Memorial Sloan Kettering Cancer Center

Fibroepithelial Lesions (FELs)

diagnostic challenges and management implications

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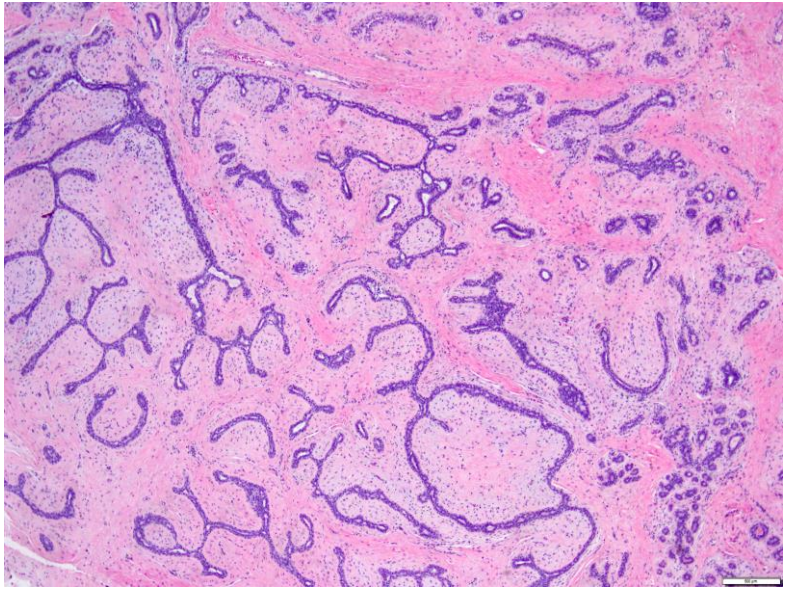
Pezcoller Seminar
September 16, 2022 – Trento, Italy

Fibroadenoma (FA) and Phyllodes Tumor (PT)

- Review of morphology and diagnostic criteria
  - WHO Classification Breast Tumours 5th ed. (2019)
  - CAP Protocol for reporting PT (March 2022)
- Common diagnostic dilemmas
  - Cellular FA vs (Benign) PT
  - Juvenile FA vs (Benign) PT
  - Malignant PT vs Metaplastic Spindle Cell Carcinoma
- Core Needle Biopsy (CNB)
- Local recurrence and distant metastases
- Update on management
- Molecular alterations and possible diagnostic applications

Fibroadenoma

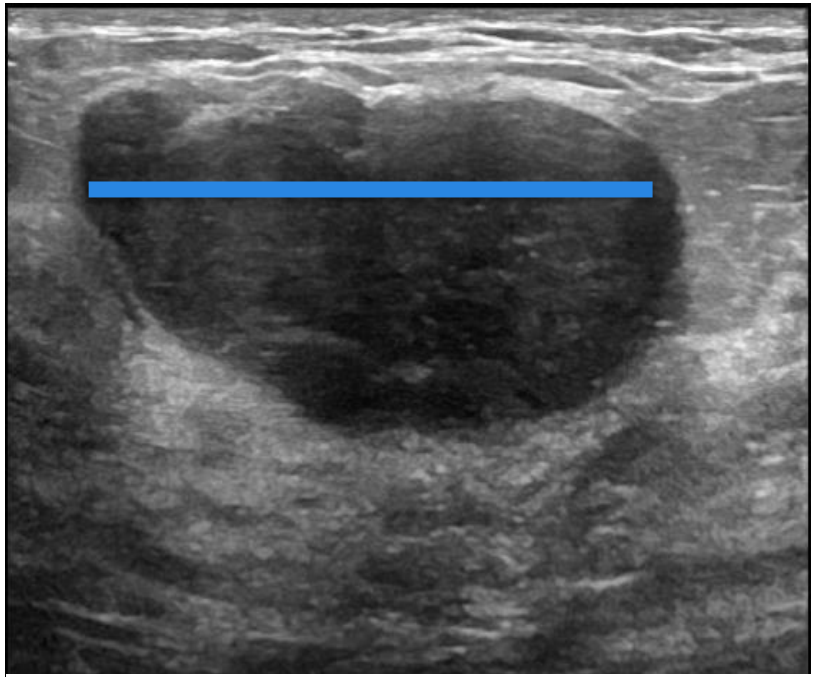


circumscribed benign neoplasm of the terminal duct lobular unit (TDLU) with biphasic proliferation of epithelial and stromal components

Fibroadenoma (FA)

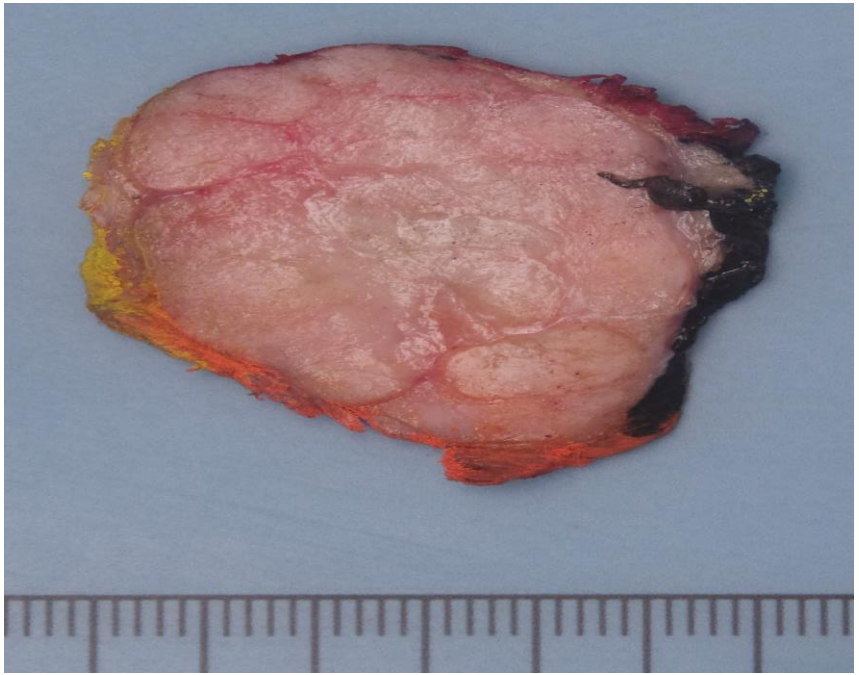
- A common benign neoplasm of the breast
- Occurs at any age, but detected most frequently in young women
- No known predisposing factors
  - exception: myxoid FA
- Presentation
  - palpable painless mass, well-defined, rubbery to firm, mobile
  - in older women detection often prompted by Ca^{2+}
- Size usually ≤3 cm

Imaging studies



well-circumscribed, round to ovoid, hypoechoic, isoechogenic, minimal to no posterior shadowing, parallel orientation (= major axis is parallel to the skin)

Macroscopic appearance



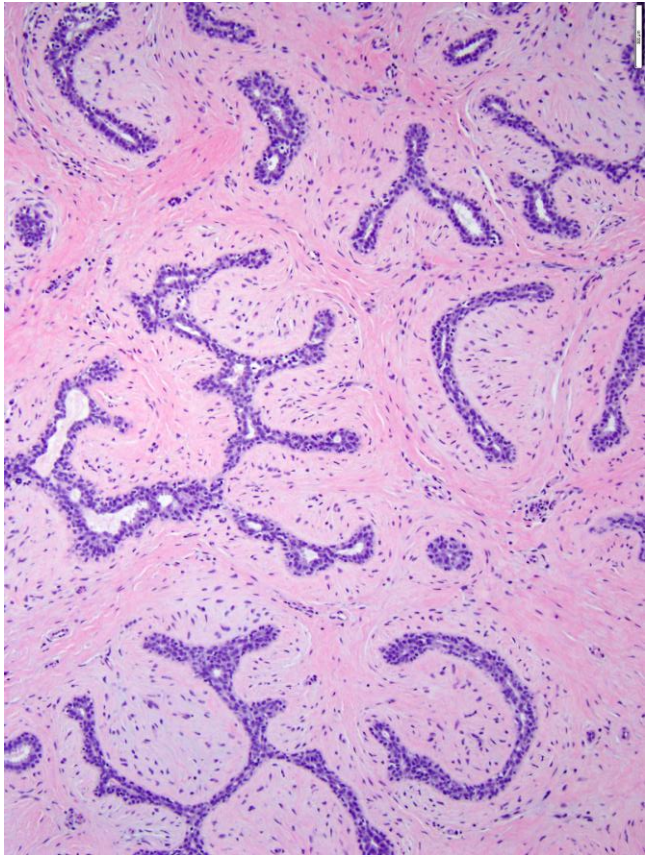
solid and rubbery mass, grey to white bulging cut surface, slightly lobulated

Fibroadenoma: microscopic features

- Well-circumscribed border
- Balanced biphasic proliferation of glandular and stromal elements
- Low stromal cellularity
- No stromal nuclear atypia
- Stromal mitoses absent or very low

  exception: young or pregnant women

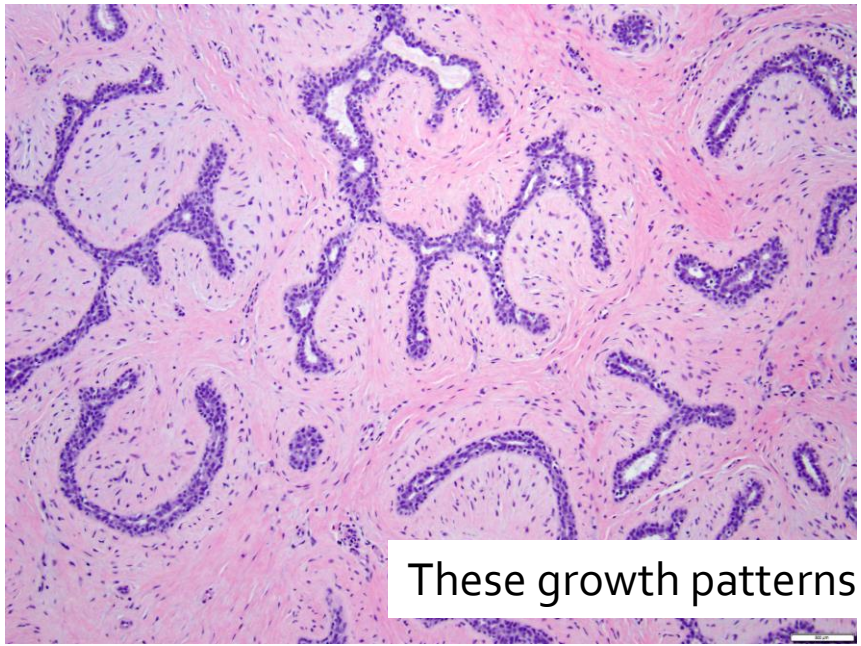
Molecular alterations: MED12 exon 2 mutations in 60-80% FAs



Two possible growth patterns

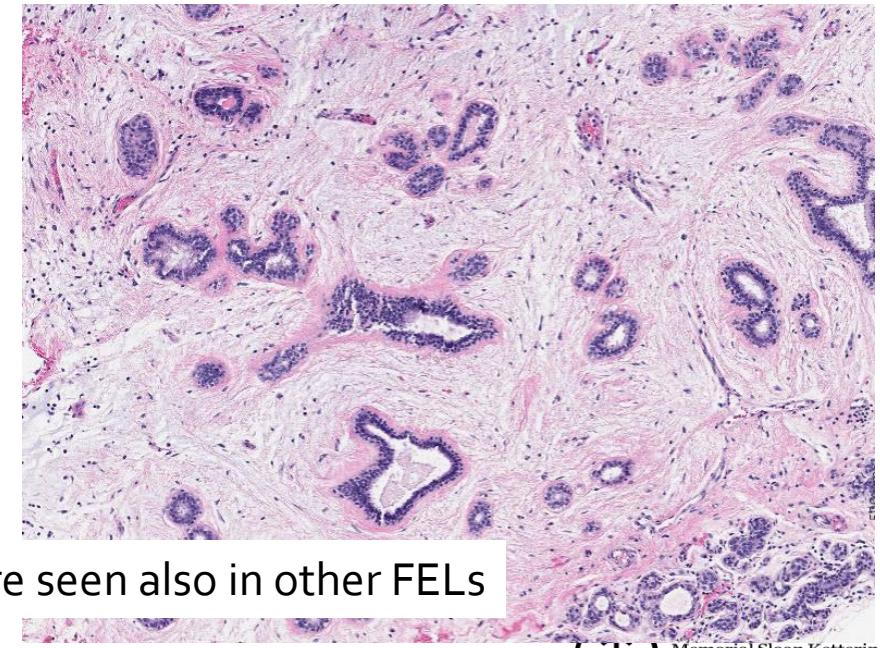
INTRACANALICULAR

compression of benign ductal elements by stroma leads to the formation of arciform slit-like, epithelium-lined luminal spaces



PERICANALICULAR

stroma grows around patent rounded tubules

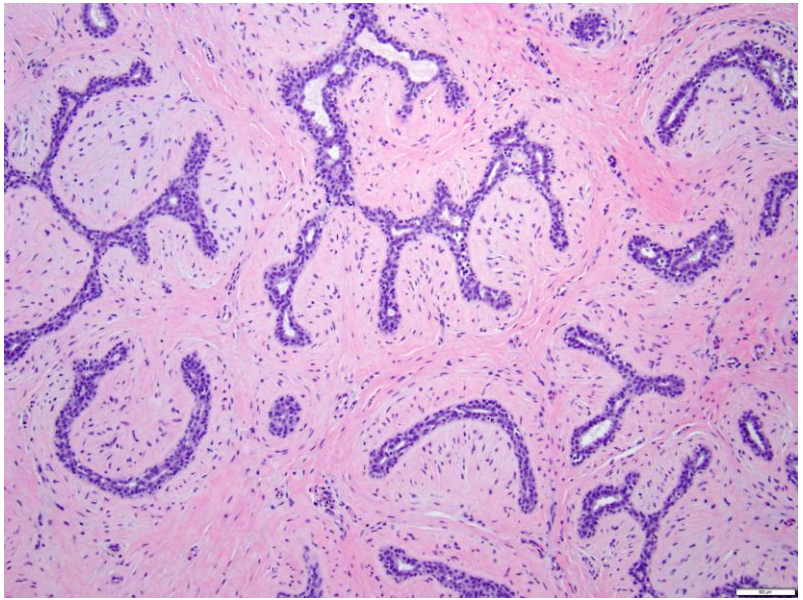


These growth patterns are seen also in other FELs

Fibroadenoma (FA): morphologic variants

- "myxoid" FA
- "complex" FA
- "juvenile" FA
- "cellular" FA

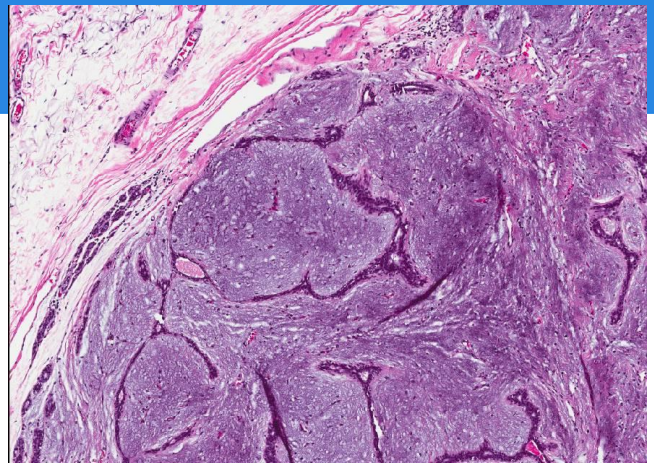
"usual/ adult/ simple" FA



Myxoid FA

Myxoid alterations of the specialized mammary first described in 21 patients (20 females, 1 male) with Carney's syndrome

- autosomal dominant disorder, due to mutations of *PRKAR1A (*regulatory subunit 1A of protein kinase A)

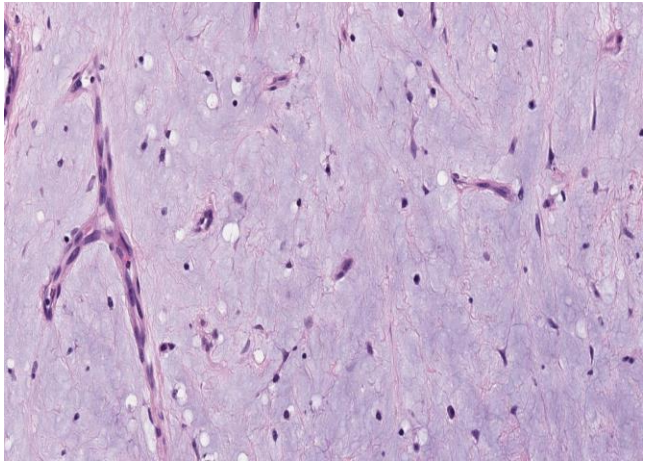


Myxoid FA: "**Circumscribed but unencapsulated tumor featuring normal and elongated acini, embedded in a hypocellular hypofibrillar (myxoid) stroma**".

No stromal nuclear atypia.

