Invasive Breast Carcinoma

General Background

<u>Most common cancer in women</u> and leading cause of female cancer death worldwide.

Presenting signs and symptoms:
Unscreened populations—mass, skin erythema and edema due to cancer in dermal lymphatics.
Screened populations—spiculated mass, architectural distortion, MRI enhancement

Three pillars of diagnosis: physical exam, imaging, needle biopsy/cytology
When these are concordant, the risk of missing cancer is extremely low, but must do careful correlation.

General Risk factors:
Increased estrogen—seen with early menarche, fewer children, less lactation, and obesity.
Increased Alcohol

Pathogenesis/Molecular

Two main pathways separated by Estrogen Receptor (ER) status:

ER-Positive: ER+, HER2-, Diploid with specific chromosomal gains/losses (e.g., gain 1q, loss of 16q)→ usually low to intermediate-grade cancers

ER-Negative: ER-, HER2+/-, Aneuploid with complex karyotypes, Frequent TP53 mutations → frequently high-grade tumors with high proliferation

<u>*Both*</u> pathways show PIK3CA mutations, but it is more common in ER-positive tumors.

<u>Molecular classification:</u> *(based on hierarchical cluster analysis of gene expression)*

	Lumina A	Luminal B	HER2-Positive	Basal type
Percent of all tumors	~45%	~25%	~15%	~15%
Classic ER/HER2 status	ER+ (high), HER2-	ER+ (lower), HER2-	ER-, HER2+	ER-, HER2-
Ki67	Low	Intermediate	High (~40%)	High (>80%)
Actual ER/HER2	ER+ → HER2+			Triple Negative
Grade	Low → High			
Recurrence Risk	Low, but long term → High, but short term			
Therapies used	Hormone Rx → HER2 Rx → Chemotherapy			

Note: *Other molecular classifications exist and include additional/alternate groupings. This is just the most well-established and frequently utilized.*

Grading

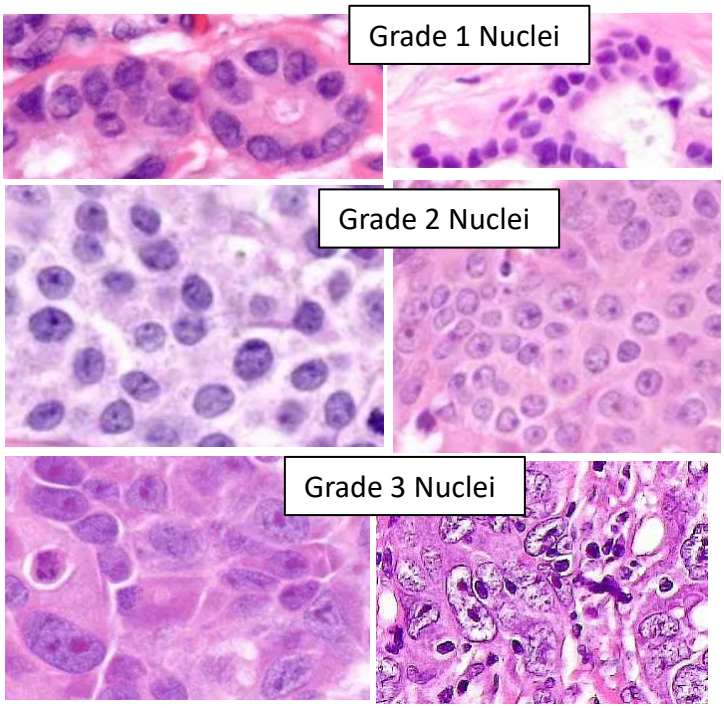
Grade using the ***Nottingham system*** with its 3 independent characteristics.

1) Tubule/Gland formation: Assessed throughout the *whole* tumor at low magnification.
Only structures with central lumina surrounded by polarized tumor cells are counted. Complex, inverted tubules, and cribriform glands are included. Papillae and intracytoplasmic lumens do NOT count.

