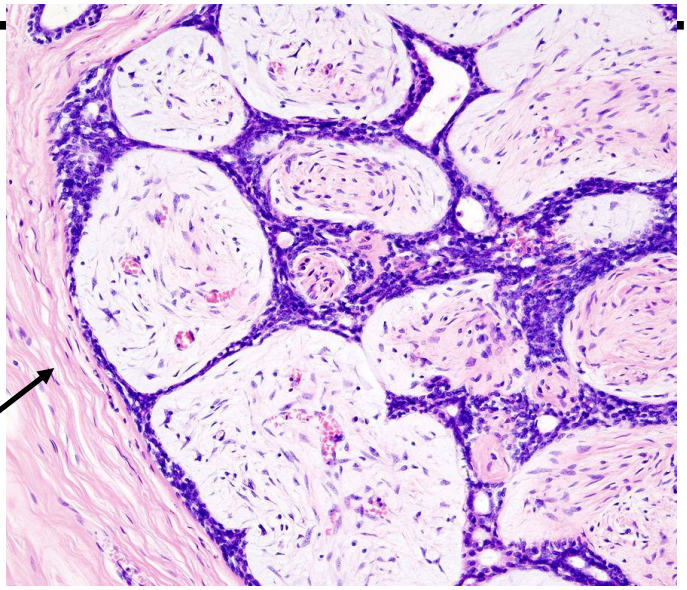
Fibroepithelial and Mesenchymal/Spindle Cell Lesions

Fibroepithelial Lesions

Fibroadenoma



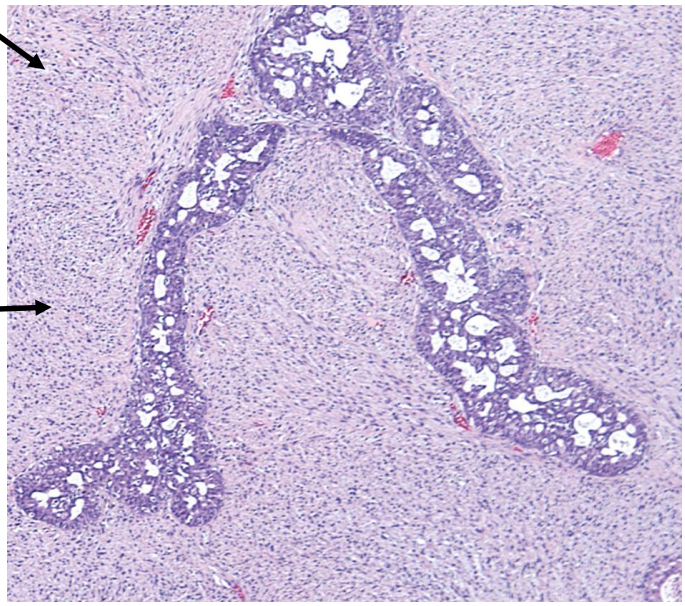
Circumscribed, **benign** neoplasm of the Terminal Duct Lobular Unit (TDLU) with a **biphasic** proliferation of **epithelial and stromal cells**.

Painless, solitary, slow-growing mobile masses.
Most common in younger women.
Hormone-sensitive, can grow during pregnancy.

Molecular: Not usually monoclonal, but frequent MED12 mutations in stromal cells

Intracanalicular pattern→ expansion of stroma compresses ducts into slit-like spaces

Pericanalicular pattern→ stroma grows around open ducts



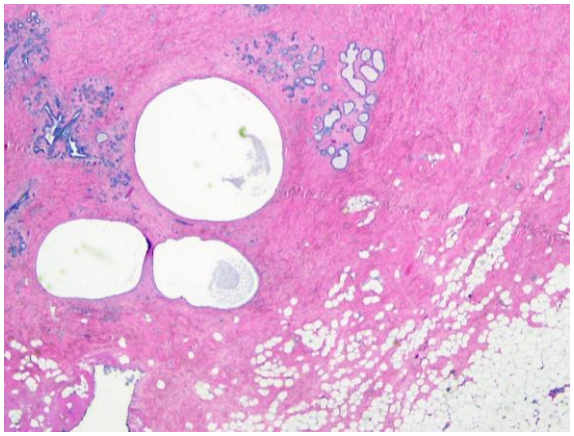
NO stromal overgrowth, cytologic atypia, significant mitotic activity or well-developed fronds (otherwise consider Phyllodes tumor!)