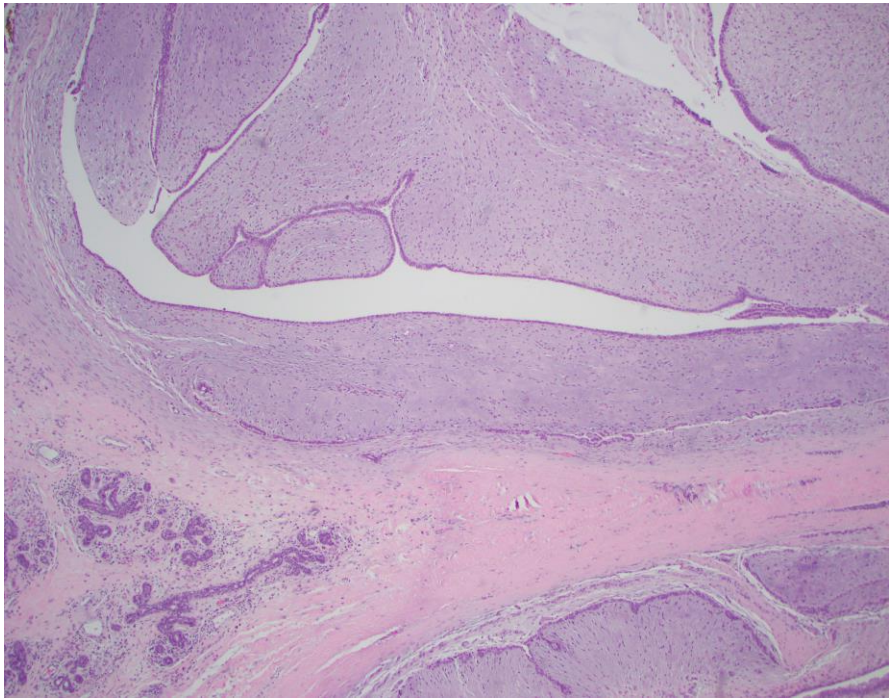
Some myxoid FAs have cysts and sclerosing adenosis.

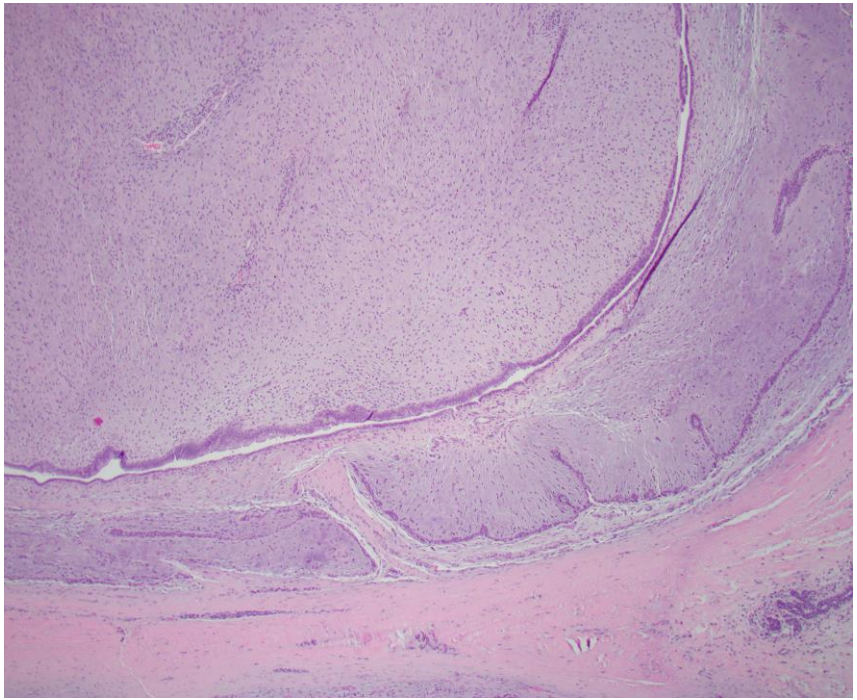
Carney A Toorkey BC Am J Surg Pathol 1991 15:713-21



Differential DX includes PT with myxoid stroma

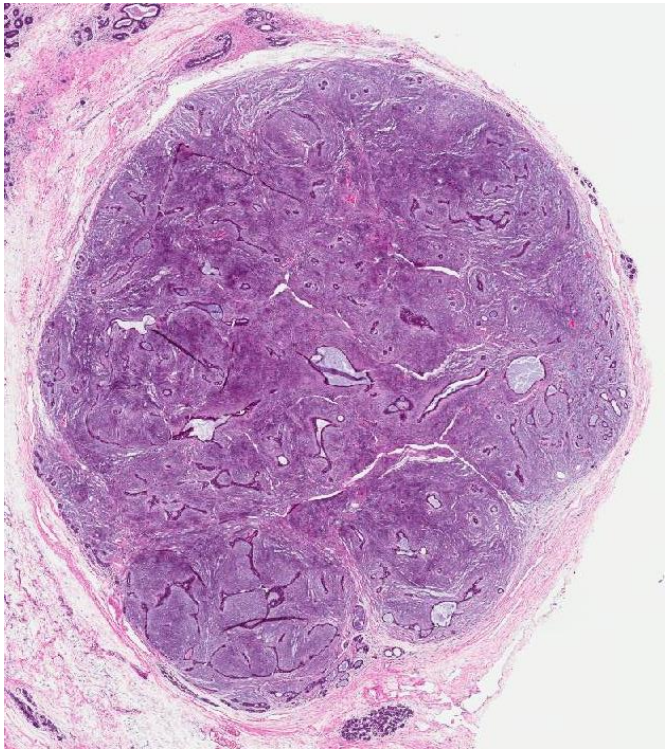
PT with areas of myxoid stroma has increased and heterogenous stromal cellularity and some stromal atypia



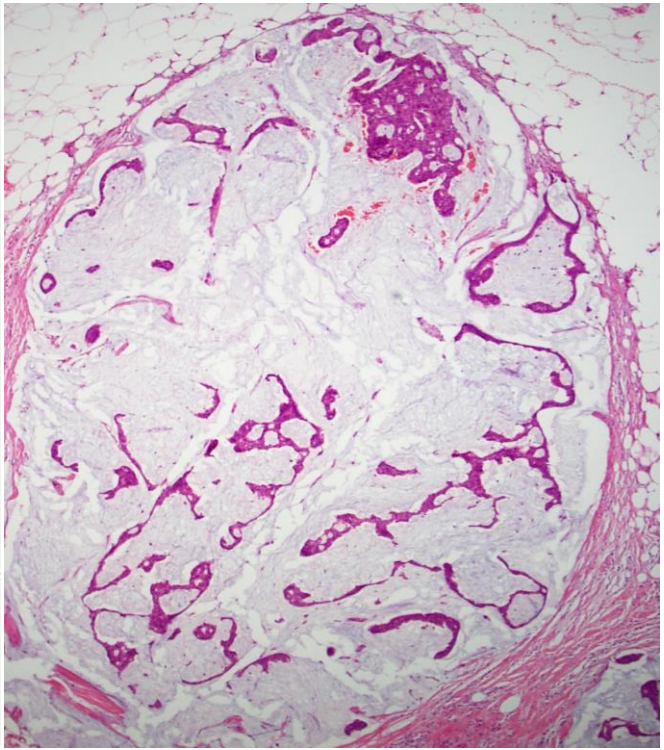


Myxoid FA: Differential DX

myxoid FA



mucinous carcinoma

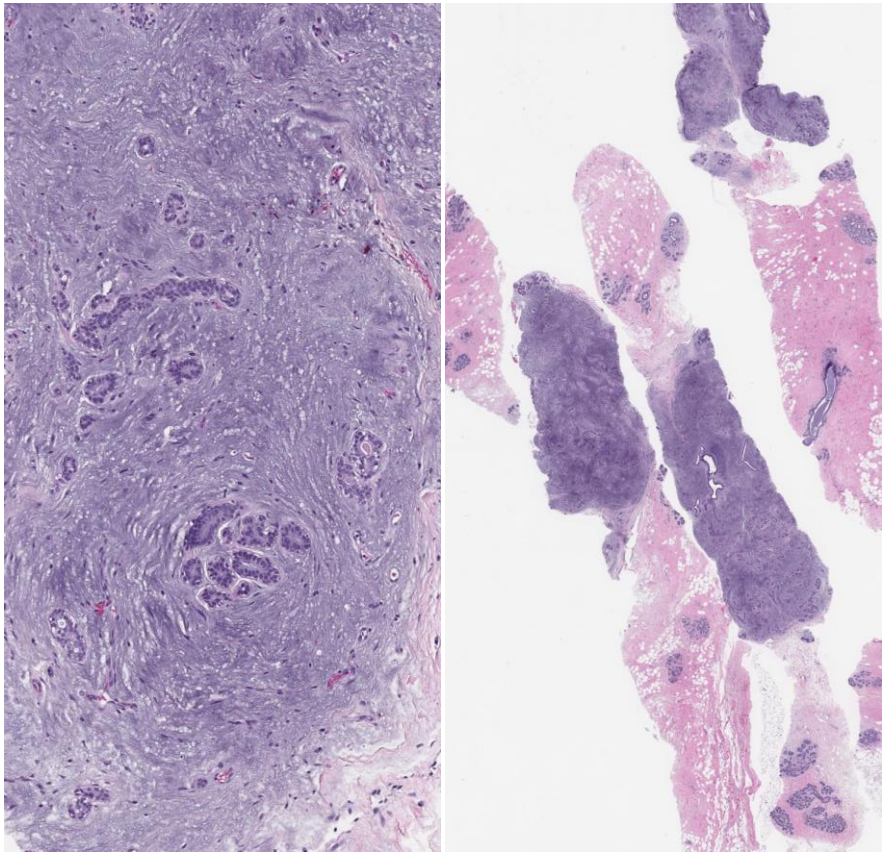


Myxoid FA may mimic hypocellular mucinous carcinoma

- Similar imaging features
- Pitfall in the evaluation of breast FNA material

Simsir et al. *Diagn Cytopathol*. 2001;25:278-284

- Possible pitfall in the evaluation of CNB material



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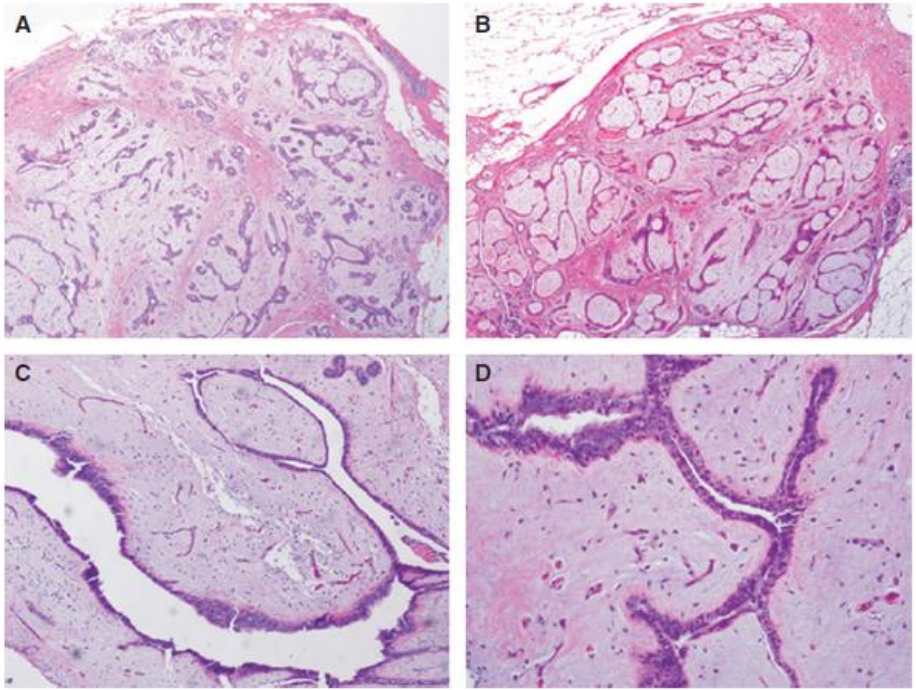
Myxoid fibroadenomas differ from conventional fibroadenomas: a hypothesis-generating study

John R Lozada, Kathleen A Burke, Aoife Maguire, Fresia Pareja, Raymond S Lim, Jisun Kim, Rodrigo Gularte-Merida, Melissa P Murray, Edi Brogi, Britta Weigelt, Jorge S Reis-Filho & Felipe C Geyer

Histopathology 2017, 71, 626–634.



11 myxoid FAs

No *MED12* exon 2 mutations identified

(MED12 exon 2 mutations in 60-80% usual FAs)

The stromal component of one myxoid FA harbored a somatic inactivating mutation of *PRKAR1A* → *myxoma*

Complex FA

FA with at least one of the following features:

- sclerosing adenosis
- papillary apocrine metaplasia
- cysts ≥3 mm
- epithelial Ca^{2+}

22.7% of 2458 FAs

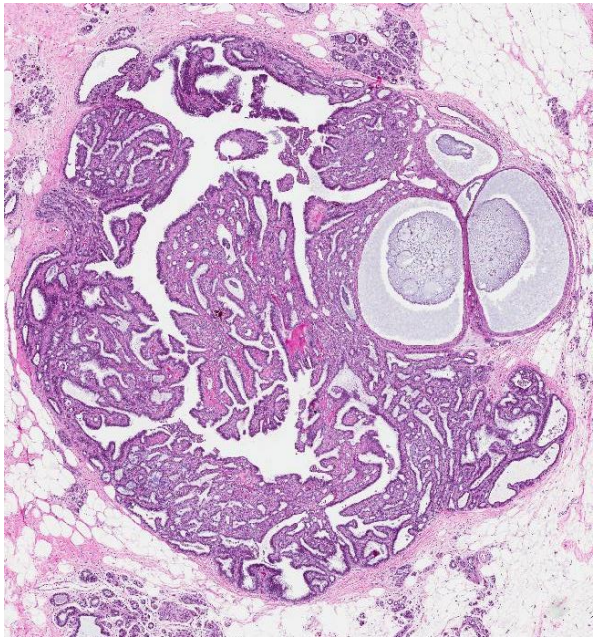
Dupont WD et al. *N Engl J Med*. 1994;331:10-15

- complex features in 40.4% of 396 FAs

  Kuijper A et al. *Am J Clin Pathol*. 2001;115:736-742
- 15.7% of 403 FAs

  Sklair-Levy M et al. *Am J Roentgenol* 2008;190:214-218
- 14.1% of 1835 FAs

  Nassar A et al. *Breast Cancer Res Treat*. 2015;153:397-405



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CFA: usually older age and smaller size than usual FA

Mean age 34.5 y vs 33.4 years for all FAs

Kuijper A et al. *Am J Clin Pathol*. 2001;115:736-742

Median age 47 y vs 28.5 years for usual FA

Sklair-Levy M et al. *Am J Roentgenol* 2008;190:214-218

Mean age 50.2 y vs 45.8 years for usual FA

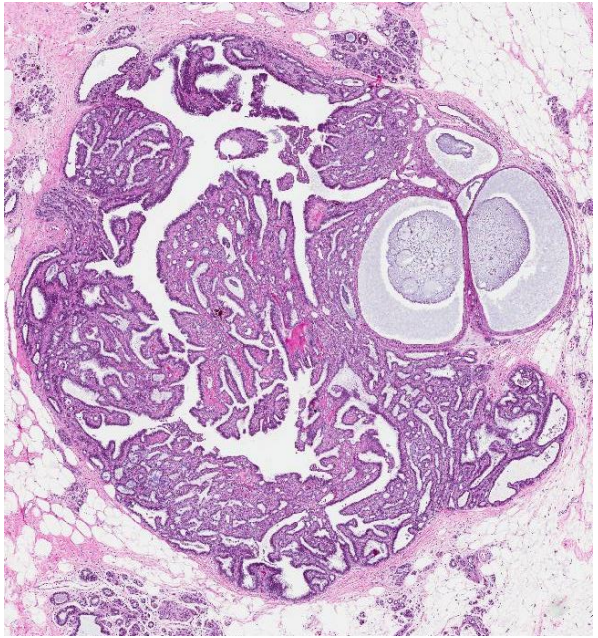
Nassar A et al. *Breast Cancer Res Treat*. 2015;153:397-405

Average size 1.3 cm vs 2.5 cm for usual FAs ($p<0.001$)

Sklair-Levy M et al. *Am J Roentgenol* 2008;190:214-218

Many complex FAs detected due to associated Ca^{2+}

Nassar A et al. *Breast Cancer Res Treat*. 2015;153:397-405



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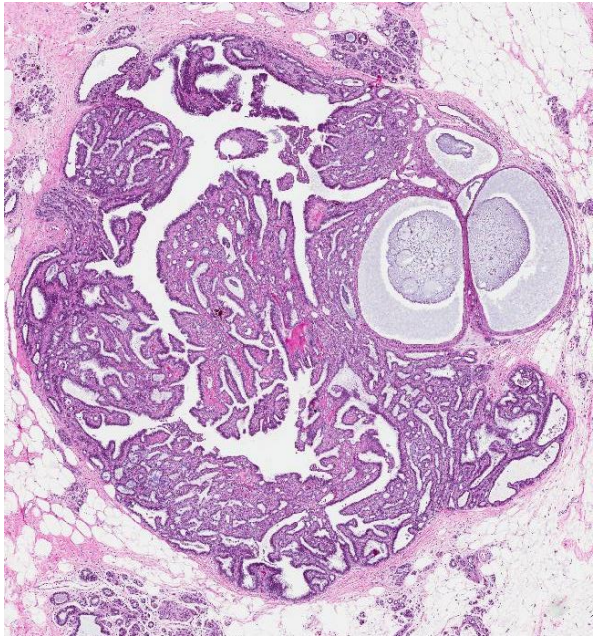
Complex FA is not an independent risk factor of breast carcinoma

