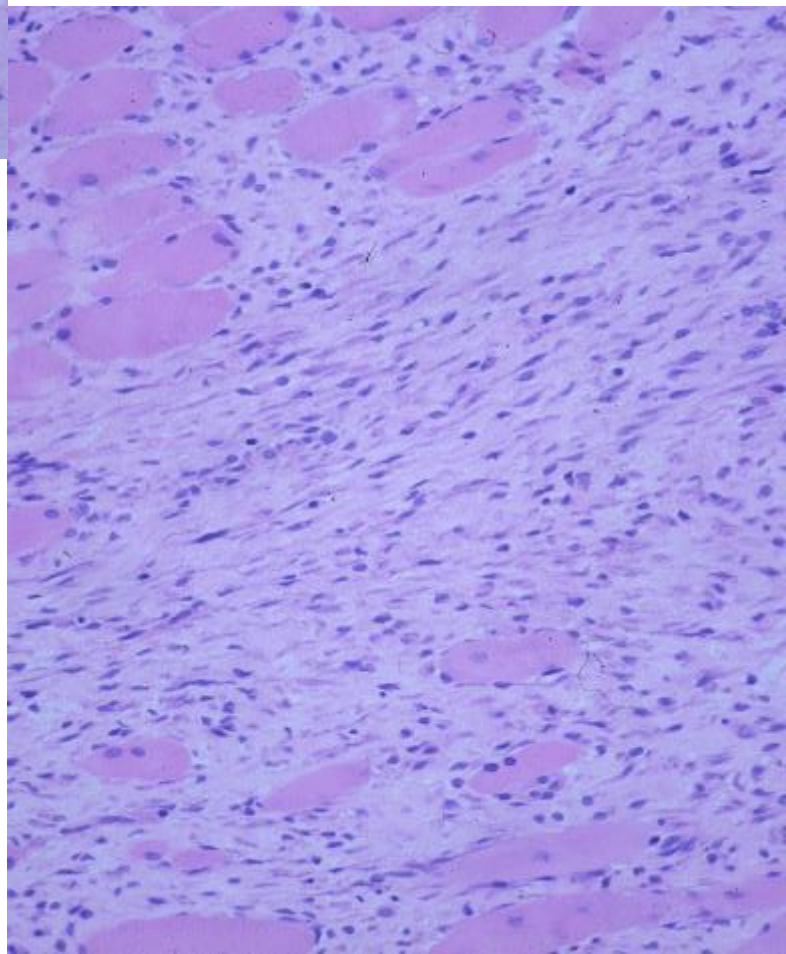
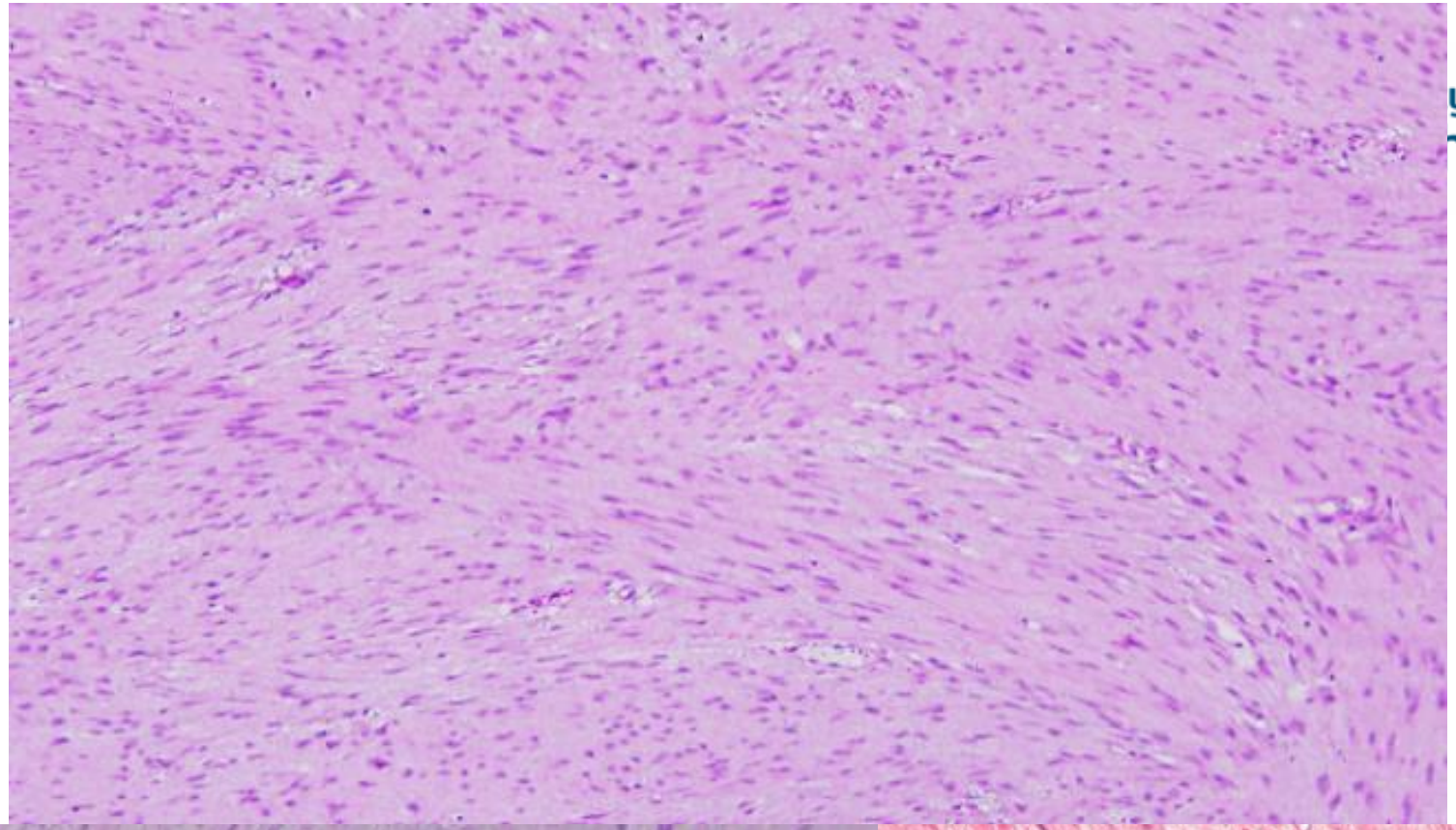