Can have lipomatous or smooth muscle *metaplasia*.
Can have *superimposed* DCIS, etc..

Juvenile Fibroadenoma:
More common in adolescents. Large and grow rapidly. Pericanalicular growth with increased stromal cellularity. Intraductal gynecomastoid UDH

Most FA do not recur after complete surgical excision

Hamartoma

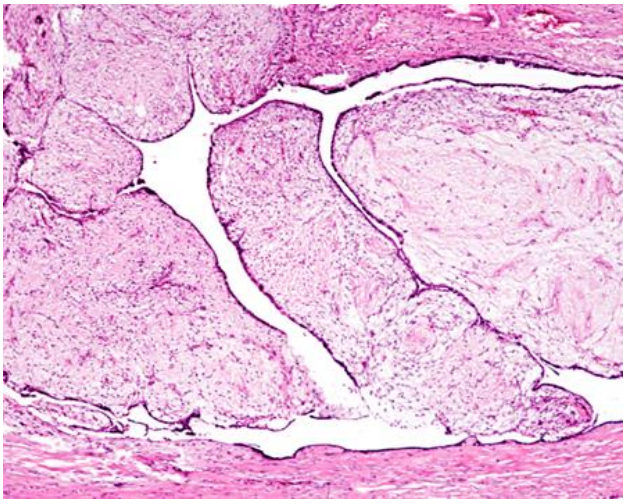


Well-demarcated, generally **encapsulated** mass composed of **normal breast** tissue components.

Lobulated and show ducts, lobules, fibrous tissue, and adipose tissue in varying proportions (normal components). Sometimes called “adenolipoma.”

Requires clinical and/or imaging correlation to distinguish from normal breast→ Round and well-circumscribed lesion

Phyllodes Tumor



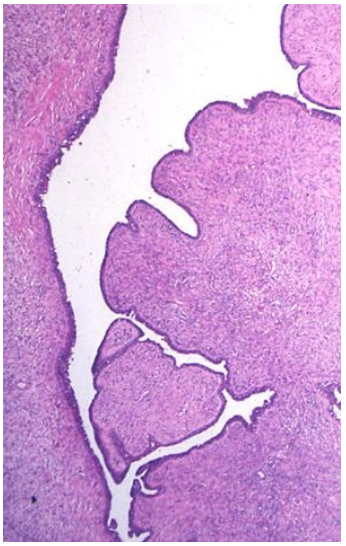
Fibroepithelial neoplasm with prominent **intracanalicular growth** and **stromal hypercellularity**

Exaggerated intracanalicular growth→ **"Leaf-like" projections into variably dilated lumina**

Increased stromal cellularity, particularly accentuated adjacent to the epithelium. Sometimes heterogeneous.

Malignant phyllodes show:

- Stromal overgrowth (4x field without epithelium)
- Increased mitoses (≥10 per 10 HPFs)
- Increased stromal cellularity (Often diffuse)
- Infiltrative borders
- Malignant heterologous elements (except well-differentiated liposarcoma, as it has a low metastatic risk)



When a Tumor has some but not all the features of malignancy, consider "Borderline."

Molecular: Recurrent MED12 mutations support a *shared pathogenesis with fibroadenomas*. Additional mutations include: **TERT, TP53,** PTEN, RB1, and EGFR

Risk of recurrence can also be calculated using the Singapore General Hospital Nomogram

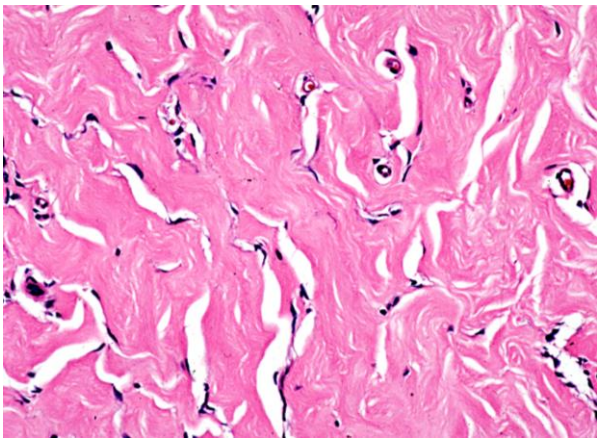
If unsure FA vs Phyllodes on core biopsy→ consider "fibroepithelial tumor," with a DDX.