- 3.1 Relative Risk (RR) of breast carcinoma (BC)
  - vs 2.17 RR of FA any type

  Dupont WD et al. *N Engl J Med*. 1994;331:10-15

- 2.27 RR of BC in women with complex FA
  - 1.6 RR of BC for women with simple FA
- 6% women with complex FA had breast atypia
  - vs 1.6% of women with simple FA
- Complex FA not an independent risk factor of BC in multivariate analysis

  Nassar A et al. *Breast Cancer Res Treat*. 2015;153:397-405



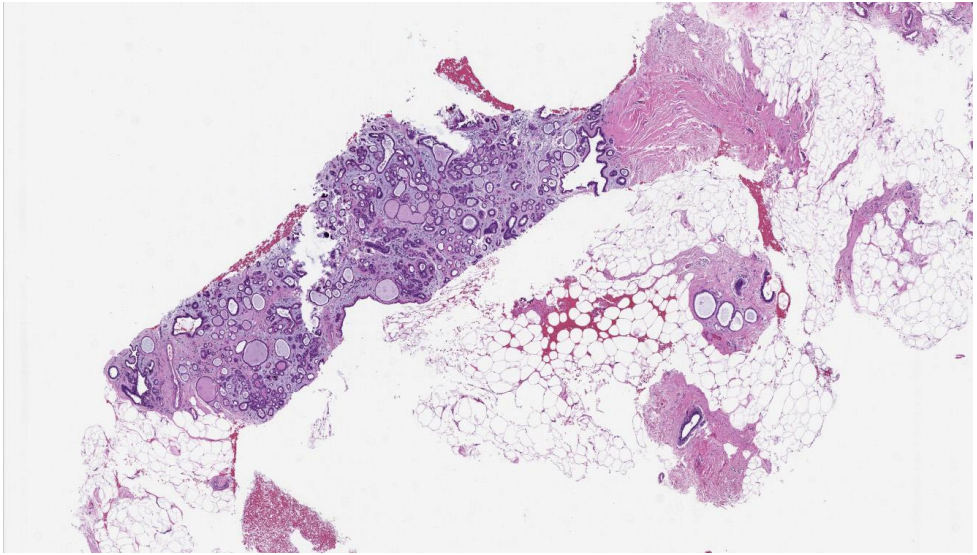
– *MED12* exon 2 mutations in the stromal component of only 17% of complex FAs

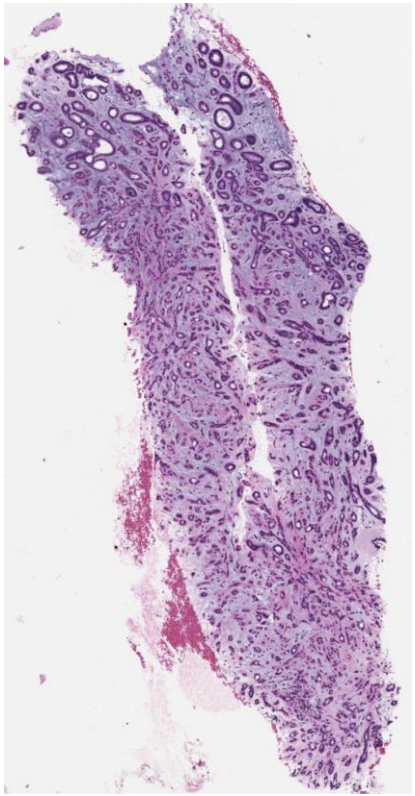
DaSilva EM et al. *J Clin Pathol.* 2022;75(2):133-136.

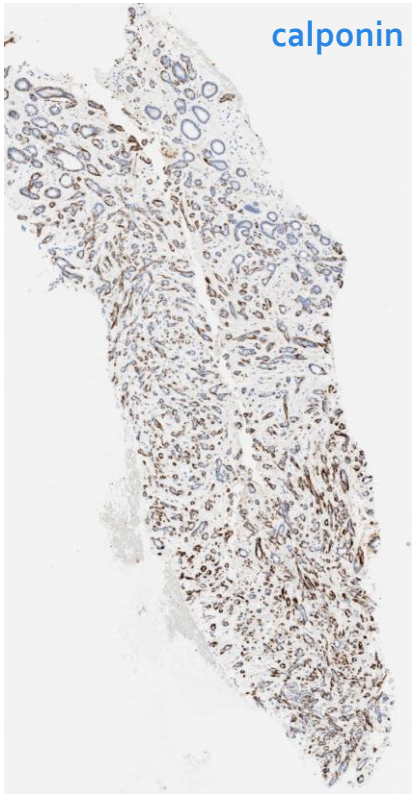
Complex FA – Differential Dx @CNB

- adenosis or tubular adenoma
- papilloma
- **invasive carcinoma**

  (mass + adenosis/sclerosing adenosis)





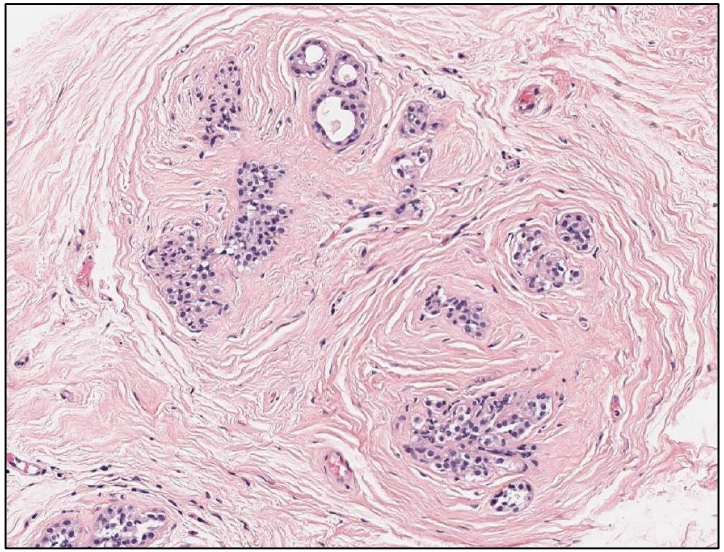


CNB initial dx: invasive carcinoma

ALH / LCIS in FA

ALH / classic LCIS: not uncommon

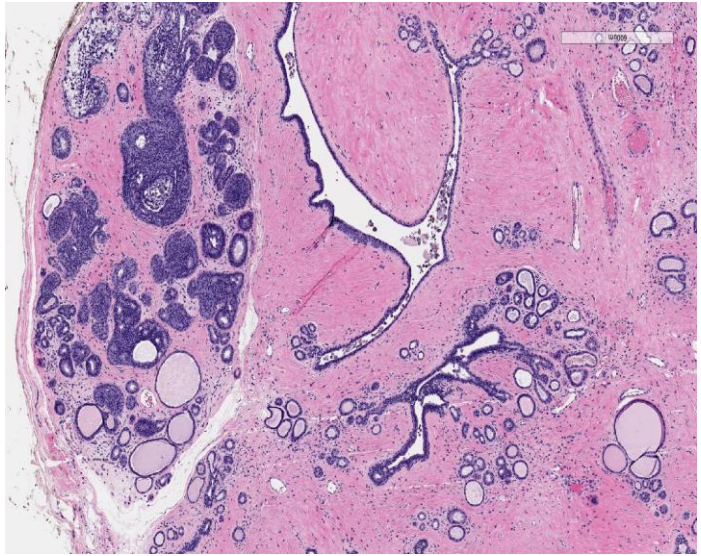
Florid and Pleomorphic LCIS: very uncommon



@MSK: no EXC for rad-path concordant CNB dx of FA with ALH/ classic LCIS

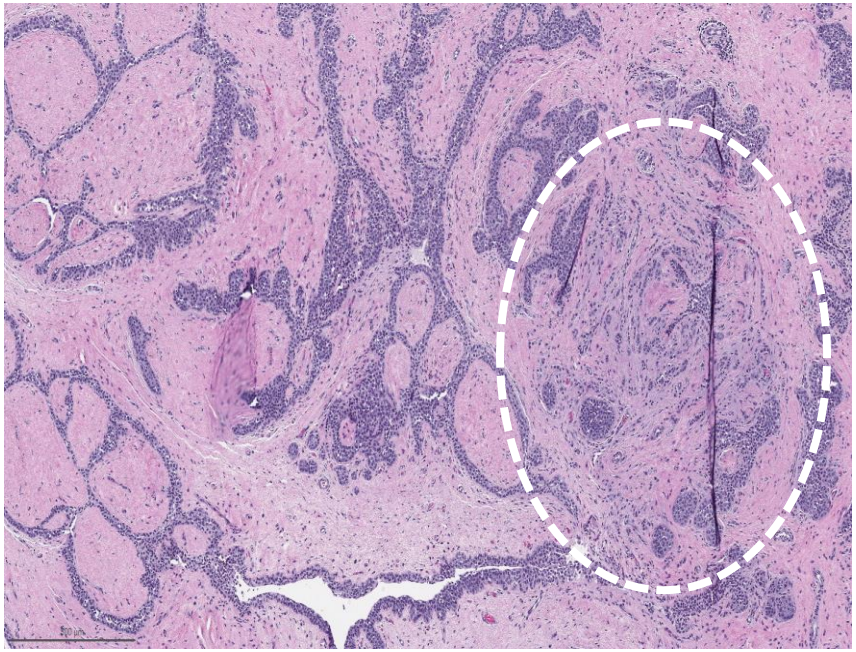
ADH/ DCIS

CBX → excision required

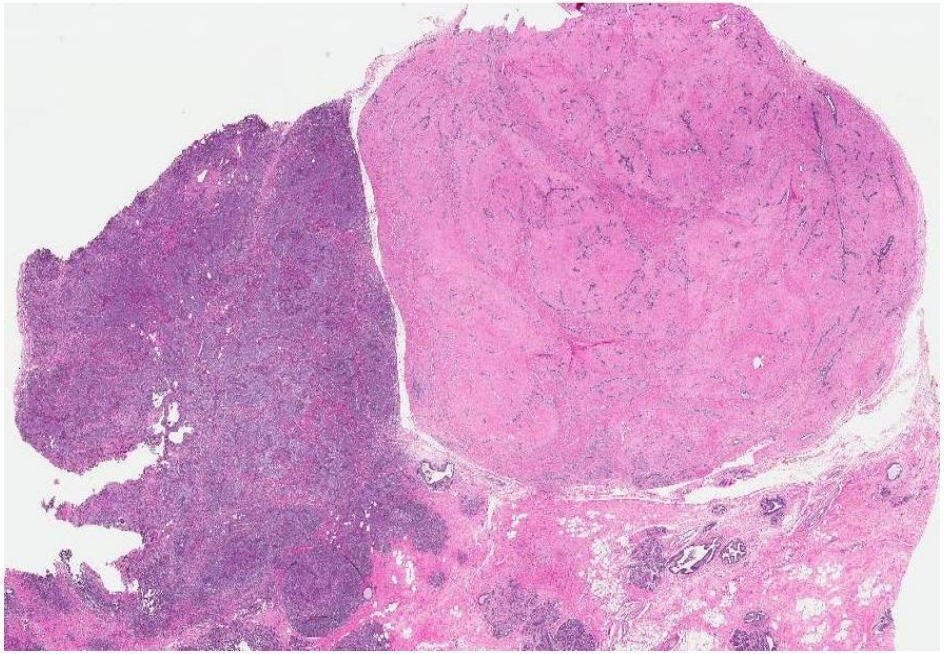


Invasive carcinoma

within a FA



near a FA



Summary: Fibroadenoma

– **Benign tumor**

– ***MED12* exon 2 mutations in 60-80% cases**

– **Morphology, variants, DDX and pitfalls**

- Simple/ usual/ adult FA: most common FA

- Myxoid FA: uniformly myxoid stroma
  no MED12 exon 2 mutations (is it really a FA?)
  DDx: PT with myxoid stroma, mucinous carcinoma
- Complex FA: 3.1 RR of subsequent invasive carcinoma
  CNB DDx: papilloma and invasive carcinoma

- "Juvenile" FA: see discussion on PTs
- "Cellular" FA: see discussion on PTs

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Phyllodes Tumor

Phyllodes tumor (PT)

Rare

- 0.3-1% of all primary breast tumors
- 2.5% of all fibroepithelial tumors

Occurs in women

Age: 40 to >60 years (range 6-90)

- rare and usually benign in ≤25 years old
- extremely rare before menarche
- reports of rapid growth in pregnancy

Firm painless mass, +/- rapid growth

Size range 3-10 cm

Predisposing factors

- p53 germline mutation

Birch JM et al Oncogene 2001

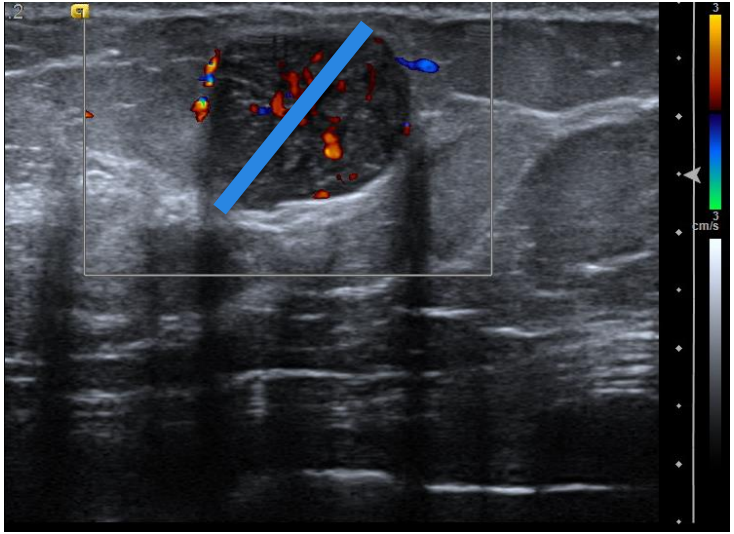
- 550 pts with PTs and germline testing; 2/21 (9.5%) pts tested for *P53* had deleterious *mutation*

Rosenberger LH et al. Ann surg Oncol 2020

- Asian ethnicity

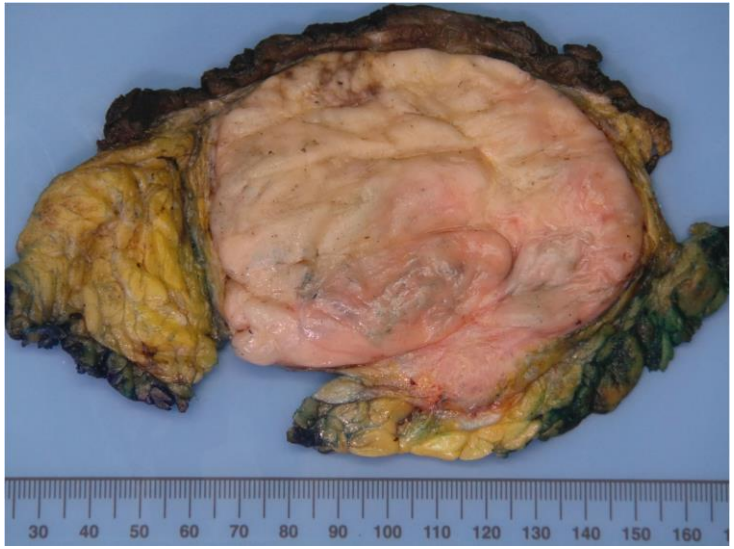
Karim RZ et al. *Breast* 2009

Imaging studies



rounded or oval, well-circumscribed, solid mass, heterogeneous, may contain cystic spaces, non-parallel orientation (= major axis not parallel to the skin)

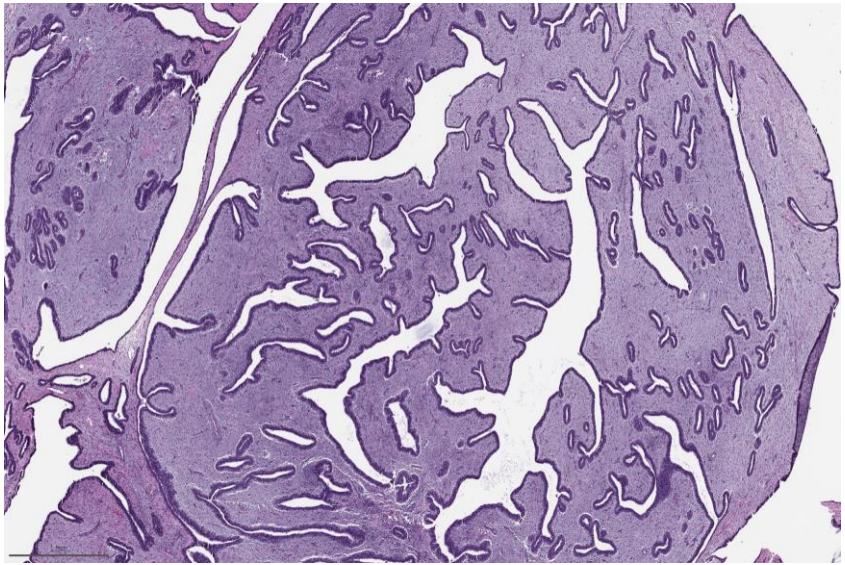
Macroscopic appearance

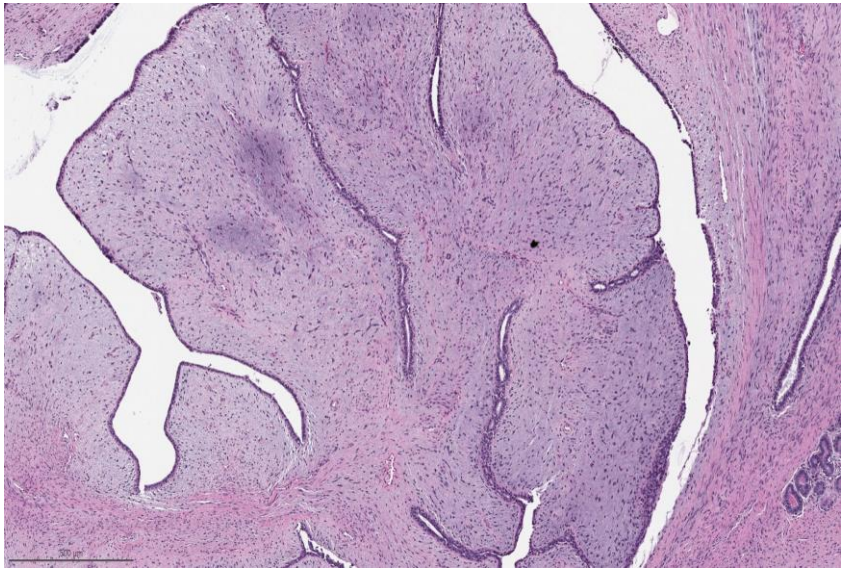


Well-circumscribed, firm mass
Tan, pink to grey, whorled cut surface with curved clefts resembling leaf buds

WHO 5th ed (2019) definition

PT is a generally circumscribed fibroepithelial neoplasm showing a prominent intracanalicular architectural pattern with leaf-like fronds, capped by luminal epithelial and myoepithelial cell layers, accompanied by stromal hypercellularity.