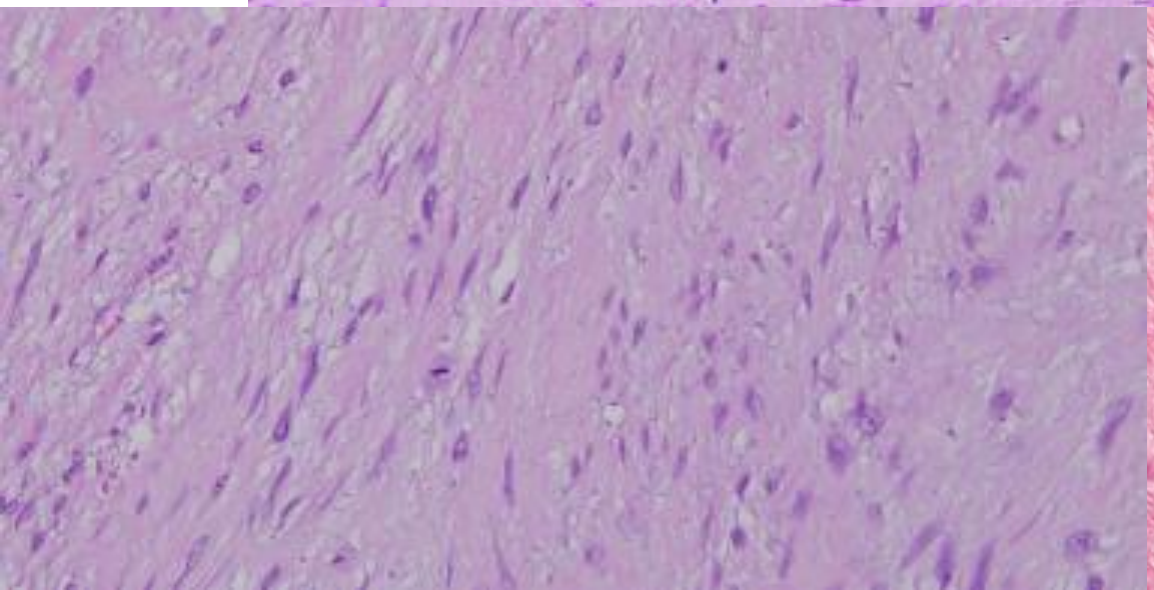
Infiltrative margins