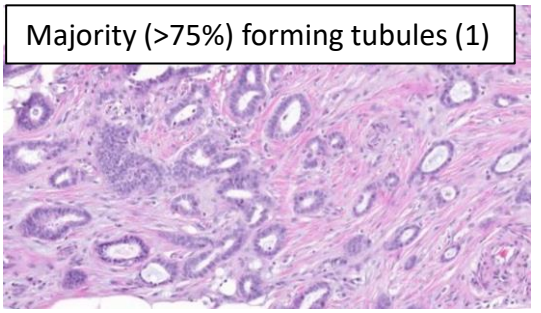
2) Nuclear pleomorphism: Assessed in the area showing the *worst* cytologic atypia

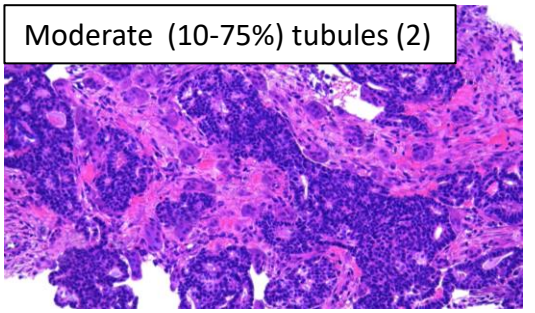
3) Mitotic count: Assessed in *mitotic "hot spot*." Remember to factor in your field area!

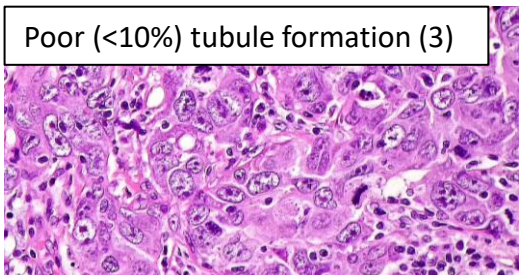
Feature	Score
Tubule formation	
Majority of tumor (>75%)	1
Moderate degree (10-75%)	2
Little or none (<10%)	3
Nuclear pleomorphism	
Small, regular, uniform (<1.5x the size of normal nucleus)	1
Moderate increase in size and variability (1.5-2x cell size)	2
Marked variation (>2x cell size) vesicular chromatin, often prominent nucleoli	3



Mitotic count			Score
Per 10 HPF *Olympus, 10x oculars [most attending scopes], 40x objective*	**Per 10 HPF** *Olympus, 15x oculars [most resident scopes], 40x objective*	**Per 2 mm²**	
0-8	0-3	≤ 7	1
9-17	4-7	8–14	2
≥18	≥8	≥ 15	3







Add the scores for gland formation, nuclear pleomorphism, and mitotic count:

Total Score	Final Grade
3-5	Grade 1
6 or 7	Grade 2
8 or 9	Grade 3

NOTE: Remember, the size of an HPF varies depending on your scope and magnification, so be sure to factor this in when counting mitoses!

Breast Origin and IHC

There is no absolutely specific marker of breast origin!

Breast carcinomas *usually* stain with low-molecular weight cytokeratins (including CK7 and CK19), EMA, GATA-3, and TRPS1.

Luminal/Well-differentiated tumors will often stain with: ER, GCDFP-15 (BRST2), and mammaglobin.

Higher-grade triple-negative tumors will often stain with basal markers including high-molecular weight cytokeratins and sometimes S100, SOX10, and/or p63.

Almost all ER+ tumors are GATA3 positive, so if it's ER+ GATA3-, it's likely not breast.
Metastases often have the same profile as the primary… but not always!

All of these stains can be positive in non-breast tumors, so they must be interpreted in context and molecular may be helpful in inconclusive cases.

Is it invasive?

Invasive breast cancer is defined by the **absence of peripheral myoepithelial cells**.

Stains for myoepithelial cells, "myoeps," (see below) should be employed as part of a *panel or cocktail* with at least one nuclear *and* one cytoplasmic stain (e.g., p63 and SMMHC).

However, do not rely solely on negative myoepithelial stains to diagnose invasion. The H&E findings must be concordant. Nests of in situ carcinoma may well be surrounded by reduced numbers of myoepithelial cells and those present may stain weakly.