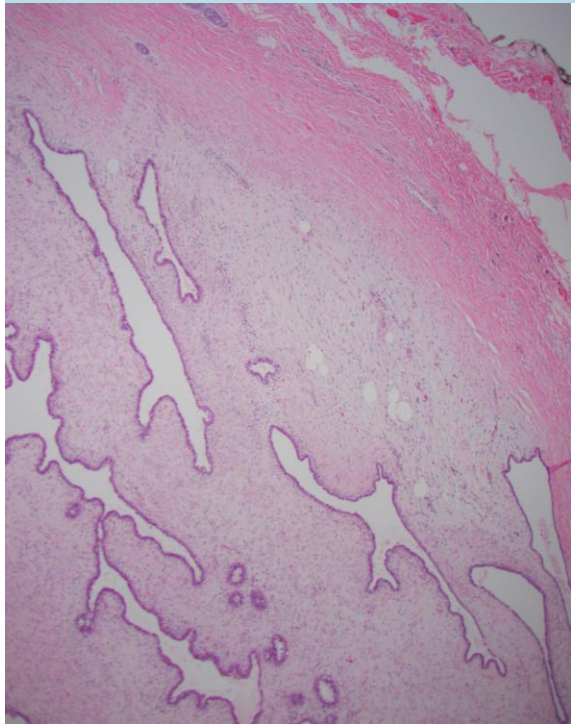


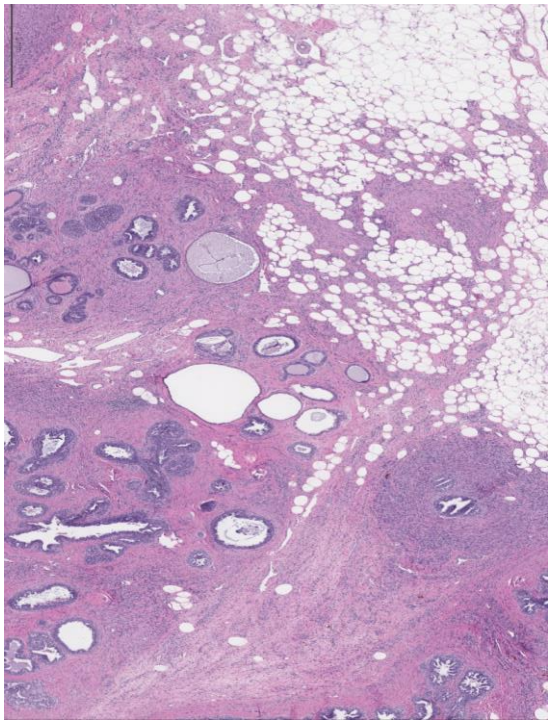
WHO 5th (2019)

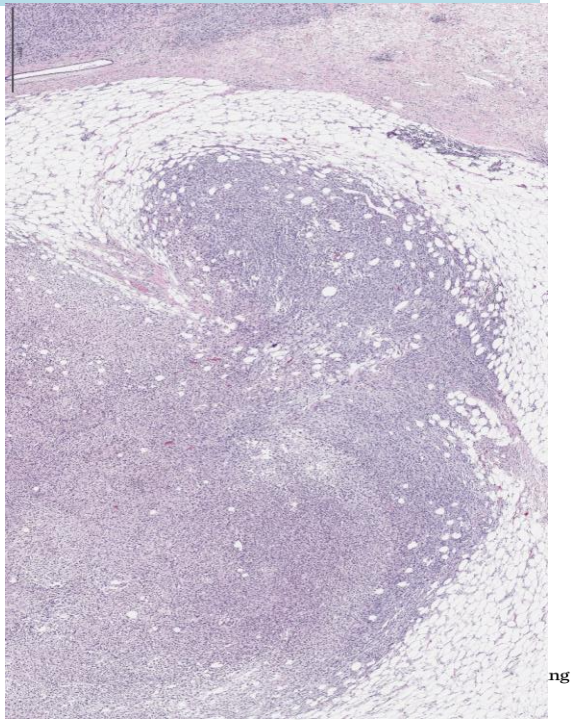
Feature	Benign PT	Borderline PT	Malignant PT
Tumor border	Well-defined	Well-defined, may be focally permeative	Permeative
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	Usually few; <2.5 mitoses/ mm2 (< 5 mitoses/10 HPF)	Usually frequent; 2-5 mitoses/mm2 (5-9 /10 HPF)	Usually abundant; >5 mitoses/ mm2 (≥10 per 10 HPF)
Stromal overgrowth	Absent	Absent, or very focal	Often present
Malignant heterologous elements	Absent	Absent	May be present

WHO 5th (2019) – Tumor Border

Benign	Borderline PT	Malignant PT
Well-defined	Well-defined, may be focally permeative	Permeative

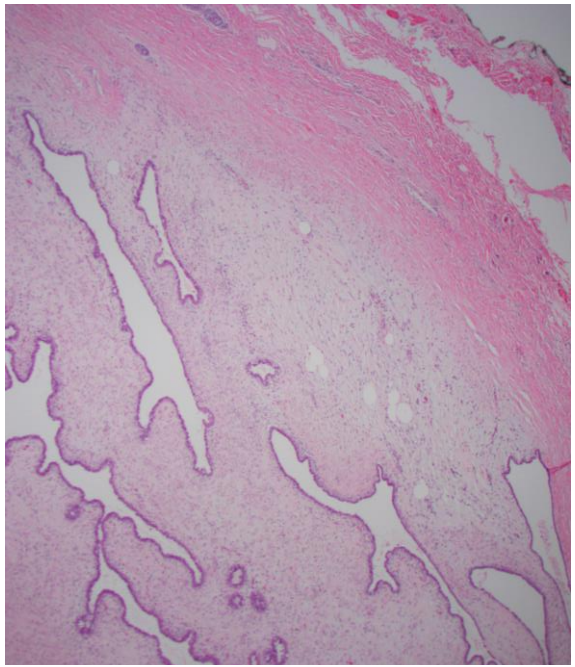


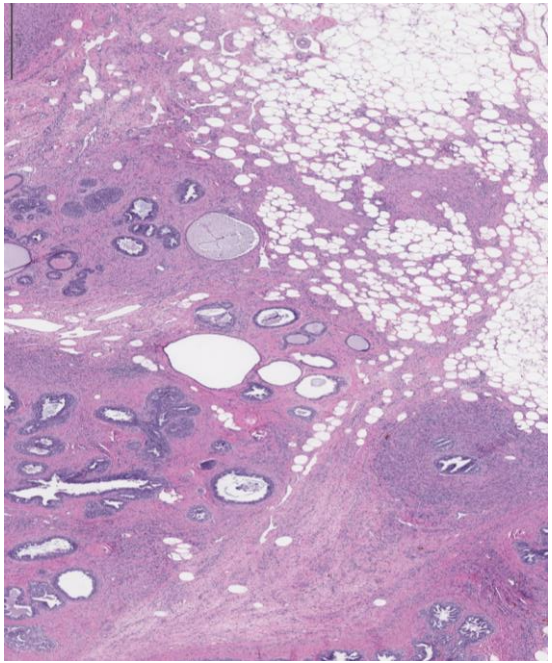


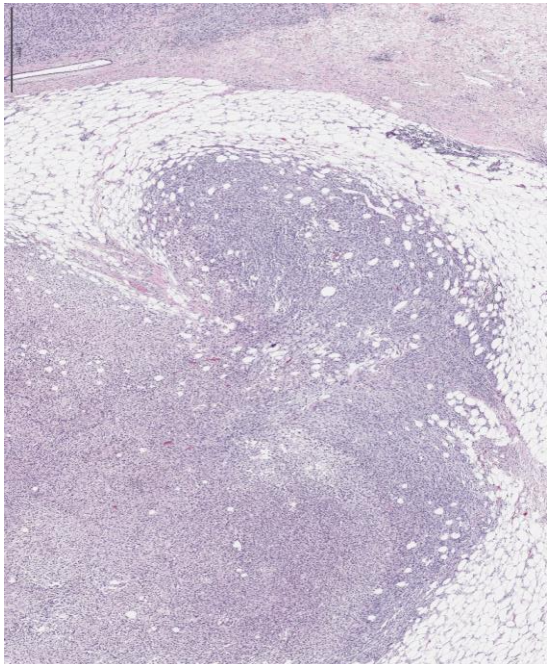


Tumor border (CAP protocol for reporting PT- March 2022)

Circumscribed	Focally infiltrative	Extensively infiltrative
Smooth and well defined or shows minimal irregular interface with adjacent stroma	Unequivocal invasion into adjacent stroma in one low power field	Unequivocal invasion in a wide area or in multiple foci along the tumor periphery

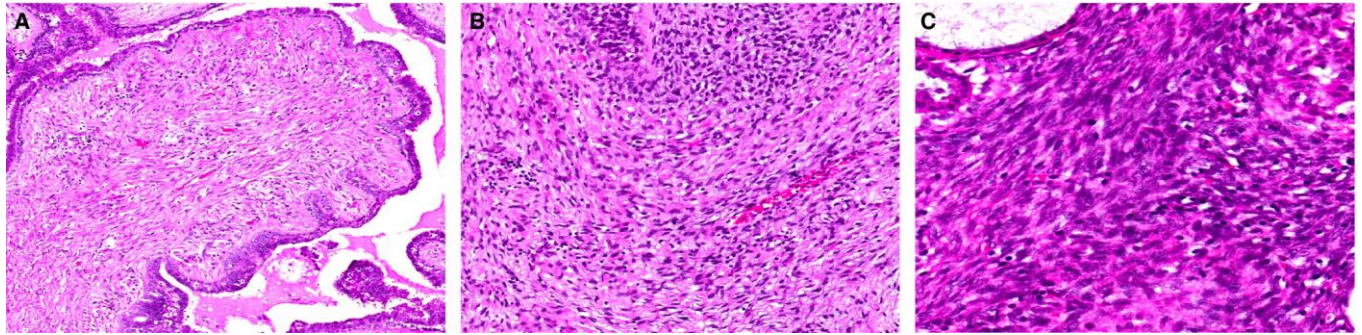






https://documents.cap.org/protocols/Breast.Phyllodes_1.0.0.0.REL_CAPCP.pdf

Stromal cellularity



Mild

slight increase in stromal cells, with evenly spaced nuclei that are not touching or overlapping

Moderate

Intermediate findings, with some overlapping stromal nuclei

Marked

Confluent areas of densely overlapping nuclei

Tan BY et al. Phyllodes Tumors: consensus review. *Histopathology* 2016

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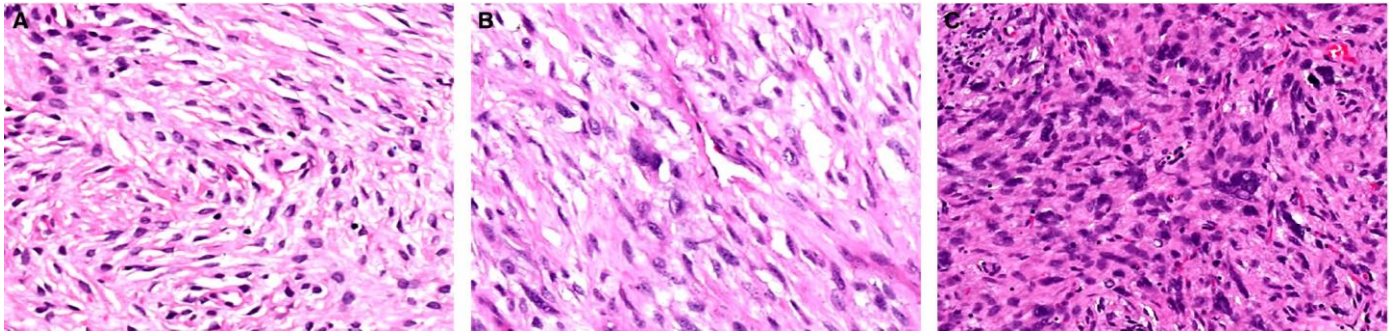
Stromal atypia



Mild

nuclei with little variation in size, with smooth nuclear contours

Moderate

some variation in nuclear size, with wrinkled nuclear membranes

Marked

marked variation in nuclear size, coarse chromatin, and irregular nuclear membranes with discernible nucleoli

Tan BY et al. Phyllodes Tumors: consensus review. *Histopathology* 2016

WHO 5th (2019)

Feature	Benign PT	Borderline PT	Malignant PT
Mitotic activity	Usually few <2.5 mitoses/ **mm²** (<5 mitoses/10 HPFs)	Usually frequent 2 to <5 mitoses/ **mm²** (**5-9**/10 HPFs)	Usually abundant ≥5 mitoses/ **mm²** (**≥10**/10 HPFs)

- Identify most mitotically active areas
  - avoid biopsy site and areas near necrosis
- Identify a stromal mitosis → count mitotic activity in 10 HPFs
  - Random HPFs nearby

Tan BY et al. Phyllodes Tumors: consensus review. *Histopathology* 2016

WHO 5th (2019)