Histologic Feature	Fibroadenoma	Benign Phyllodes	Borderline Phyllodes	Malignant Phyllodes
Tumor Border	Well-defined	Well-defined	Well-defined, maybe focally infiltrative	Permeative
Stromal Cellularity	Variable, usually uniform and scant	Cellular, usually mild, may be non-uniform of diffuse	Cellular, usually moderate, may be non-uniform or diffuse	Cellular, usually marked and diffuse
Stromal Atypia	None	Mild or none	Mild or moderate	Marked
Mitotic Activity	Usually none (<2 per 10 HPF)	Usually low (<5 per 10 HPFs)	Frequent (5-9 per 10 HPFs)	Abundant (≥10 per 10 HPFs)
Stromal Overgrowth	Absent	Absent	Absent (or very focal)	Often present
Malignant heterologous elements	Absent	Absent	Absent	Maybe present
Frequency	Common	Uncommon	Rare	Rare
Proportion of all Phyllodes tumors	N/A	60-75%	15-26%	8-20%
Behavior	Benign. Recurrence rare	Benign. Recurrence more common	Benign. Recurrence even more common.	Malignant.

Modified from: WHO Classification of Breast Tumors. 2019.

Spindle Cell Lesions

Pseudoangiomatous Stromal Overgrowth *aka "PASH"*

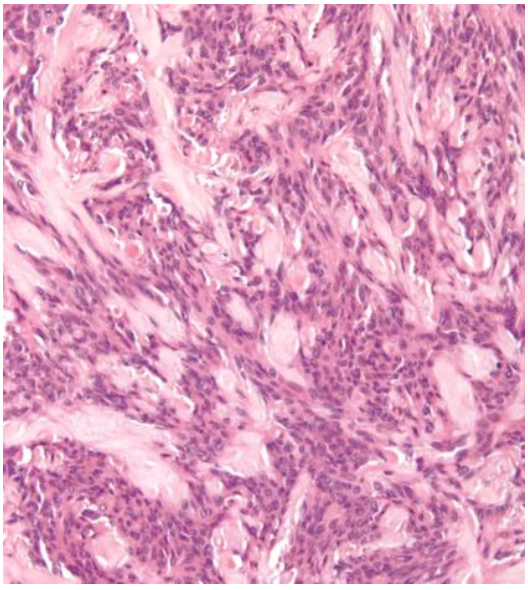


Proliferation of **myofibroblasts amongst collagenous stroma forming anastomosing slit-like channels** (resembling blood vessels, but *not* actually vascular, hence the "*pseudo*").

PASH is non-neoplastic and is thought to be an aberrant stromal response to hormones and typically presents as an incidental mass-forming lesion.

It is benign and needs no treatment.

Myofibroblastoma



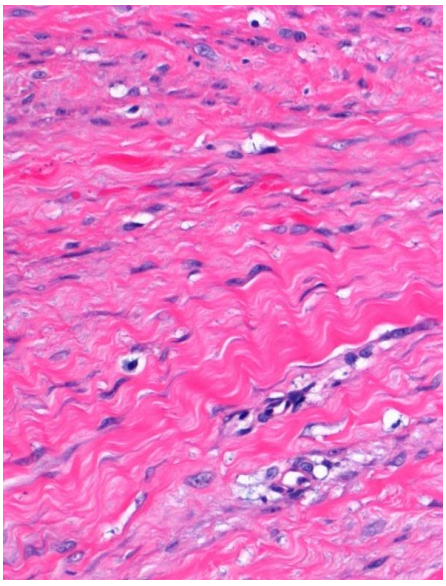
Benign tumor of mammary stroma composed of fibroblasts and myofibroblasts. Often presents as slow-growing painless mass. Cured by local excision

Purely mesenchymal (no epithelium or myoepithelial cells)
Well-circumscribed, unencapsulated
Bland, spindled cells; rarely epithelioid
Short, haphazardly intersecting fascicles
Interspersed thick collagen bundles
Minimal mitoses and atypia

IHC: **(+) Desmin, CD34, ER**/PR/AR; Loss of RB1

Molecular: 13q14 deletions by FISH in majority of cases (contains RB1)

Desmoid Fibromatosis



Benign (never metastasize), but infiltrative with strong tendency to recur (>25%). Interestingly, microscopic margins do NOT predict recurrence.