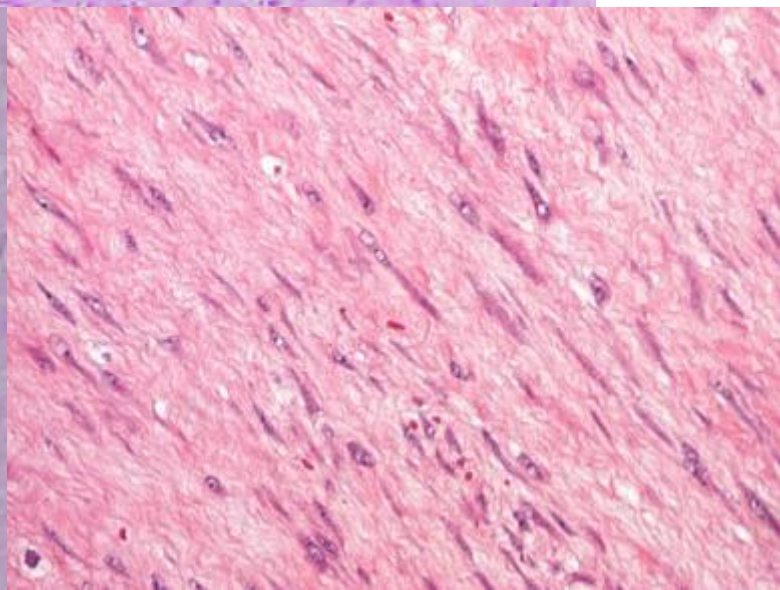


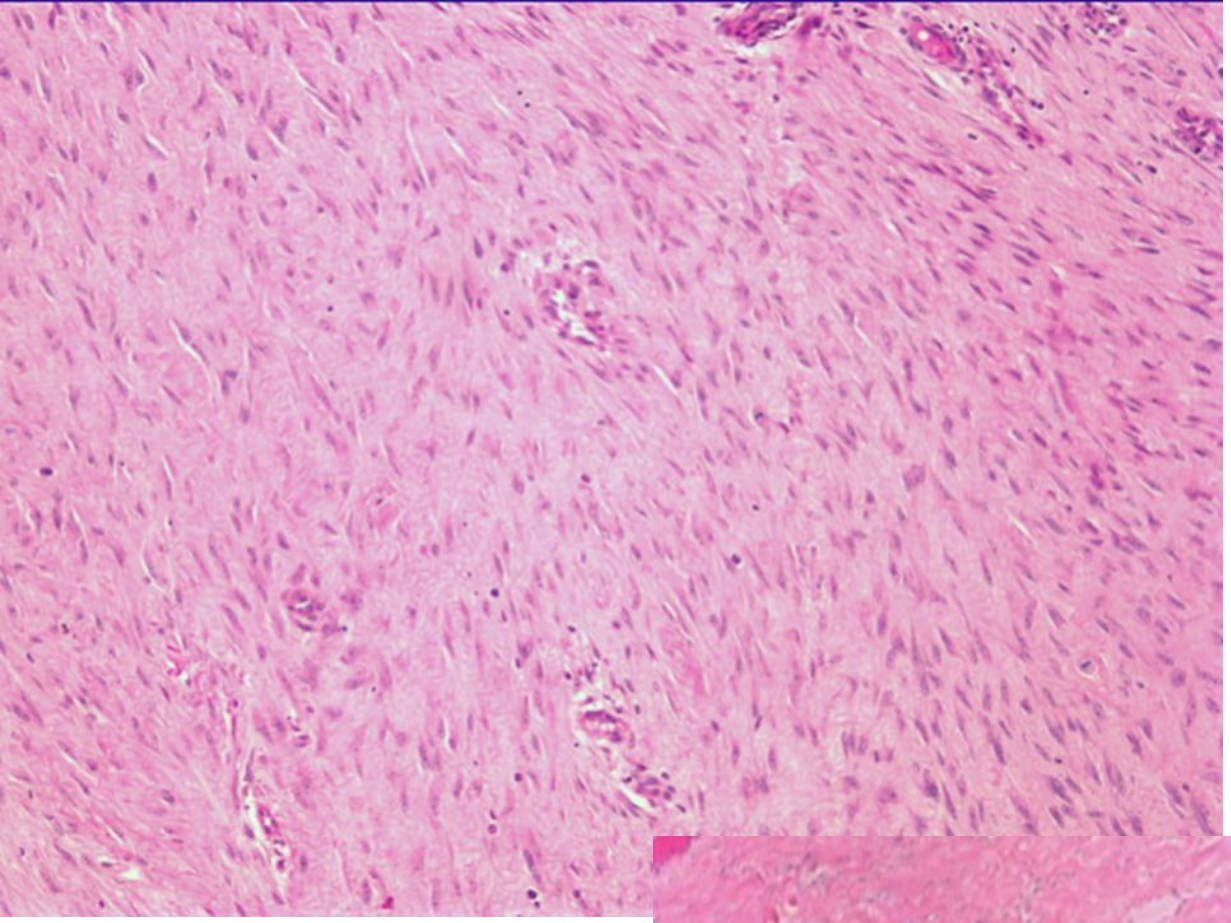