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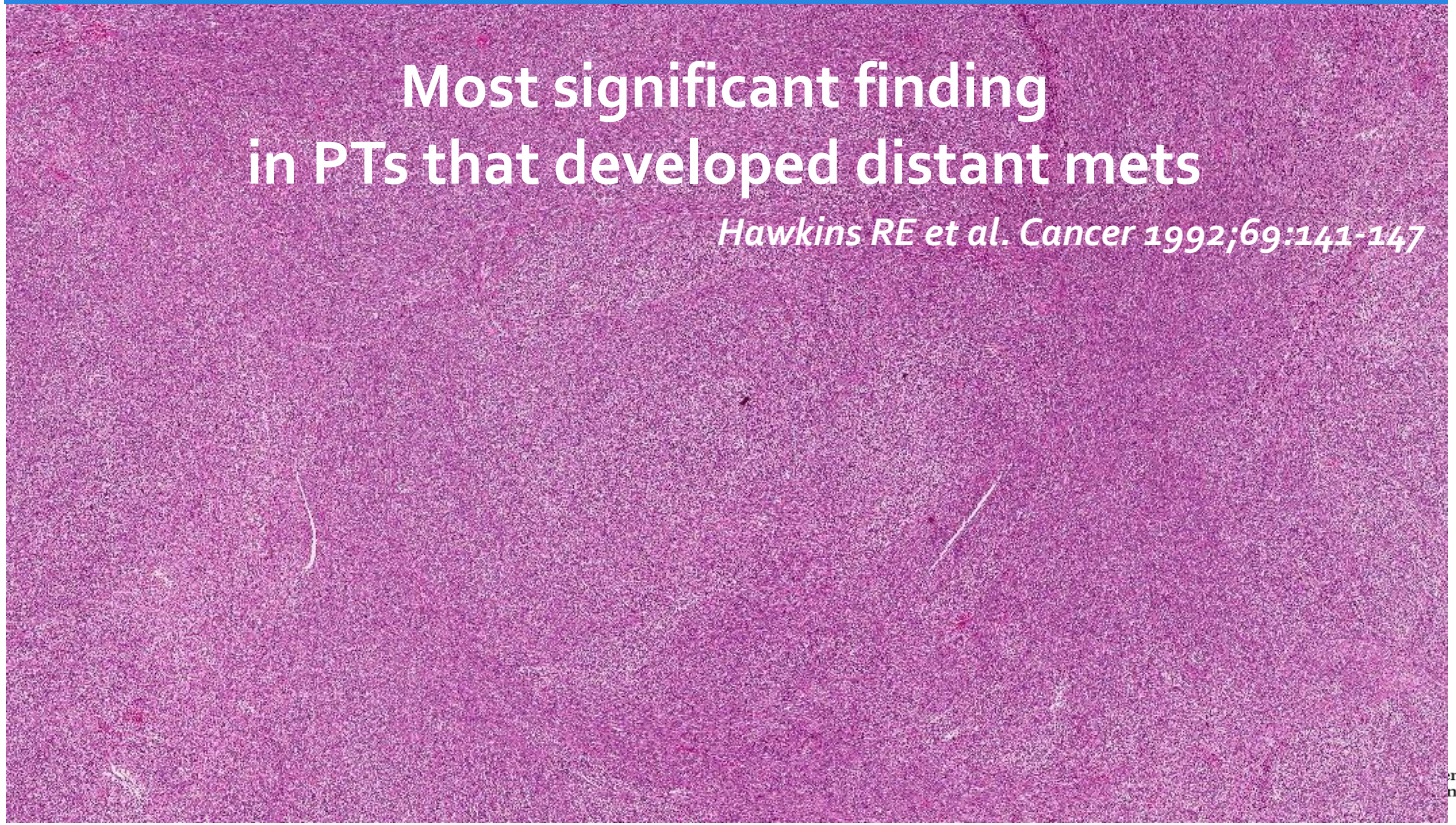
Stromal overgrowth	Absent	Absent (or very focal)	Often present

stromal overgrowth

no epithelial component in a final 40X field of view (=10x eye piece and 4x objective) (22.9 mm²)



stromal overgrowth

no epithelial component in a final 40X field of view (=10x eye piece and 4x objective) (22.9 mm²)

67 patients with PTs

- 15 borderline and 52 malignant
- 18 (27%) PTs with stromal overgrowth

median F/U 10 years

15 patients (22%) developed distant metastases + died of disease

- 11/18 (61%) PTs with stromal overgrowth
- 4/49 (8.1%) PTs without stromal overgrowth

5-year cancer specific survival

- 32.2% of patients with PT with stromal overgrowth
- 97.7% of patients with PT without stromal overgrowth

Hazard Ratio of PT with stromal overgrowth was 22.52 fold higher than for PT without stromal overgrowth

Onkendi et al. Ann Surg Oncol (2014) 21:3304–3309

WHO 2019

Feature	Benign PT	Borderline PT	Malignant PT
Tumor border	Well-defined	Well-defined, may be focally permeative	Permeative
Stromal cellularity	Cellular, usually mild, may be non-uniform or diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal atypia	Mild or none	Mild or moderate	Marked
Mitotic activity	Usually few; <2.5 mitoses/ mm^2 (< 5 mitoses/10 HPFs)	Usually frequent; 2 to <5 mitoses/mm^2 (5-9 /10 HPFs)	Usually abundant; ≥5 mitoses/ mm^2 (≥10/ 10 HPFs)
Stromal overgrowth	Absent	Absent (or very focal)	Often present
Malignant heterologous elements	Absent	Absent	May be present

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Malignant heterologous elements occur *ONLY* in malignant PTs

20.9% of 29 malignant PTs

- liposarcoma
- osteosarcoma
- chondrosarcoma
- alone or in combination

(number of cases not specified)

Slodkowska et al *Mod Pathol* (2018) 31:1073–1084

19.3% of 83 malignant PTs

- 6 liposarcoma
- 4 osteosarcoma
- 3 chondromyxoid matrix
- 1 leiomyosarcoma
- 1 chondrosarcoma + osteosarcoma
- 1 liposarcoma + rhabdomyosarcoma + pleomorphic sarcoma

Koh et al *Virchows Arch* (2018) 472:615–621

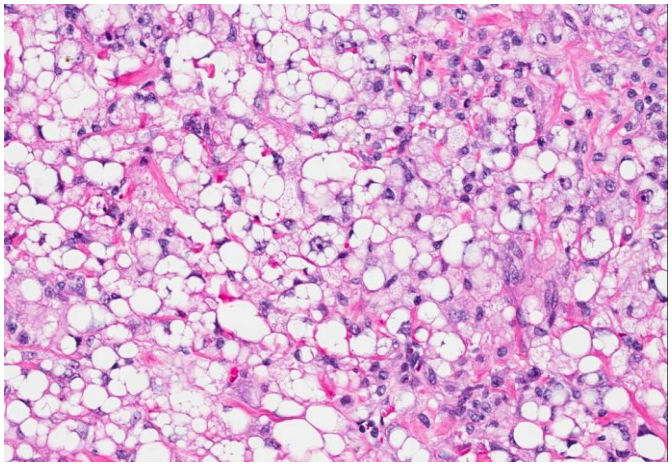
Liposarcoma-like areas in PT

No *MDM2* expression by IHC

No *MDM2* or *CDK4* amplification by FISH

Lyle P, *Histopathology* 2016;68:1040-45
Inyang A, *Breast J* 2016;22:282-286
Bacchi C, *Ann Diagn Pathol* 2016;21:1-6

Liposarcoma-like area in PT



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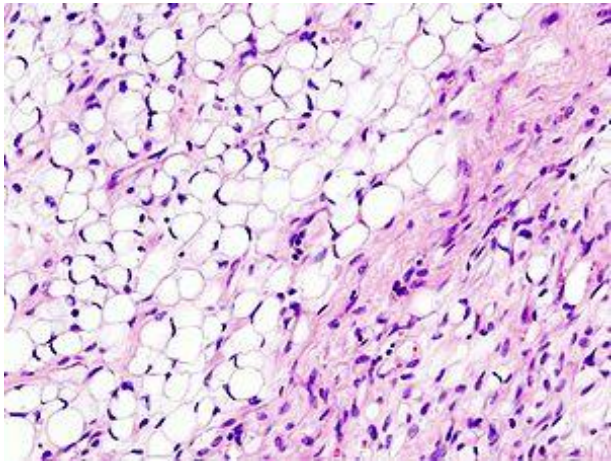
Liposarcoma



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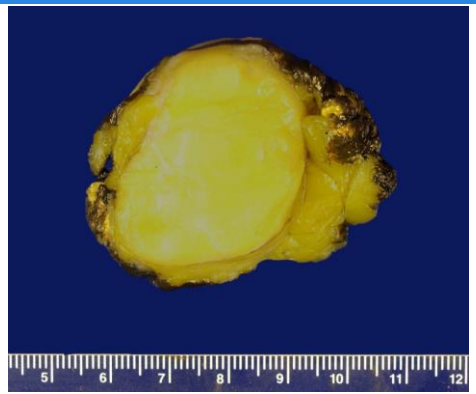
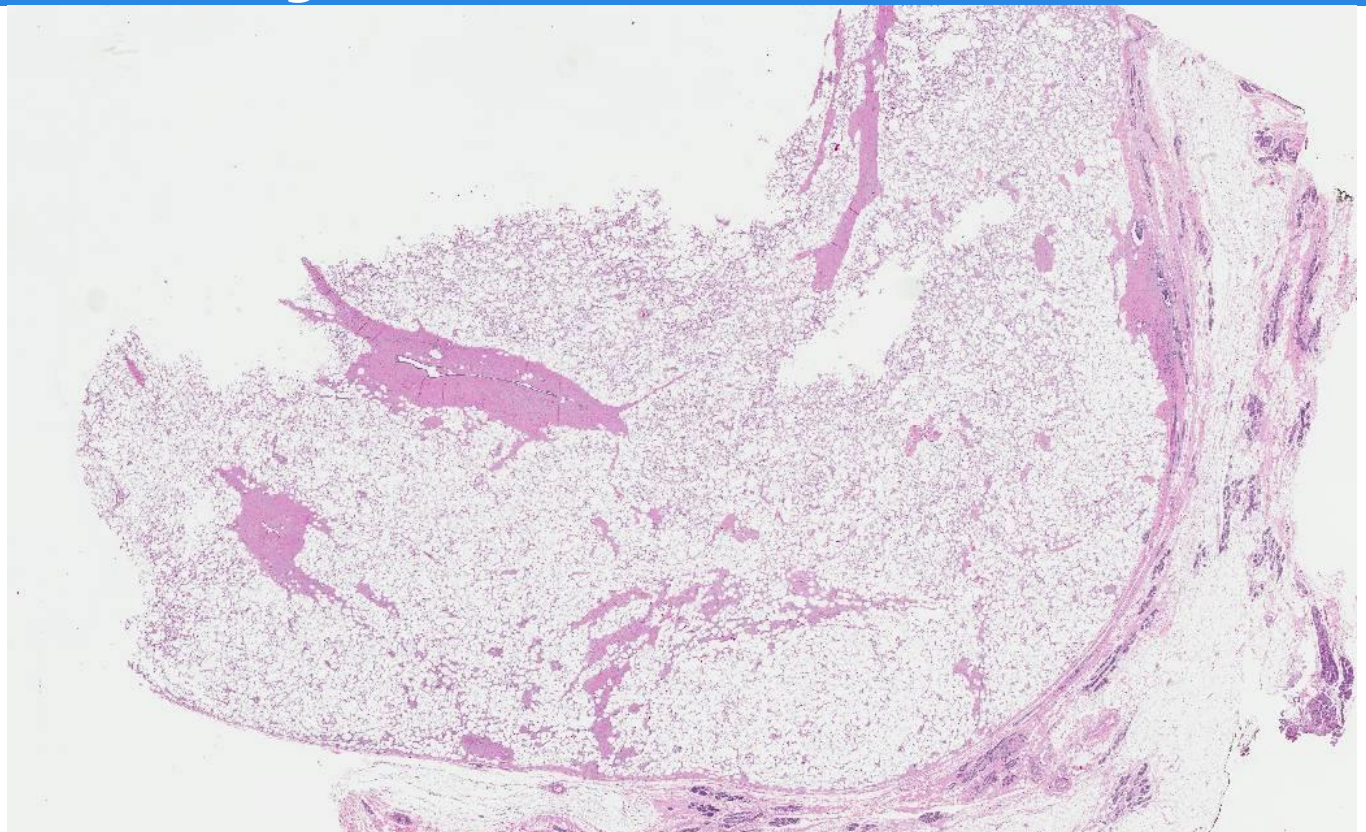
WHO 5th ed (2019): "lipomatous component alone does not warrant a diagnosis of malignant PT in the absence of other morphologically malignant features"





WHO 2019

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Mitotic activity	Usually few; <2.5 mitoses/ mm2 (< 5 mitoses/10 HPF)	Usually frequent; 2-5 mitoses/mm2 (5-10 /10 HPF)	Usually abundant; >5 mitoses/ mm2 (>10 per 10 HPF)
Stromal overgrowth	Absent	Absent (or very focal)	Often present
Malignant heterologous elements	Absent	Absent	May be present
Relative proportion of all PTs	60-75%	15-26%	8-20%

March 2022 CAP Protocol: reporting of PT resection specimens

PT elements to be included in report

- tumor size (mm)
- histologic type
- stromal cellularity
- stromal atypia
- stromal overgrowth
- mitotic rate
- histologic tumor border
- malignant heterologous elements
- margin status

Dx of Malignant PT requires ALL of the 5 following features

- *marked* stromal cellularity
- *marked* stromal atypia
- *stromal overgrowth*
- ≥*10* mitoses/ 10 HPFs
- *permeative* tumor border

OR

- *malignant heterologous elements* (not including atypical lipomatous areas/ well diff liposarcoma-like areas)

https://documents.cap.org/protocols/Breast.Phyllodes_1.0.0.0.REL_CAPCP.pdf

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Phyllodes Tumors - Clinical behavior and prognosis

Local Recurrence (LR)

Grade progression in LR

Distant metastases

Total 605 PTs (1992-2010)
440 Benign
111 Borderline
54 Malignant

Patients median age 43 years

Tan PH *J Clin Pathol* 2012;65:69-76

	Local Recurrence (LR)
Total 605 PTs (1992-2010)	73/605 (12%)
440 Benign	48/440 (10.9%)
111 Borderline	16/111 (14.4%)
54 Malignant	9/54 (16.6%)

Patients median age 43 years

Mean and median time to recurrence 29.8 and 24.6 months, respectively

Local recurrence rate significantly associated with PT grade (<0.001)

Tan PH *J Clin Pathol* 2012;65:69-76

PTs diagnosed 1992-2010	Local Recurrence (LR)	Grade LR	LR grade same or lower (%)	LR grade higher (%)	Grade Progression (%)
440 Benign	48/440 (10.9%)	Benign	27/440 (6.1%)	-	NO 27/440 (6.1%)
		Borderline	-	17/ 440 (3.9%)	**YES 21/440 (4.8%)**
		Malignant	-	4/440 (0.9%)	

Tan PH *J Clin Pathol* 2012;65:69-76

PTs diagnosed 1992-2010	Local Recurrence (LR)	Grade LR	LR grade same or lower (%)	LR grade higher (%)	Grade Progression (%)
440 Benign	48/440 (10.9%)	Benign	27/440 (6.1%)	-	NO 27/440 (6.1%)
		Borderline	-	17/ 440 (3.9%)	YES 21/440 (4.8%)
		Malignant	-	4/440 (0.9%)	
111 Borderline	16/111 (14.4%)	Benign	4/111 (3.6%)	-	NO 14/111 (12.6%)
		Borderline	10/111 (9.0%)	-	
		Malignant	-	2/111 (1.8%)	YES 2/111 (1.8%)

Tan PH *J Clin Pathol* 2012;65:69-76

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440 Benign	48/440 (10.9%)	Benign	27/440 (6.1%)	-	NO 27/440 (6.1%)
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		Malignant	-	4/440 (0.9%)	
111 Borderline	16/111 (14.4%)	Benign	4/111 (3.6%)	-	NO 14/111 (12.6%)
		Borderline	10/111 (9.0%)	-	
		Malignant	-	2/111 (1.8%)	**YES 2/111 (1.8%)**
54 Malignant	9/54 (16.6%)	Malignant	9/54 (16.6%)	-	NO 9/54 (16.6%)

Local recurrence with grade progression is infrequent

Tan PH *J Clin Pathol* 2012;65:69-76

Morphologic features associated with local recurrence?