Infiltrative growth into surrounding structures (esp. skeletal muscle).
Broad, sweeping fascicles.
Uniform spindled cells with small, pale nuclei with pinpoint nucleoli.
Moderate amounts of collagen, surrounding cells, in slightly myxoid background.
Microhemorrhages and scattered chronic inflammation.

IHC: Nuclear β-catenin (more cells with deep than superficial).
Some actin (+)

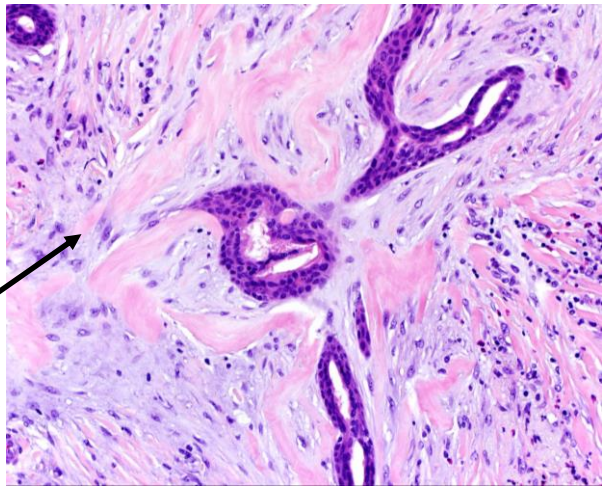
Molecular: Associated with FAP and mutations in the APC/β-catenin (CTNNB1) pathway

Metaplastic Carcinoma

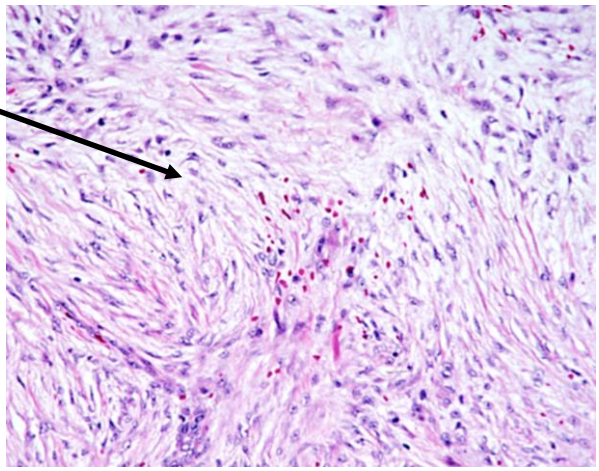
Invasive Breast Cancers with differentiation of epithelium towards squamous or mesenchymal-looking elements.

Usually present as a mass; **Rare**, <1% of all breast cancers.

Several distinct patterns (with some overlap, often mixed):

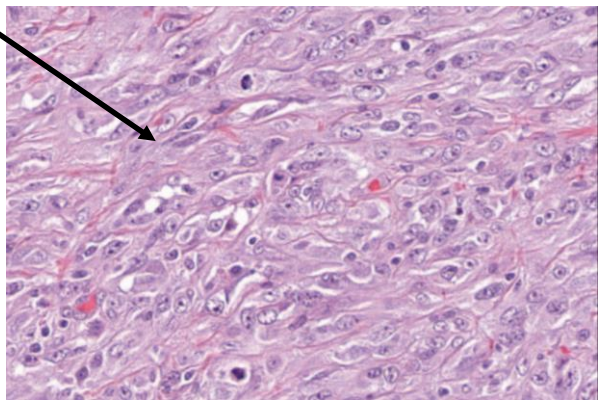


Low-grade Adenosquamous Carcinoma
Well-developed, rounded glands and tubules associated with solid squamous nests infiltrating through desmoplastic stroma. Sometimes associated "cannon ball" lymphoid aggregates. Good prognosis.