Marker	Nuclear vs Cytoplasmic	Comments
p63 / p40	N	One of the most sensitive & specific myoepithelial markers. Stains squamoid epithelium.
SMMHC	C	More sensitive than p63, but cross-reacts with stromal myofibroblasts and vessel smooth muscle.
Calponin	C	Good myoep marker, but some cross reactivity.
SMA	C	Sensitive but not specific for myoeps. Marked cross-reaction with myofibroblasts.
CK5/6	C	Stains squamoid epithelium.

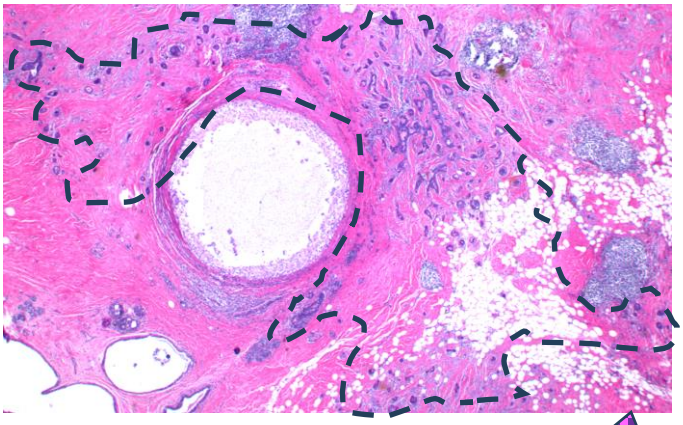
Morphologic features of Cancer vs Mimics:

Feature	Invasive cancer	Complex sclerosing lesions	DCIS involving sclerosing adenosis
Stroma	Desmoplastic	Dense	Dense
Cytology	Atypical	Bland	Atypical
Gland profile	Angulated	Compressed	Solid/cribriform
Architecture	Infiltrative	Lobulated	Lobulated
Myoepithelial cells	Absent	Present	Present

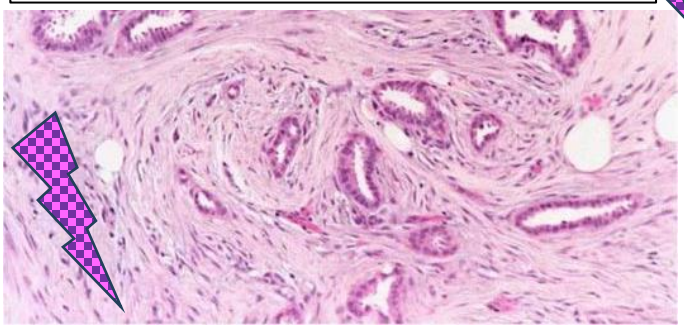
Modified From: Peng et al. Update on Immunohistochemical Analysis in Breast Lesions. Archives of Pathology & Laboratory Medicine: August 2017, Vol. 141, No. 8, pp. 1033-1051.

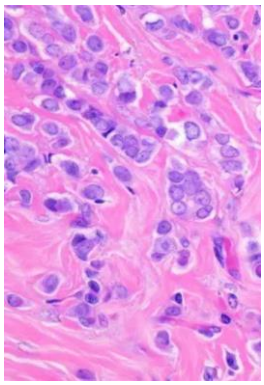
Invasive (Cancer)

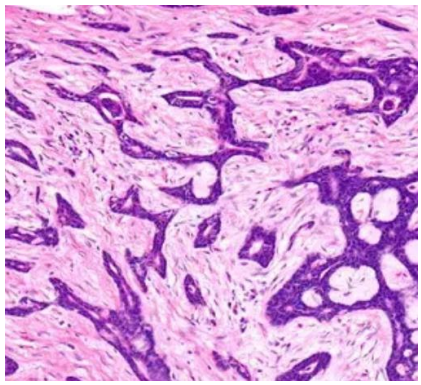
Infiltrative
Best appreciated at low magnification.
Glands infiltrate around other structures and cross boundaries. Appear “haphazard.”