- 52 PTs with local recurrence

- Morphologic features observed in the primary tumors
  - Epithelioid stromal cells (3 cases)
  - Gland-rich (8 cases)
  - Fibroadenoma-like (20 cases)
  - **Myxoid fibroadenoma-like (5 cases)**
  - PASH-like areas (4 cases)
  - Usual PT morphology (12 cases)

Bi J. et al *Virchows Archives July 2022* (e-pub)

PTs with myxoid stroma

5/ 52 (9.6%) PTs with LR

- 1 PT recurred three times

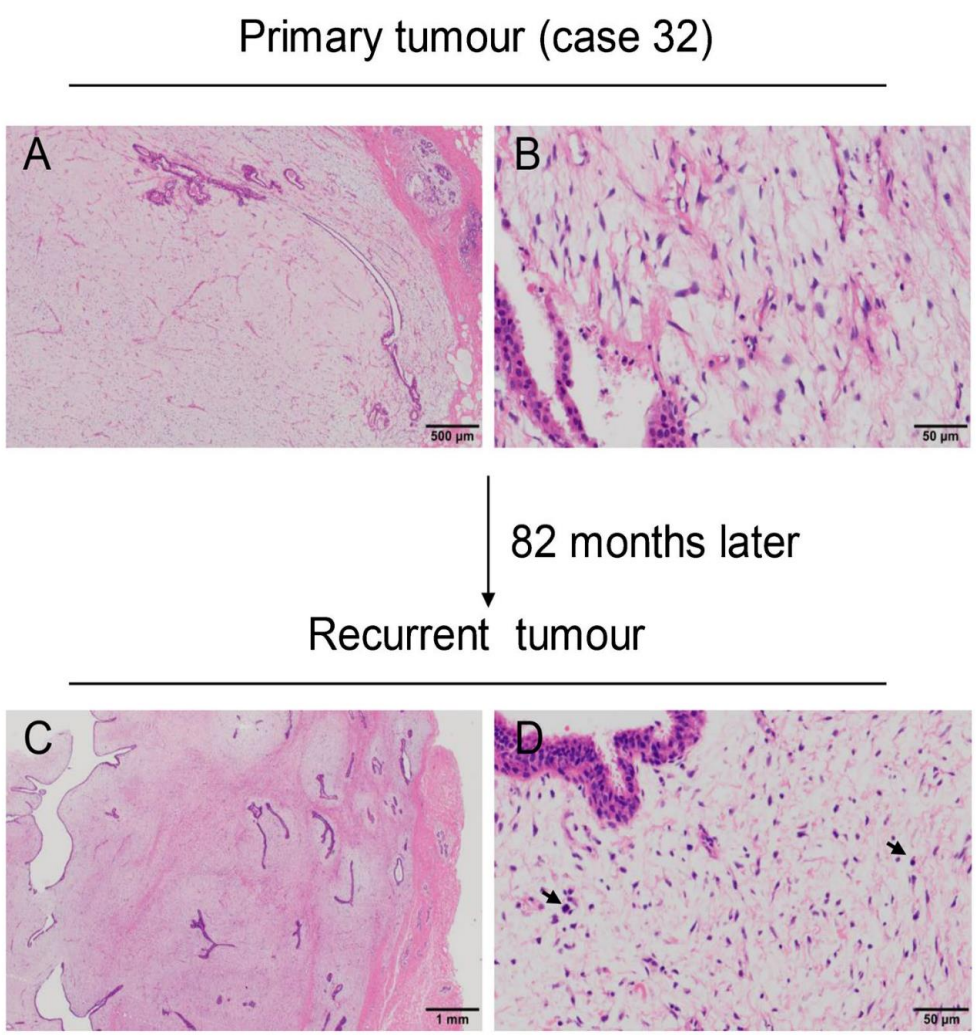
PT grade at first Dx

- 2 benign, 3 borderline

Morphologic features

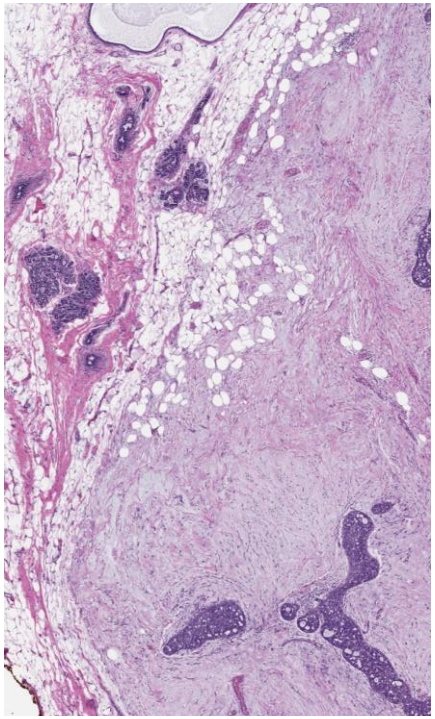
- Permeative border (4/5)
- Mild cellularity (5/5)
- Mild nuclear atypia (5/5)
- No leaf-like fronds (0/5)
- Vascular proliferation (5/5)
- CD34(-) stromal cells (4/5)

Bi J. et al *Virchows Archives July 2022* (e-pub)

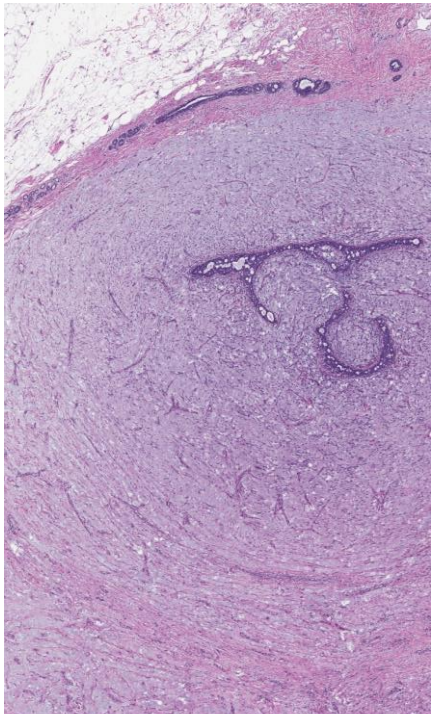


PT with myxoid stroma

peripheral infiltration

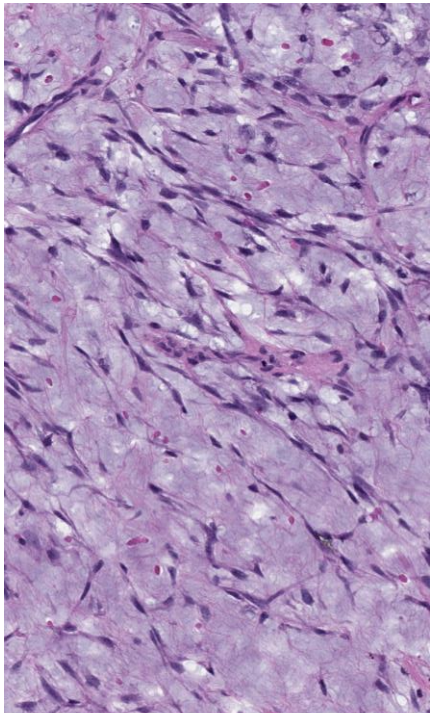


increased stromal cellularity



intratumoral heterogeneity

nuclear atypia



>50% myxoid stroma significant predictor of LOCAL recurrence, but not of distant metastases

Slodkowska E et al *Mod Pathol* 2018:31:1073-1084

Benign PT – Local Recurrence– contemporary series

Author year	#	months F/U	LR (%)	grade LR	Margin and LR
Teo 2012	42	median 43	None (0)	-	margin(+) in 15/42 (36%)PTs
Cowan 2016	52	median 22 mean 56.5	1 (2%)	1 benign	margin not predictive
Kim 2016	126	median 31.1 (6.7-142.5)	3 (2.4%)	1 benign 1 borderline 1 malignant	1 margin(+) and 2 margin(-); margin not predictive
Borhani-Khomani 2016	354	mean 98 (1.1-192)	22 (6.2%)	17 (77%) benign 5 (23%) borderline	margin not predictive
Moo 2017	216	median 35.5	4 (1.9%)	4 benign	2 margin(+) and 2 margin(-); margin not predictive
Moutte 2016	67	median 58 (0-126)	2 (3%)	2 benign	2 margin(+)
Tremblay-LeMay 2016	81	median 1.29 y	3 (3.7%)	2 benign 1 malignant	margin <1 mm
Total cases	**938**		**35 (3.7%)**	**27/35 (77%) benign 6/35 (17%) borderline 2/35 (5.7%) malignant**	

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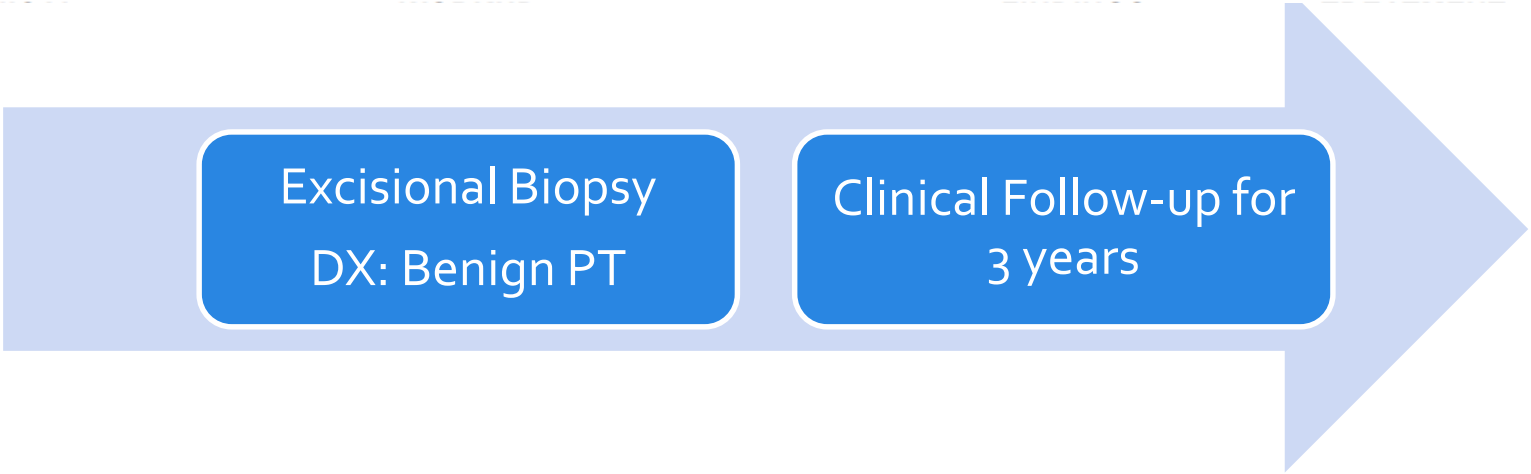
Summary: Benign PT- Local recurrence and grade progression

In contemporary series:

- **The LR rate of Benign PT is ≤5%**
- **The overall rate of LR with grade progression is low (≤1%)**
- **Margin width does not seem to affect LR**

Important to accurately assess PT grade

- *Thorough sampling (at least 1-2 sections per cm)*
- *Sample more solid/ fleshier areas, tumor periphery*



Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins

*CAP guidelines (March 2022) still recommend reporting margins of Benign PT

Borderline & Malignant PTs: Clinical behavior and prognosis

- Local Recurrence rates of approximately 12% and 20% for Borderline and Malignant PTs, respectively
- Borderline PTs: LR with Grade progression is ≤1%
- Distant metastases ???

(only) Malignant PTs may develop distant metastases

Local recurrence (LR) and distant metastases (Mets) by PT grade

Cases	PTs with Events (%)	Only LR	Metastases	LR and Metastases
440 Benign	48 (10.9)	48	0	0
111 Borderline	16 (14.4)	16	0	0
54 Malignant	16 (29.6)	4	7	5
Total 605 PTs	**80 (12.3%)**	**68**	**7**	**5**

Malignant PTs carried a metastasis and death rate of 22%

Tan PH et al. *J Clin Pathol* 2012;65:69-76

Size >9 cm *and* heterologous elements significantly associated with reduced metastasis-free survival (p=0.043, multivariate analysis)

Koh, Thike et al. Virchows Arch (2018) 472:615–621

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Phyllodes Tumor
NCCN Evidence Blocks™

DX:
Borderline and Malignant PT

Wide excision
(≥1 cm surgical margin)

Clinical Follow-up
for 3 years

Wide excision = excision with the intention of obtaining surgical margins ≥1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve a margin width ≥1 cm.

No prospective randomized data supports the use of radiotherapy (RT) for PT. In the setting where LR would create significant morbidity (eg, chest wall LR following mastectomy), RT may be considered (same principles as soft tissue sarcoma)

Malignant PT: usually no adjuvant chemotherapy is administered in the primary setting

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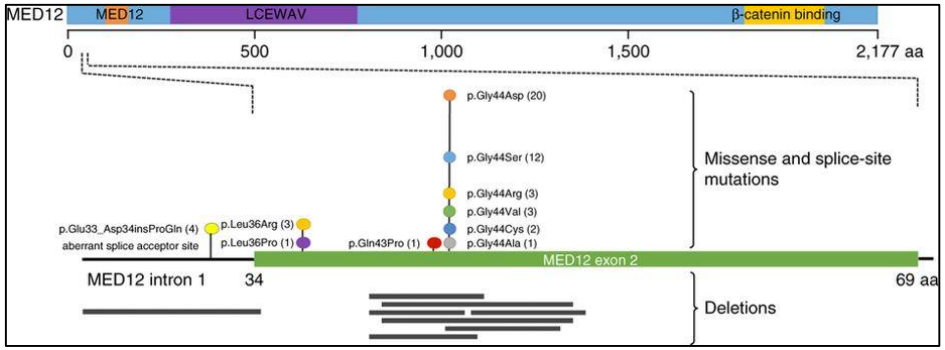
Molecular alterations in FELs

MED12 exon 2 somatic mutations in FA and PTs

- *MED12* (gene encoding mediator complex subunit 12)
- *MED12* mutations alter estrogen signaling and extracellular matrix organization
- Somatic *MED12* mutations detected in the stromal cells of most FAs and PTs



Lim WK et al. *Nat Genet*. 2014; 46:877-880

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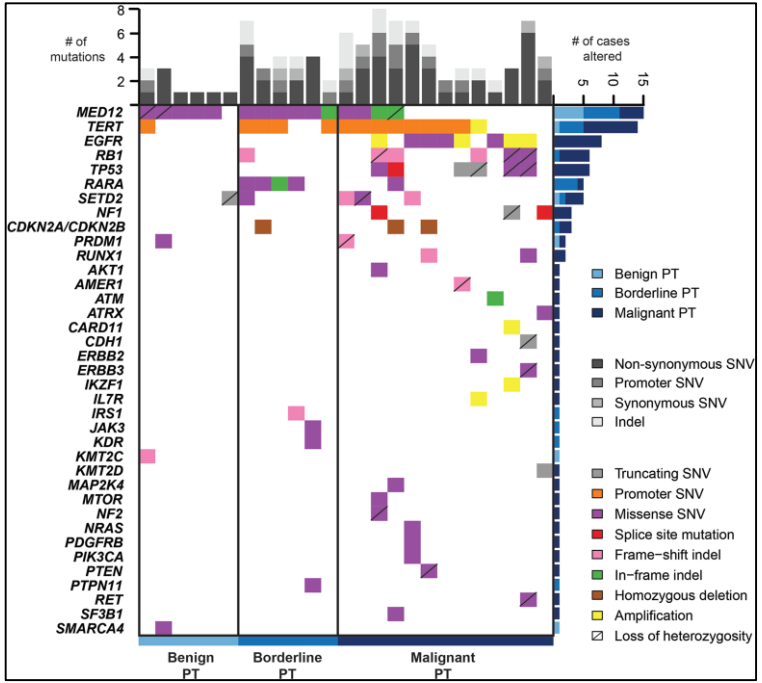
TERT promoter mutation and amplification common in Borderline and Malignant Phyllodes Tumors

TERT alterations are more frequent with increasing PT grade

- in 18% of benign PTs
- in 57% of borderline PTs
- in 68% of malignant PTs

No *TERT* alterations in FAs

Malignant PTs also harbor pathogenic somatic mutations of known oncogenes: *EGFR*, *RB1*, *TP53*, *NF1* …



Piscuoglio S et al. *J Pathol*. 2016; 238:508-518

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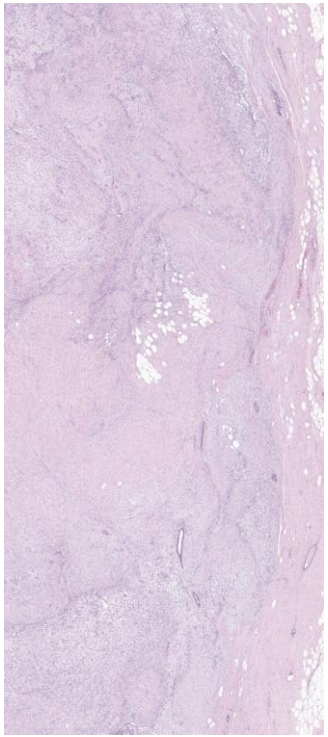
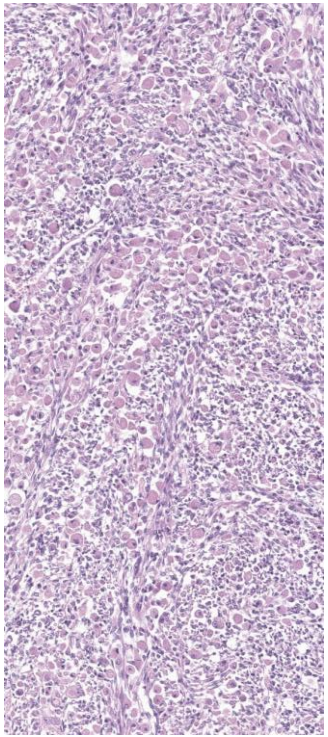
Malignant spindle cell neoplasm difficult to classify? Molecular analysis *may* provide a definitive classification

Case Example
- High grade spindle cell morphology
- Rhabdoid areas
- No epithelial component
- No definitive leaf-like arrangement
- Rare benign small peripheral ducts
- Negative CKs and p63

Dx: Favor Malignant PT, but Metaplastic Spindle Cell Carcinoma with mesenchymal heterologous elements cannot be ruled out; consider molecular testing





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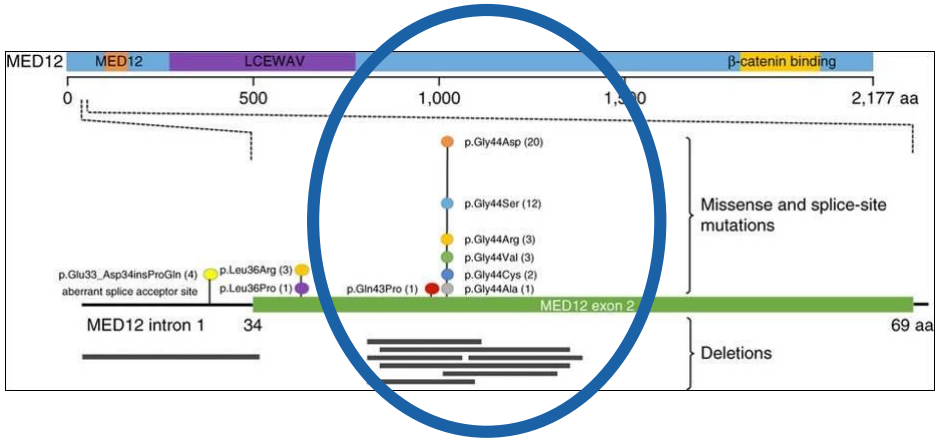
DDx high grade malignant spindle cell neoplasm
Molecular analysis *may* provide a definitive classification

Hello Dr. Brogi,
I hope that this e-mail finds you well. I'm following up on the sarcomatoid breast case that came your way from RI a few months ago.