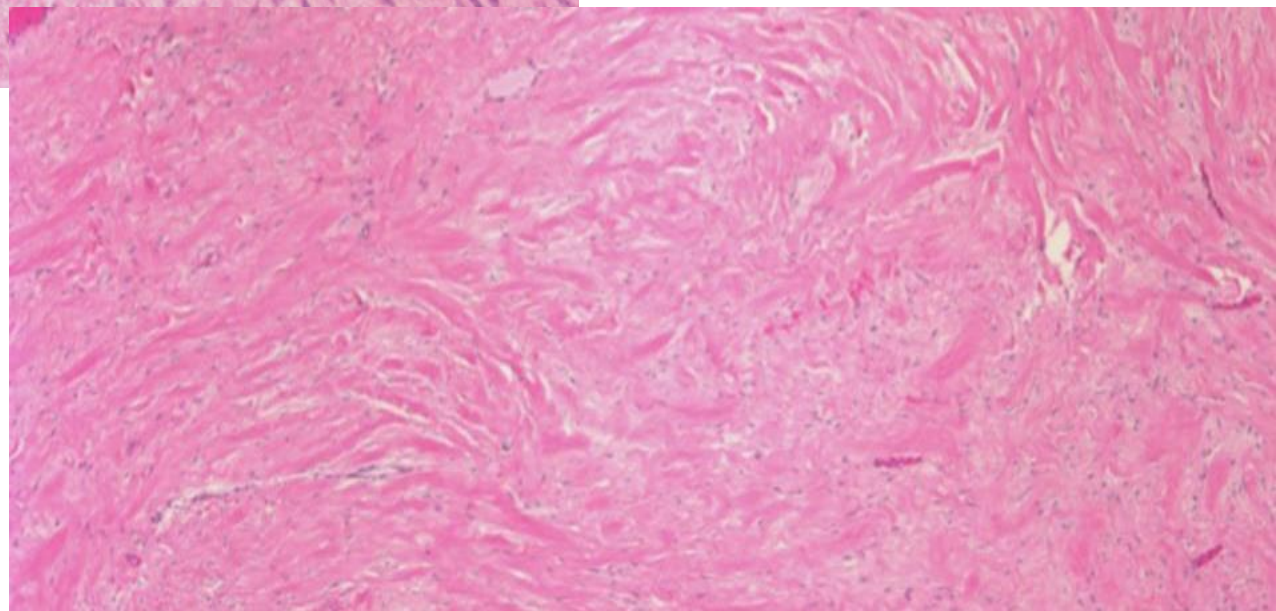




Diagnosis?