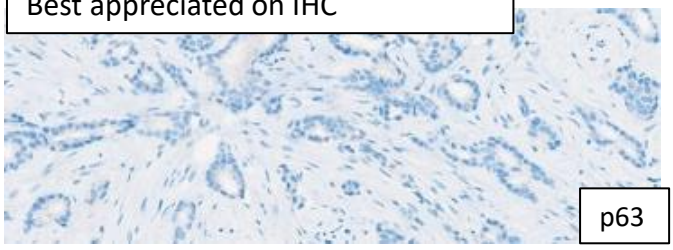
Angulated
Tumor nests have irregular, pointed contours.
Can see single cell infiltration.





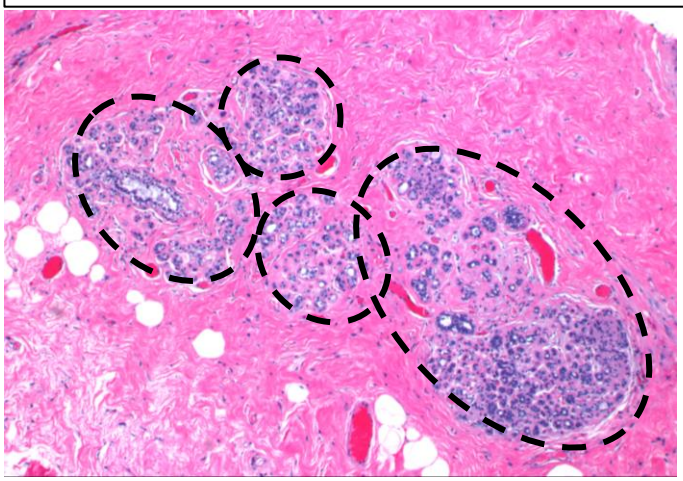


Loss **of Myoepithelial cells**
Best appreciated on IHC

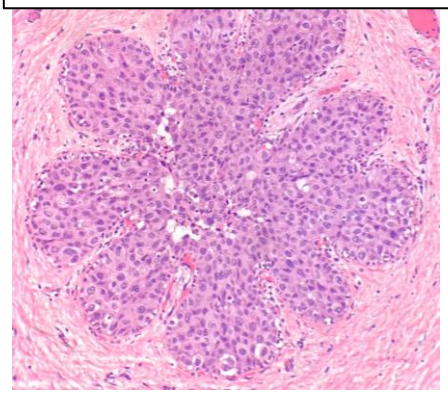


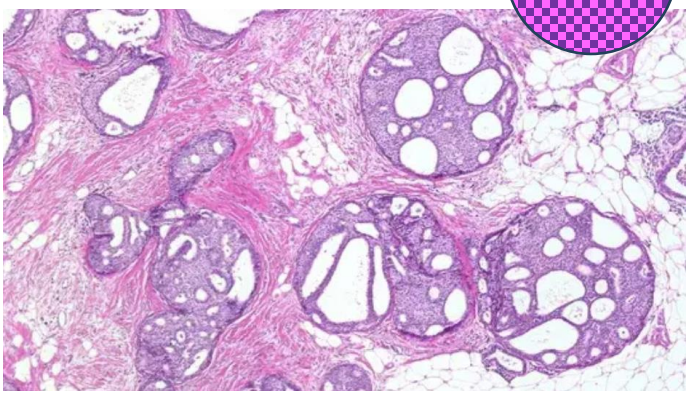
Non-invasive

Well-circumscribed and/or **lobulated**
Cells confined to normal lobular/ductal structures.

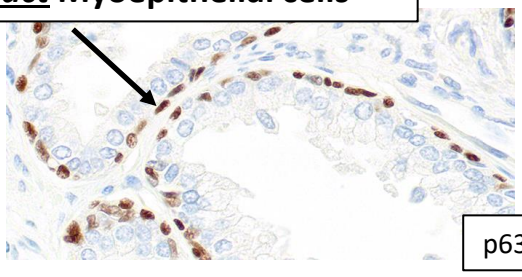


Rounded
Epithelial nests have rounded outlines.