Company X testing was not definitive ("no reportable alterations with companion diagnostic claims"), though there was a med12 G44D substitution as well as several other alterations.



In the appropriate clinic-radiologic and histologic setting, the identification of MED12 exon 2 mutation supports the diagnosis of a FEL (malignant PT in this case)

Malignant and Borderline PT - Take home messages

~20% Malignant PT develop mets

CAP 2022 Malignant PT DX requires:

- Widely infiltrative/ permeative border
- Marked stromal cellularity
- Marked stromal atypia
- >10 mitoses/ 10HPFs
- Stromal overgrowth

OR Malignant heterologous elements

Except only liposarcoma-like

Borderline PT DX if not ALL of above

Management (NCCN 4.2022)

- Wide excision (≥1 cm clearance)
- Usually no Radio-TP for Malignant PT
- *Usually no Chemo-TP for Malignant PT*

Molecular alterations

MED12 exon 2 mutations in 60-70% malignant PTs

TERT promoter mutation in 50-70% malignant PTs

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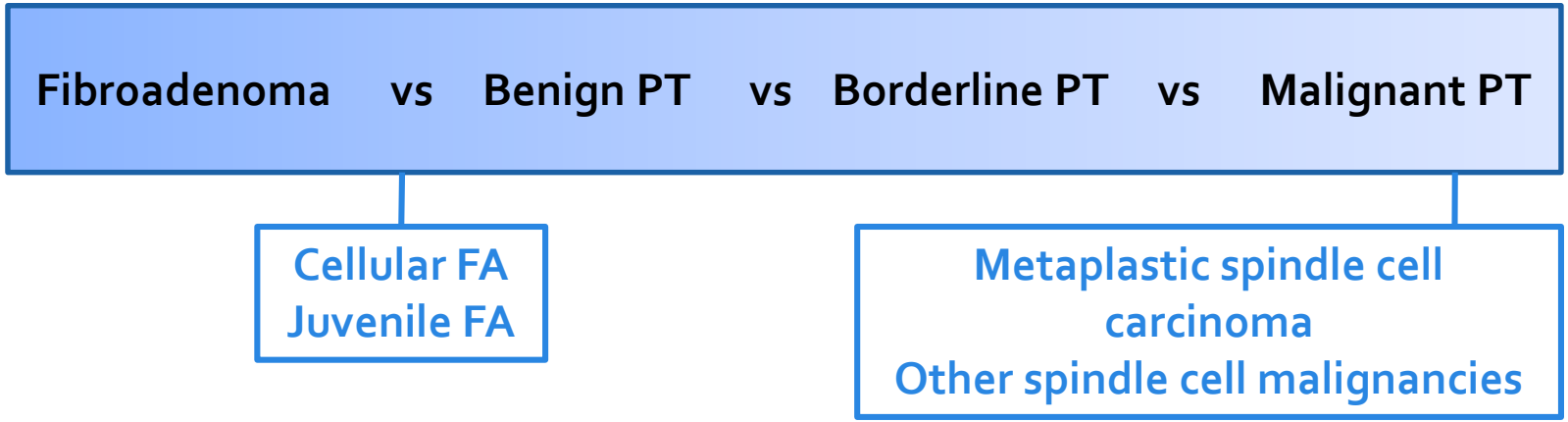
FELs: Common diagnostic dilemmas



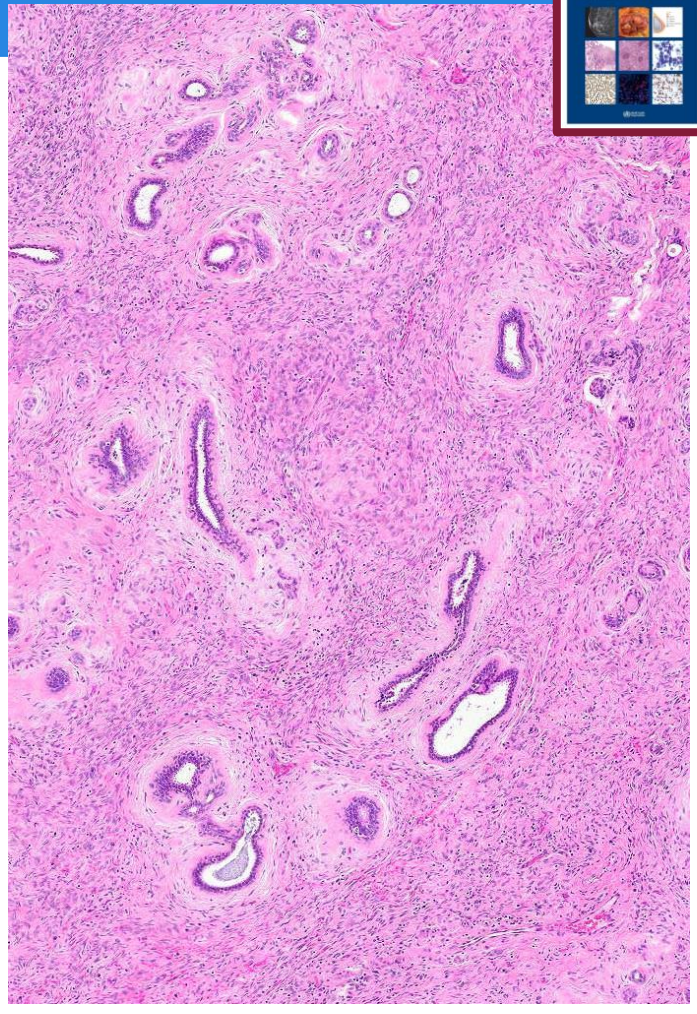
"Cellular" FA (WHO 5th ed.)

Morphologic features

- pericanalicular growth pattern
- mildly to moderately increased stromal cellularity
- usually <1 stromal mitosis/mm^2
  (<2 mitoses/10 HPFs)

Morphologic features NOT present

- stromal nuclear atypia
- exaggerated intracanalicular architecture
- periductal subepithelial stromal condensation
- intratumoural heterogeneity

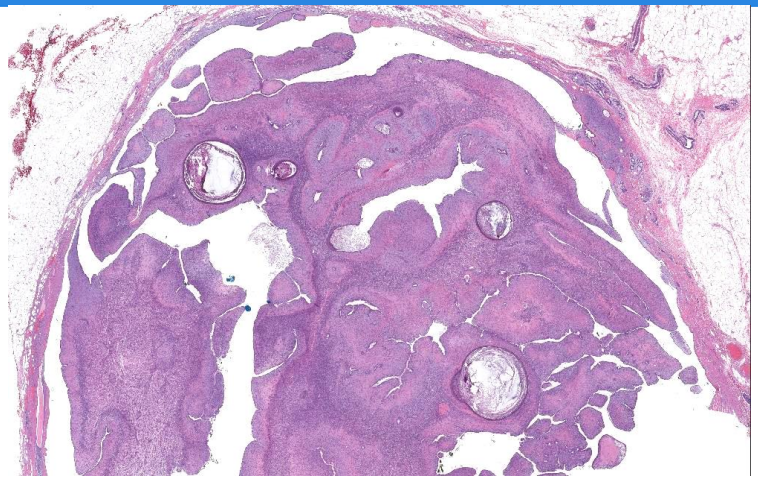


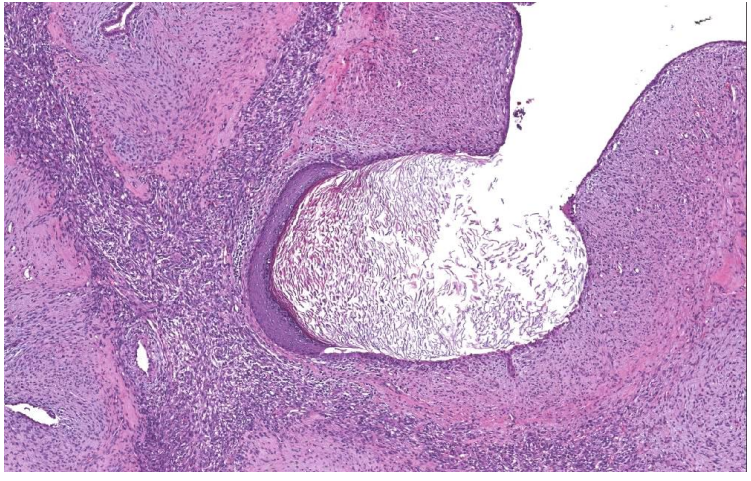
Cellular Fibroadenoma vs Benign Phyllodes Tumor

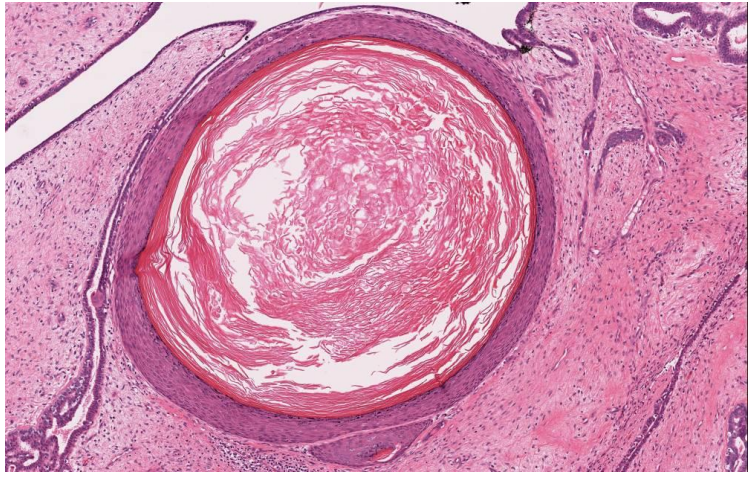
Histologic features	Cellular Fibroadenoma	Benign Phyllodes Tumor
Tumor border	Well defined	Well defined
Stromal cellularity	Variable, scant to uncommonly cellular **usually uniform**	Cellular, usually mild, may be non-uniform or diffuse
Stromal atypia	**None**	Mild or none
Mitotic activity	Usually **none**, rarely low	Usually low (< 5 mitoses per 10 HPFs)
Stromal overgrowth	Absent	Absent

- Stromal cellularity and mitotic activity of Cellular FA and Benign PT: possible overlap
- Glands:stroma ratio more homogenous in cellular FA than in benign PT
- Cellular FA: no stromal atypia or exaggerated intracanalicular growth is allowed
- **Stromal heterogeneity** favors Benign PT
- Squamous metaplasia of the epithelium favors PT

FEL with squamous metaplasia (*away from CBX site*)→ favor PT







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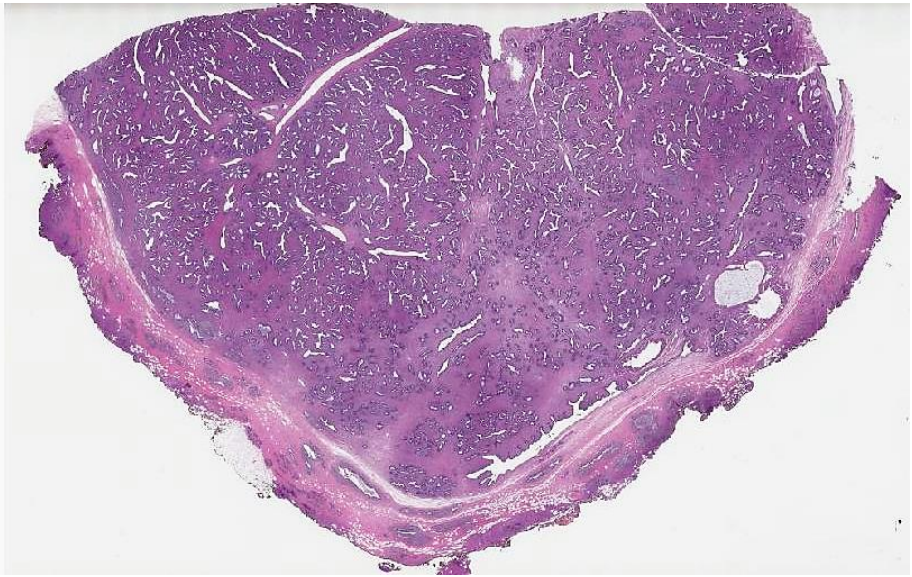
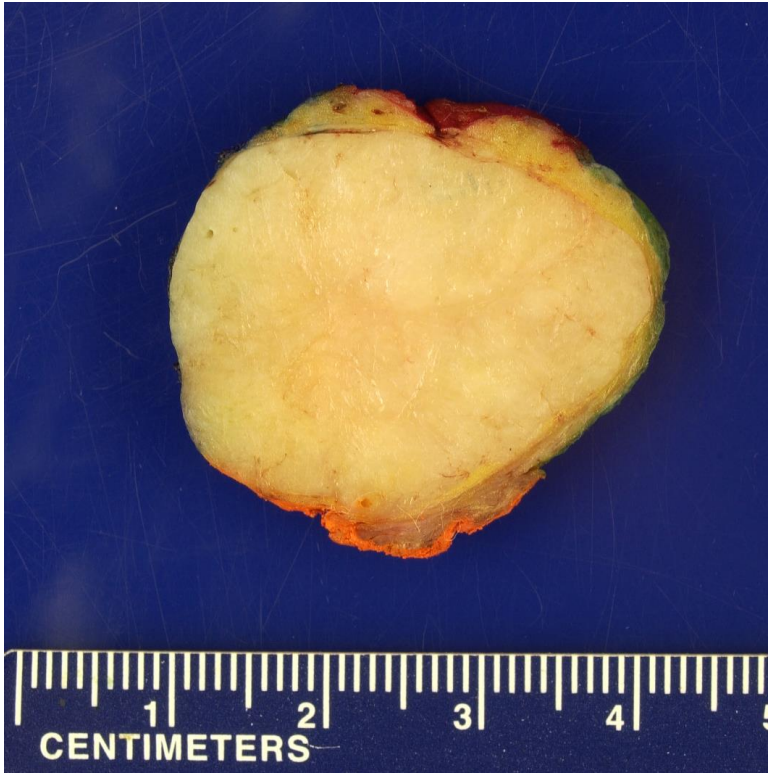
“Juvenile” FA

- Most common in adolescent girls or young women
- Can be very large, causing breast distortion





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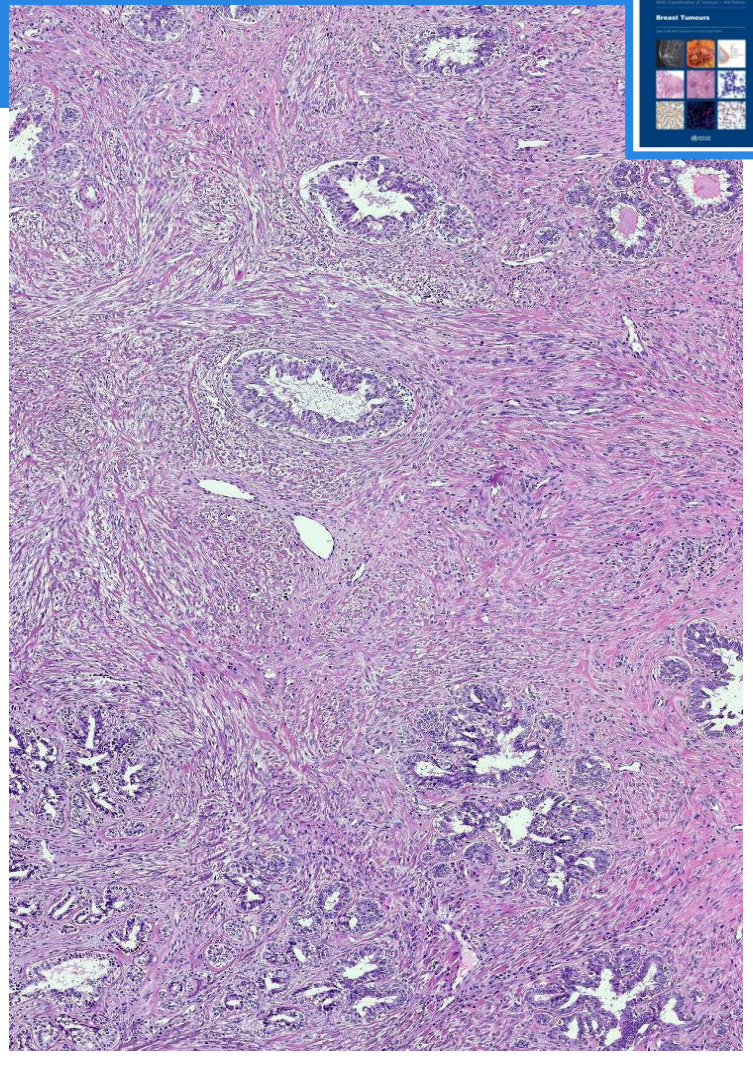
“Juvenile” FA