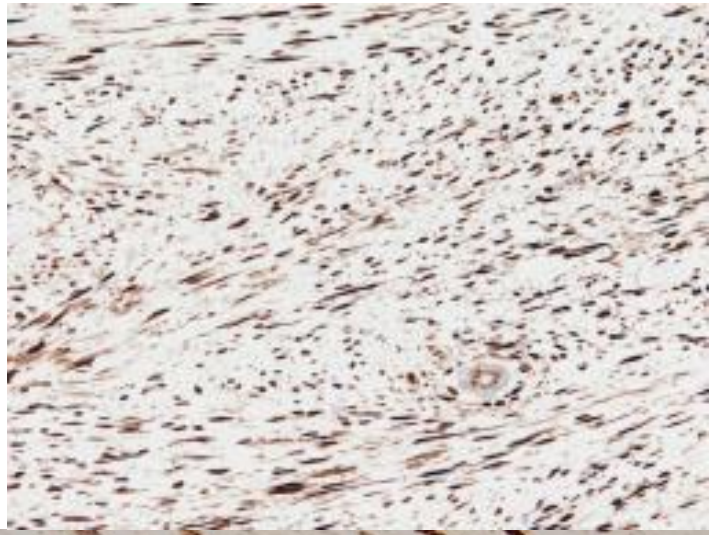
Likely Fibromatosis

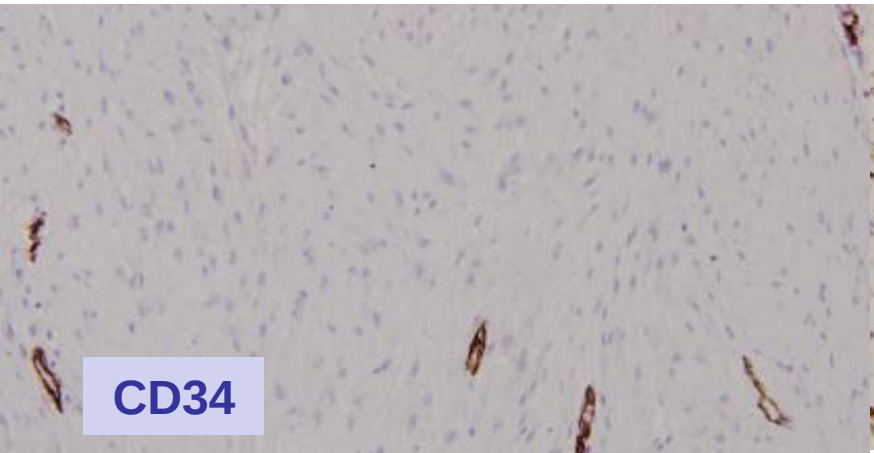
Collagenised areas

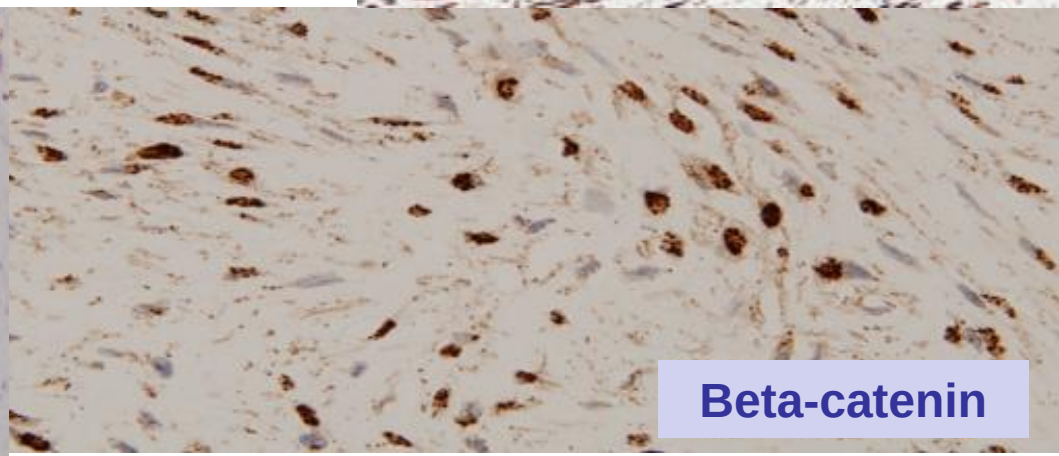


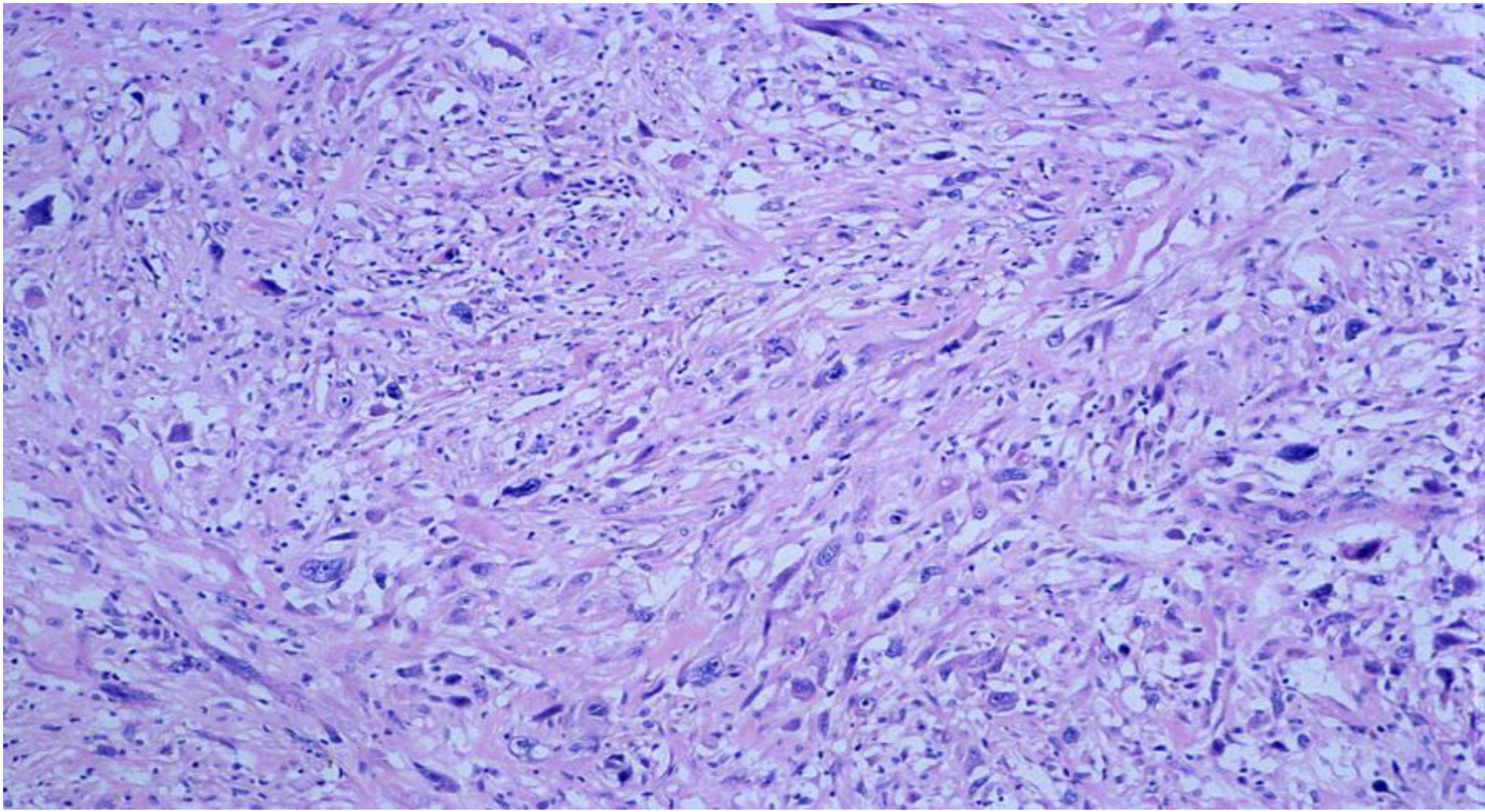
Immunohistochemistry

- CD34, CKs, p63, S100 and desmin- negative
- Beta catenin – 80% (nuclear)
- + *CTNNB1* mutations in ~70%
- Actin: positive









Fibromatosis like MBC is not high grade

Low-grade Fibromatosis like Spindle Cell Carcinoma

Key Points:

LG-FLSCCs are characterised by low genomic instability

They share no copy number aberrations with other metaplastic carcinomas.