Intact **Myoepithelial cells**



Subtypes

Tumors showing a special histologic pattern in **≥90% of the tumor** are designated as pure special tumor. Otherwise, they are designated as NST, which accounts for the majority of cases, including mixed patterns. Given this requirement, be careful on core biopsies definitely diagnosing a special type—consider using the word "*features.*"

Invasive Breast Carcinoma of "No Special Type" ("NST")

Older (but still often used) name: **Invasive Ductal Carcinoma** (IDC);
Now say: "Invasive Breast Carcinoma (IBC) of no special type (NST)"

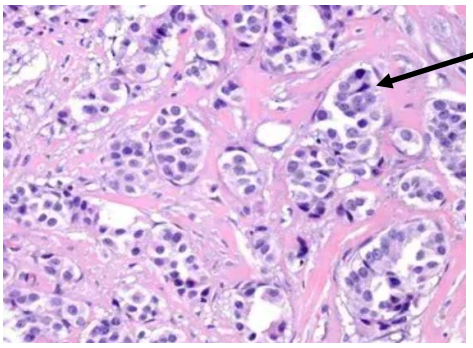
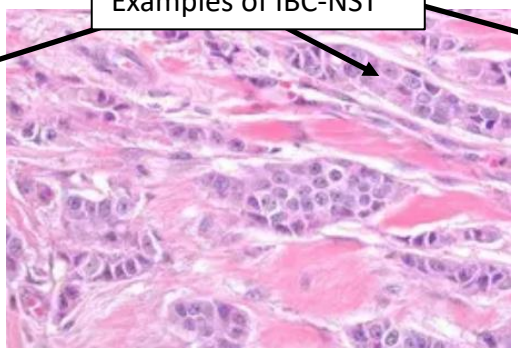
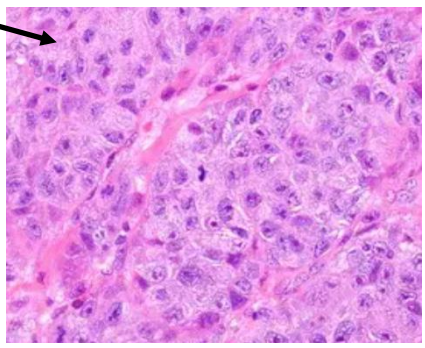
Virtual Slide 2 3 4 5

Invasive carcinoma with features of breast epithelial origin (by morphology or IHC)
A large and **heterogeneous group** that is essentially a "waste basket" including **all cancers that don't fit into one of the specific groups.**

Very variable in appearance! Can form good tubules, or have no glandular differentiation. Be well-circumscribed, or infiltrative, etc… Majority of cases have associated DCIS

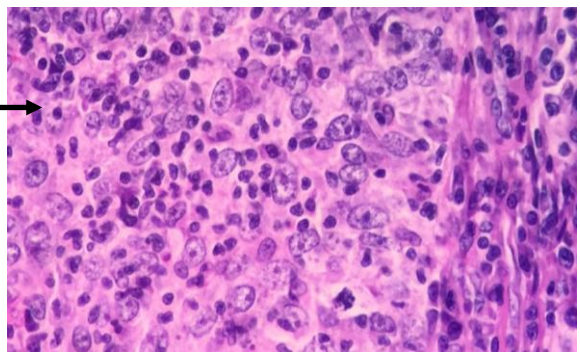
When a special type makes up 10-90% of tumor: report as "mixed" IBC-NST and special subtype

Examples of IBC-NST

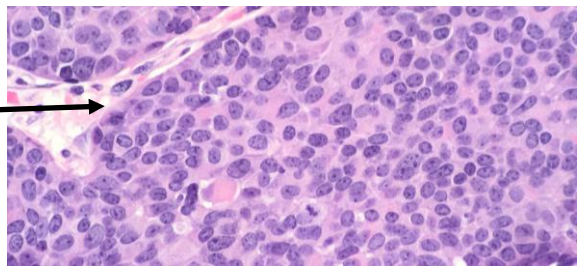




Special morphologic patterns (as opposed to subtypes):

Medullary pattern: Well-circumscribed, high-grade, pushing margins, syncytial architecture, and prominent tumor infiltrating lymphocytes (TIL). Better outcome than other stage-matched high-grade cancers (likely due to TILs). Usually triple-negative (Basal-like). Associated with BRCA1-related tumors.