- Pericanalicular growth pattern
- Uniform mild to moderate increase in stromal cellularity
- Stromal cells in fascicular arrangements
- No substantial nuclear atypia
- Stromal mitotic activity usually low: <2 mitoses per 10 high-power fields (<1 mitosis/ mm^2)
- Usual ductal hyperplasia, most commonly of gynaecomastoid type



FELs in <18 yo females (N=54)

	N= 54 (%)	Size cm	Mitoses/ 10HPF	Border		Growth pattern		Epithelial hyperplasia
				confined	infiltrative	intra-canalicular	peri-canalicular	
All FAs	**34 (63)**	**2.9**	**1.6**	**34**	**0**	**10**	**24**	**9**
Usual	11 (20)	2.6 (0.7-4.5)	1.3 (0-6)	11	0	10	1	2
Juvenile	23 (42.6)	3.1 (0.5-7)	1.8 (0-7)	23	0	0	23	7
All PTs	**20 (37)**	**6.3**	**5.6**	**12**	**6**	**14**	**6**	**8**
Benign	16 (30)	4.9	3.1 (1-7)	12	3	11	5	8
Borderline	1 (<2)	N/A	10	0	1	0	1	0
Malignant	3 (5.5)	14.5 (4, 25, N/A)	17 (12, 20, NA)	0	2 (1 NA)	3	0	0

Ross DS et al. *Breast J*. 2017; 23:182-192

FELs in <18 yo females (N=68)

Diagnosis	Number (%)
All FAs	**64 (94.1)**
Simple	29 (39.7)
Juvenile	32 (47.1)
Cellular	3 (4.4)
All PTs	**3 (4.4)**
Benign	3 (4.4)
Others • Benign FEL • Benign hybrid Juv FA/ Benign PT • Benign FEL, features of Juv papillomatosis	3 (4.4)

Tay TKY, et al. J Clin Pathol 2015;68:633–641

MED12 exon 2 mutations in 53.8% usual FAs and 35% Juvenile FA in females <18 years old

Tay TKY et al. *Histopathology*. 2018;73(5):809-818

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Core Needle Biopsy (CNB)

Core Needle Biopsy of Fibroepithelial Lesions

Features that correlate with the diagnosis of PT at surgical excision

- +/- patient older than 50 years of age
- Fragmented tissue cores
- Frond-like arrangement
- Increased stromal cellularity
- Heterogeneous stromal cellularity
- Nuclear pleomorphism
- No epithelium in at least one 100X field of view (= stromal overgrowth)
- ≥2 stromal mitoses per 10 HPFs
  - ≥3 mitoses/10 HPFs diagnostic of PT
  - atypical mitoses→ favor malignant PT
- Adipocytes admixed with stroma
- Infiltrative margins

Jacobs T. Am J Clin Pathol, 2005
Jara-Lazaro AR, Histopathology 2010
Lee AH Histopathology 2007
Tsang AK Histopathology 2011
Yasir S Am J Clin Pathol 2014

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When ≥3 of these histologic features are present → the diagnosis is PT

Jacobs T. Am J Clin Pathol, 2005
Jara-Lazaro AR, Histopathology 2010
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Tsang AK Histopathology 2011
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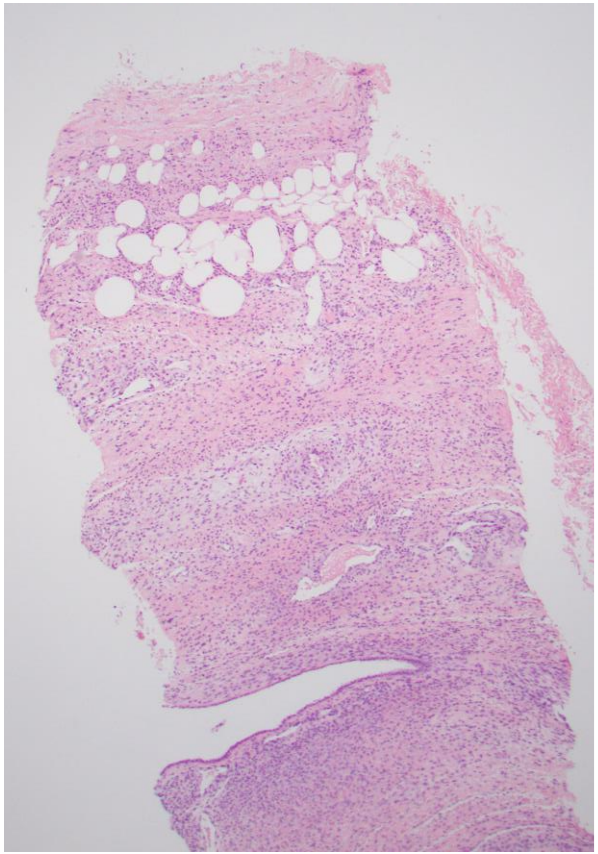
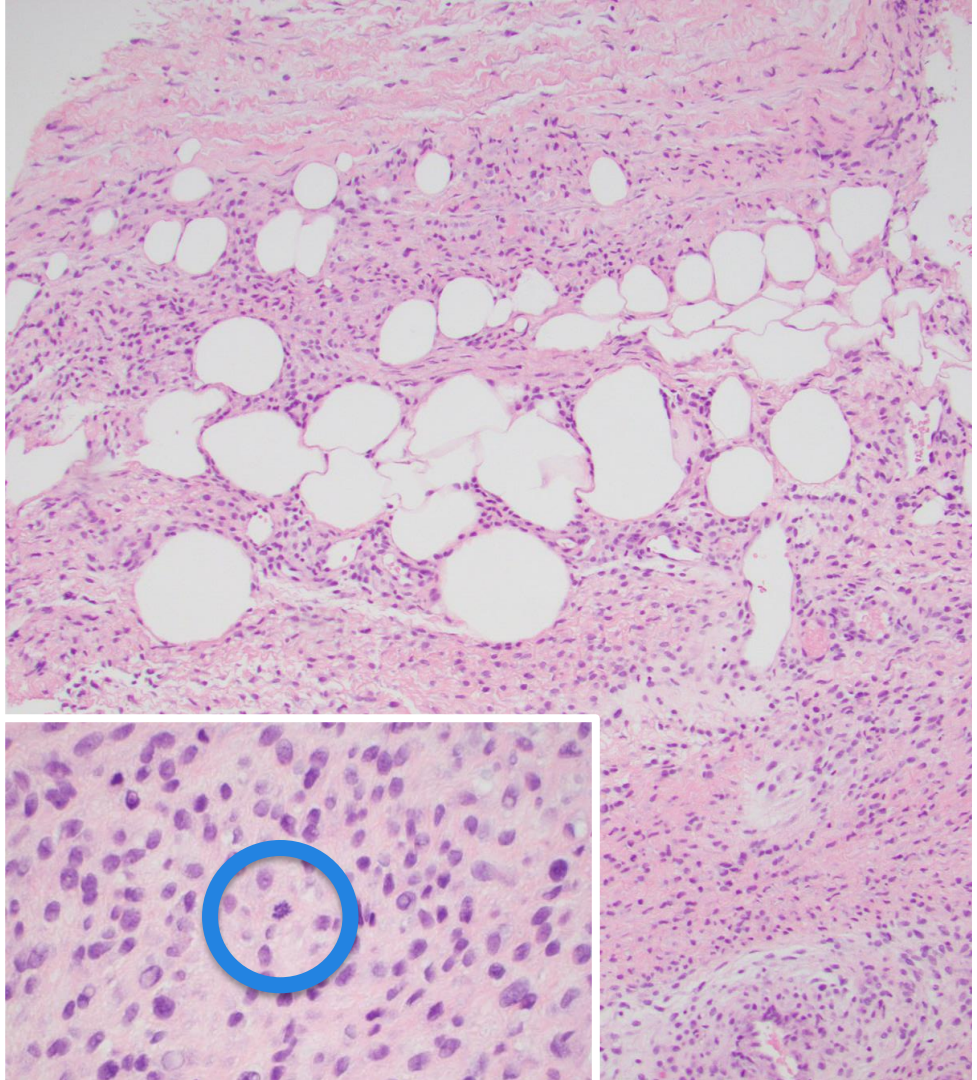
CNB DX: PT





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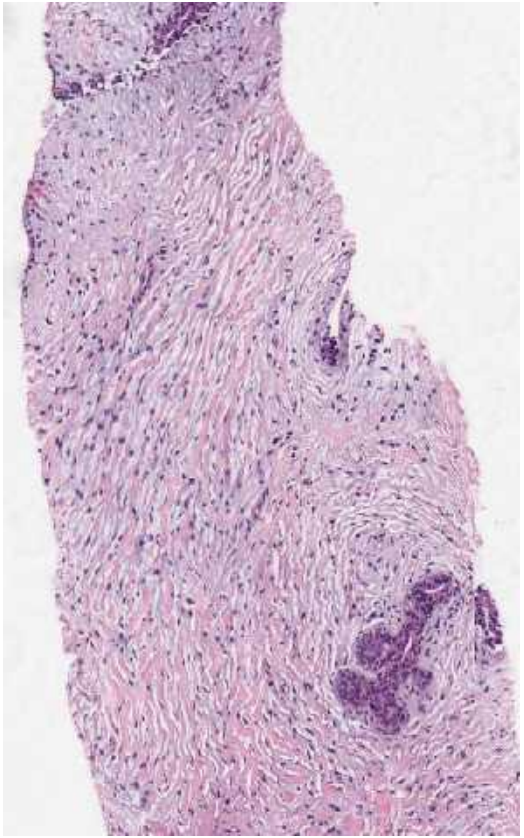
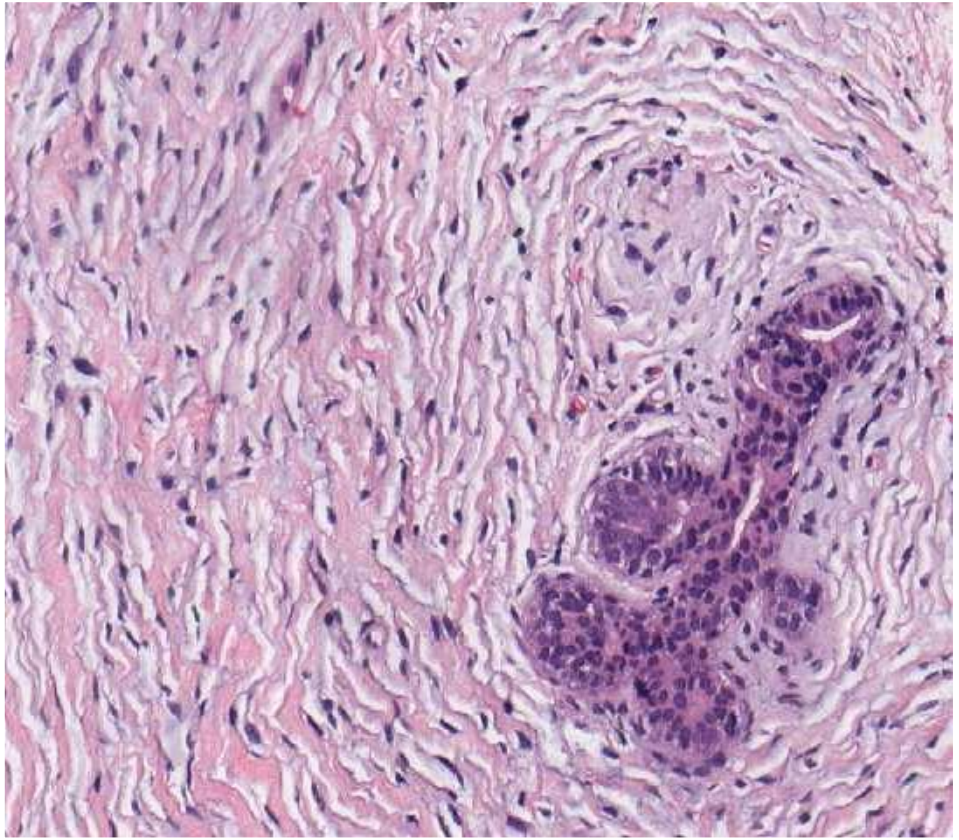
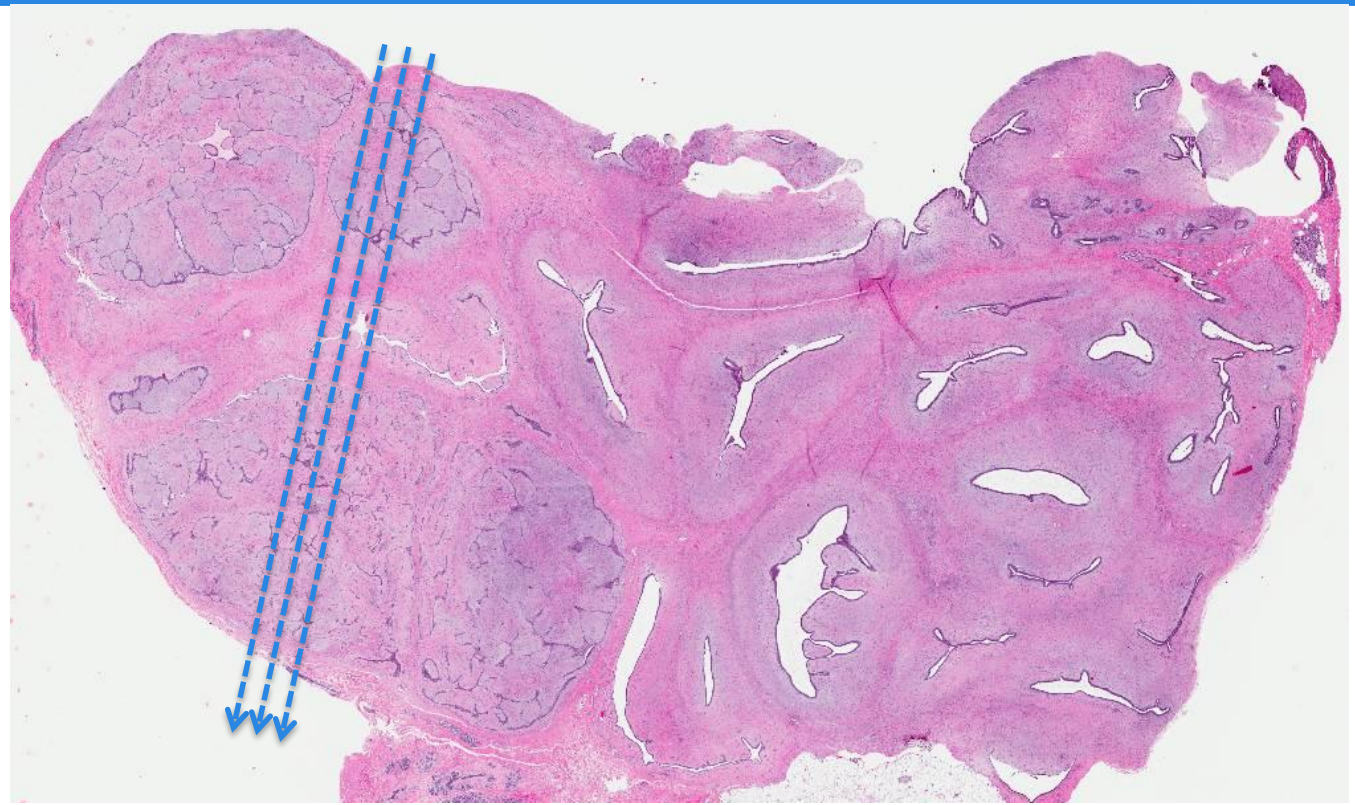
CNB DX: FEL with increased stromal cellularity





PTs are heterogeneous → limitations of CNB Dx



Core Needle Biopsy – Bland spindle cell proliferation

DDX: (Cellular) Fibroadenoma VS Benign PT: morphologic overlap

	Fibroadenomas	Benign phyllodes tumours
Stroma		
Stroma-epithelium ratio	Lower	Higher
Stromal atypia	Absent	Mild
Stromal cellularity	Lower, except in cellular variant	Higher
Mitotic count	Mostly absent, except in juvenile variant	>1/10 HPFs
Stromal expansion	Absent	Can be present
Tissue core fragment	Absent	Can be present
Adipose tissue in stroma	Absent	Can be present
Subepithelial condensation	Absent	Can be present
Giant cells	Present in both entities	Present in both entities
Immunohistochemistry		
CD34	Similar expression	Similar expression
Ki-67	Similar expression	Similar expression

"To date, no single histological feature can reliably distinguish FA (including its variants) from PT on CNB. A constellation of multiple histological parameters has to be taken into account; **in difficult cases it may not be possible to distinguish FA and PT, and a CNB diagnosis of benign fibroepithelial lesions may be appropriate, pending excision and complete histological assessment."**

Li JJ and Tse GM *Pathology* 2020:52(6);627-634

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2022
Phyllodes Tumor
NCCN Evidence Blocks™

CNB DX

Fibroadenoma → no EXC required

Benign fibroepithelial lesion → EXC

Benign PT → EXC

Excisional Biopsy DX:

Fibroadenoma

Benign PT

Clinical Follow-up

for 3 years

Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins

CAP guidelines (March 2022) recommend reporting margin status of Benign PT

Thank you