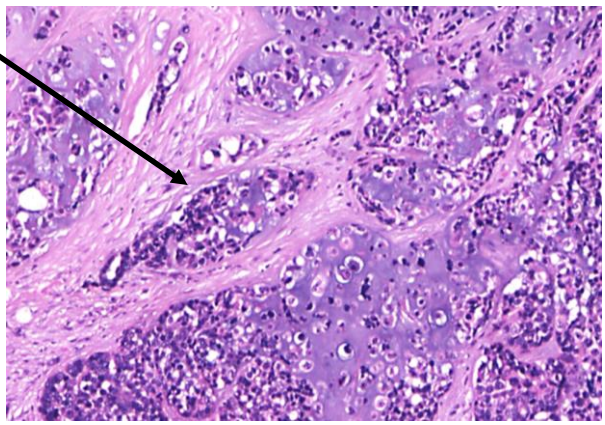
Fibromatosis-like Metaplastic Carcinoma
Bland spindled cells with pale eosinophilic cytoplasm and slender nuclei in stroma with variable collagen. Only mild nuclear atypia. Often arranged in fascicles. Some cells may be plumper/epithelioid. Good prognosis.

Spindle Cell Carcinoma
Atypical spindle cells with a variety of architectural patterns (e.g., fascicles, herringbone, etc…). Elongate to plump spindled cells with moderate to high-grade cytologic atypia. Often associated inflammation. Includes a spectrum of tumors from sarcomatoid SCC to myoepithelial carcinoma. Worse prognosis.



Squamous Cell Carcinoma
Pure squamous cell carcinoma. Often cystic. Must exclude a metastasis. Worse prognosis.

Metaplastic Carcinoma with Heterologous Mesenchymal Differentiation
Essentially a carcinosarcoma. Heterologous elements may include chondroid, osseous, and rhabdoid components. Epithelial and mesenchymal components can have variable atypia. Sometimes extensive sampling is necessary to find the epithelial component (and exclude a primary sarcoma).

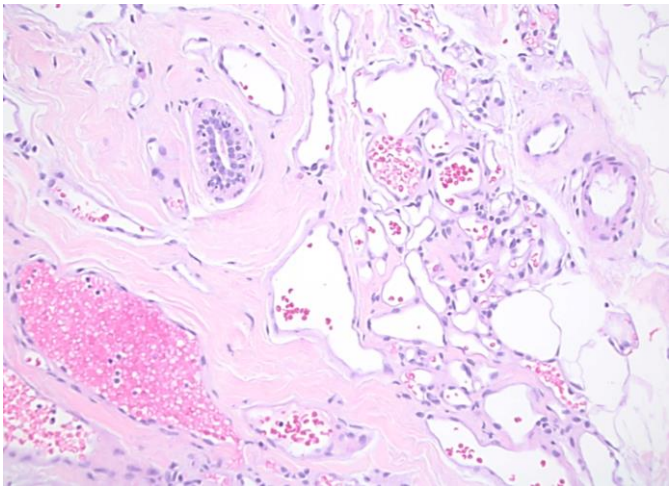


IHC: Vast majority **do not express ER, PR, or HER2** (Triple Negative). However, they do express some epithelial markers:
(+) p63, HMWCKs (e.g., CK5/6), CK AE1/AE3
(-) CK7, CD34,
(+/-) SMA, CD10, Desmin, β-catenin

Molecular: Frequent TP53, PIK3CA, and WNT pathway mutations. May be derived from late dedifferentiation or basal-like stem cells.

Clinical: Much fewer LN metastases.

Hemangioma

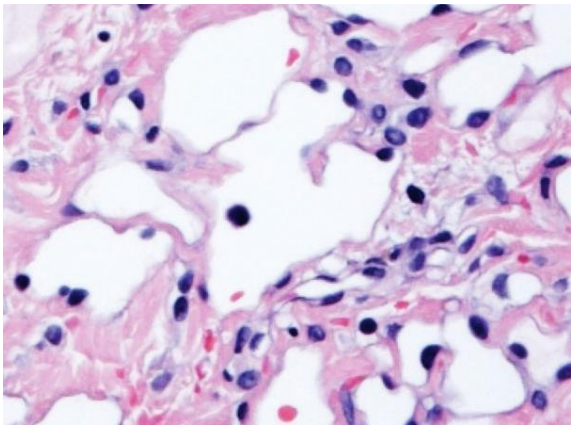


Benign proliferation of **mature blood vessels**.
Usually non-palpable, found on imaging.
Most likely non-neoplastic.