This entity is a unique group of tumours and their genotype belies their apparent homogeneous morphology and phenotype

Takano EA et al. J Clin Pathol. 2015

Low-grade Fibromatosis like Spindle Cell Carcinoma

Key Points:

Exhibits indolent behaviour akin to some locally aggressive lesions with very low metastatic potential such as fibromatosis

A malignant diagnosis using the term carcinoma or metaplastic carcinoma with triple negative status may trigger inappropriate use of aggressive adjuvant systemic chemotherapy

Gobbi H et al DL. Cancer. 1999; 85(10):2170–82. [PubMed: 10326695]

Atypical adenomyoepithelioma

Although the majority of ademomyoepitheliomas can be categorised as benign or malignant tumours, some tumours show intermediate histological features and discrimination is often difficult.

The behaviour of these lesions is often unpredictable as they show some, but not all features of malignancy

Loose JH et al. Am J Surg Pathol. 1992; 16(9):868–76.
Nadelman CM et al. Arch Pathol Lab Med. 2006; 130(9):1349–53.

Atypical adenomyoepithelioma

Diagnostic features of atypical adenomyoepithelioma remain poorly defined.

Mitoses, cytonuclear atypia and infiltration are used to assess the malignant nature of the neoplastic myoepithelial cells.

These features remain subjective and are not clearly defined and may not aligh e.g. significant cytonuclear atypia with low mitotic count.

Zhang C et al.. Breast J. 2004; 10(2):154–5.

Borderline Phyllodes Tumour

Histological and molecular features of phyllodes tumour are well described

A large proportion of phyllodes tumours can be categorised as benign or malignant tumours, but some tumours show intermediate histological features and discrimination can be difficult.

The behaviour of these lesions is often unpredictable as they show some, but not all features of malignancy

Tan B et al. Histopathology. 2016 January ; 68(1): 5–21.

Borderline Phyllodes Tumour

Issues:

The risk of distant metastasis has been mainly been observed in histologically malignant phyllodes tumours but rare events of metastasis have also been reported for borderline phyllodes tumours

Microscopic distinction between borderline and malignant phyllodes can be difficult and prediction of behaviour is consequently unreliable.

In some studies, risk of metastasis was related to individual histological features and not restricted to the histological subtyping of malignant versus borderline tumours.

Phyllodes Tumour

The University of Nottingham

Key Points:

- Grading of phyllodes tumours should aim to achieve accuracy and consistency at the benign and malignant ends of the spectrum.
- Definitive distinction between cellular fibroadenomas and benign phyllodes tumours may not be crucial, in light of similar reported recurrence rates.
- The term benign fibroepithelial lesion/neoplasm may be recommended for cases where clear diagnostic distinction cannot be made, although this should be used sparingly.

Phyllodes Tumour

Key Points:

- Malignant phyllodes tumours are diagnosed when there are marked stromal hypercellularity, atypia, increased mitoses of ≥10/10 HPFs, permeative tumour borders, and stromal overgrowth.

- The presence of a malignant heterologous component places the tumour into the malignant category regardless of other histological features.

Phyllodes Tumour

Key Points:

- A conservative approach can be accorded to benign phyllodes tumours that have been initially enucleated without margins.
- Excision with negative margins should be achieved for recurrent and malignant phyllodes tumours.
- Most would recommend that borderline tumours should also be completely excised.

Phyllodes Tumour

Key Points:

- Although the literature often refers to a margin width of at least 10 mm, a robust evidence base to support this approach is lacking. Therefore, an ideal margin width remains to be determined, and may need to be considered in relation to factors such as tumour size and cosmesis.

Phyllodes Tumour

The University of Nottingham

Key Points:

- From a diagnostic and management perspective, it is important to accurately recognize malignant phyllodes tumours, which should be surgically eradicated and effectively treated at diagnosis, as these tumours have a well-established but relatively infrequent risk of metastasis and death.

- The role of adjuvant radiation therapy in borderline and malignant tumours remains to be defined. Routine axillary dissection is not recommended

Breast Lesions of Limited Metastatic Potential

- Encapsulated Papillary Carcinoma
- Solid Papillary Carcinoma
- Low Grade Adenosquamous carcinoma
- Low Grade Fibromatosis Like Carcinoma
- Borderline Phyllodes Tumour
- Atypical Adenomyoepithelioma