Well-differentiated vessels of varying size.
Often non-anastomosing.
Endothelium without nuclear atypia (hyperchromasia or pleomorphism), mitoses, or multi-layering.

Excision is not necessary.

Atypical Vascular Lesion

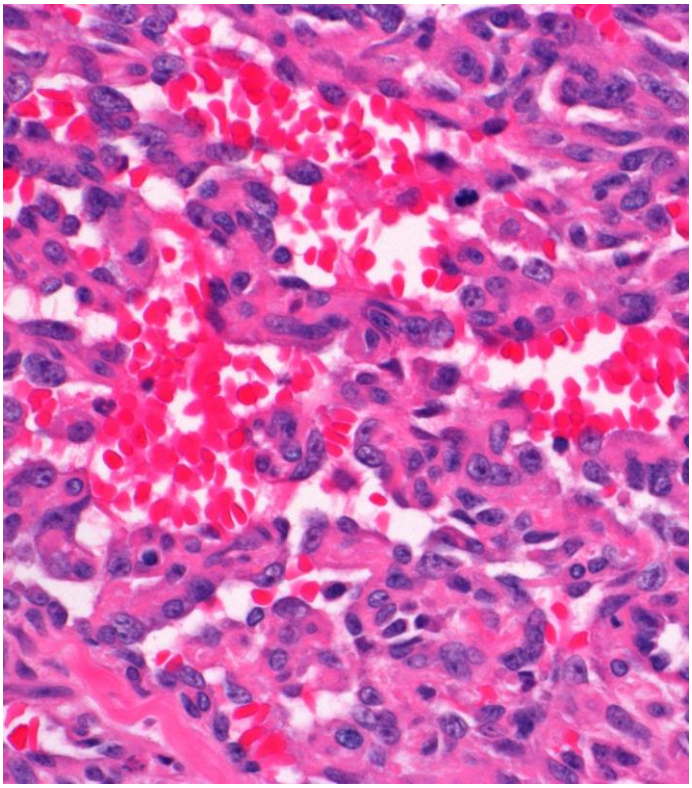


Benign. Occur in irradiated skin (often of breast).
Often small/multiple.

Irregularly-shaped thin-walled vessels with branching and anastomosing growth. Lined by a single layer of endothelium with some hobnailing and hyperchromasia.
NO endothelial cell multilayering or true cytologic atypia

IHC/Molecular: No MYC overexpression/amplification.

Angiosarcoma



Malignant. Very aggressive. Typically elderly.

Variable degrees of vascular differentiation.
Some areas show well-formed anastomosing vessels, while other areas may show solid sheets of high-grade cells.
Can be epithelioid or spindled.
Often extensive hemorrhage.

Unlike benign lesions: significant cytologic atypia, necrosis, endothelial cells piling up, and/or mitotic figures (although mitoses can be seen in some benign tumors)

Grade does **not** predict prognosis (*all* aggressive)

Post-radiation angiosarcoma:

Occurs after radiation (usu. ~5yrs).
High-level amplification of MYC (by IHC or FISH) is a hallmark of this lesion.

Adenomyoepithelioma

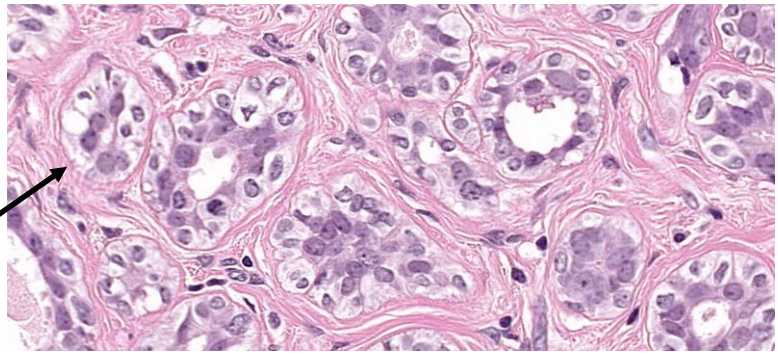
Biphasic proliferation of **inner ductal cells and outer myoepithelial cells.**

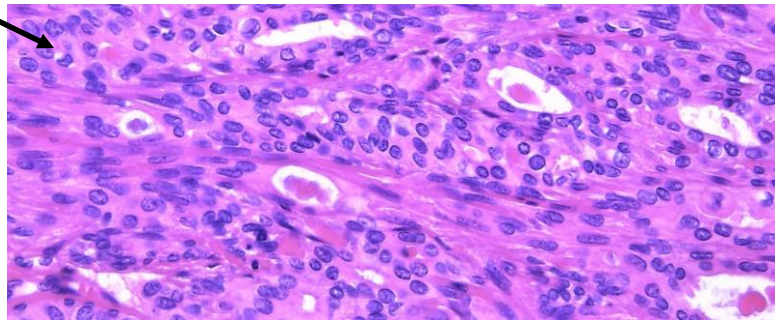
Essentially like Epithelial-Myoepithelial Carcinoma of the salivary gland.

Various patterns, but can be tubular with prominent myoeps with clear cytoplasm; or have more spindled myoeps with admixed ducts

Typically older women with palpable mass. **Usually benign** but can de-differentiate into a carcinoma.

Molecular: Frequent PIK3CA, ATK1, and HRAS mutations





Other Lesions

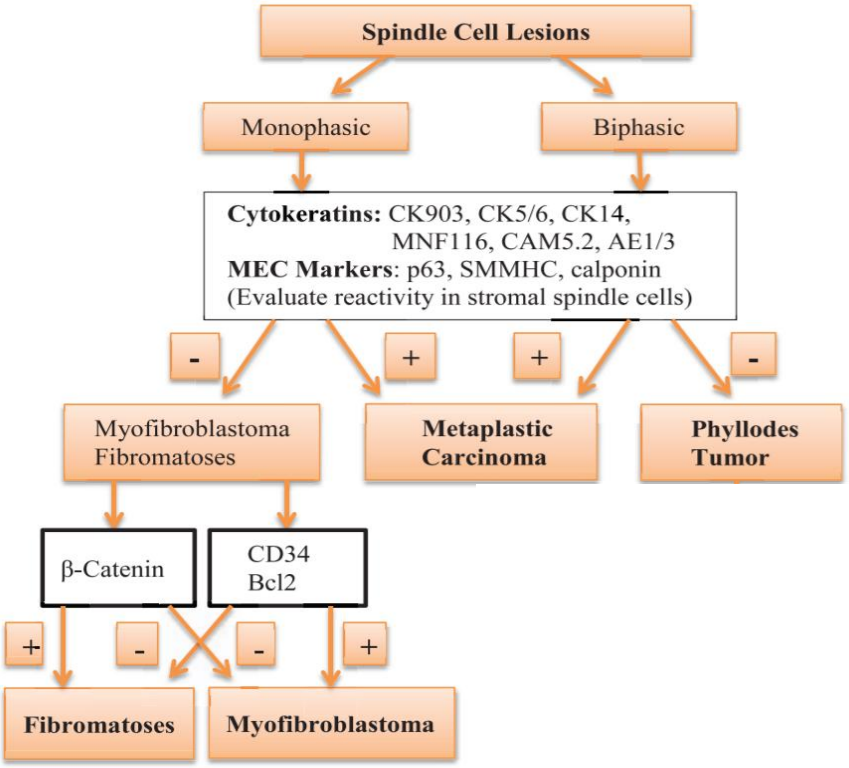
Nodular fasciitis
Inflammatory myofibroblastic tumor

Schwannoma
Neurofibroma
Granular cell tumor
Leiomyoma

Leiomyosarcoma
Lipoma
Angiolipoma
Liposarcoma

Immunohistochemical Staining

A panel should include some combination of: Multiple Cytokeratins (CK AE1/AE3, CK5/6, CK34βE12), p63, SMA, CD34, desmin, S100, ERG



For spindle cell lesions, always consider **metaplastic carcinoma** and/or **stromal overgrowth in a Phyllodes tumor.** Sample the lesion well, looking for an epithelial component and stain it with multiple epithelial markers.

Indeed, given the limitations of sampling, be particularly careful (and perhaps descriptive) on core biopsy!

Always be weary diagnosing a primary sarcoma in the breast.

From: Liu H. Application of immunohistochemistry in breast pathology: a review and update. Arch Pathol Lab Med. 2014 Dec;138(12):1629-42.