Invasive carcinoma with Neuroendocrine differentiation: Some degree of neuroendocrine differentiation by immunohistochemistry. Present in 10-30% of tumors. Not currently of any clinical significance (so don't test for it routinely). Usually ER+/HER2-. More common in mucinous and solid papillary carcinomas. Must be sure to consider a much rarer primary neuroendocrine tumor/carcinoma and metastasis



Other rare subtypes: Carcinoma with Osteoclast-like giant cells, Pleomorphic pattern, Choriocarcinomatous pattern, Melanotic pattern, Oncocytic pattern, Lipid-rich pattern, Glycogen-rich clear cell pattern, and Sebaceous pattern

Invasive Lobular Carcinoma *"ILC"*

Invasive breast carcinoma most often composed of **dyscohesive monotonous cells** that are dispersed or arranged in **single-file linear cords with minimal or no stromal reaction.**

~10% of all invasive breast carcinomas.

Due to dyscohesive, single-file growth with little host reaction → very sneaky → often bigger than expected

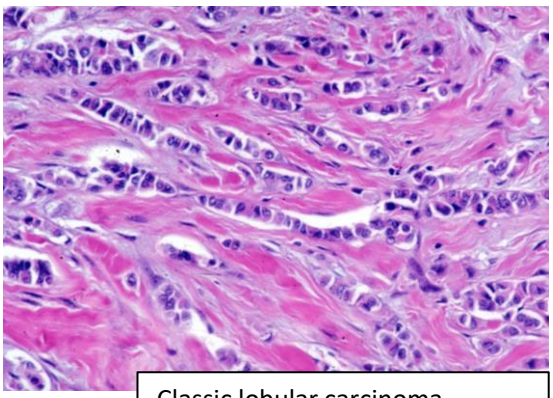
Better short-term outcome, but higher late recurrences.

Pathogeneis: CDH1 mutations→ Loss of E-cadherin function→ cellular discohesion→ single cell infiltration

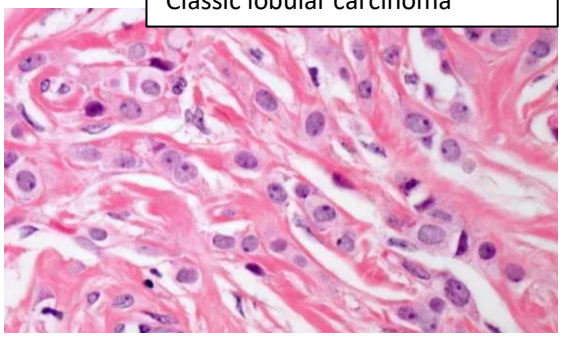
Occasional intracytoplasmic lumina.
Can have signet-ring cells.

***Classic* ILC**: Low-grade nuclei. Few mitoses. Most are Luminal A (**ER and PR positive**, HER2 negative)

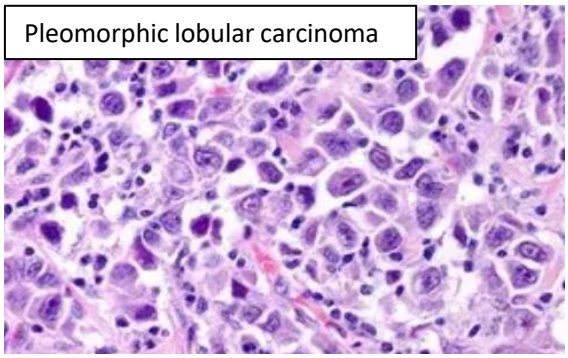
***Pleomorphic* lobular carcinoma:** Same discohesive growth, but with marked nuclear pleomorphism: Grade 3 nuclei (>4x size of lymphocyte = high-grade DCIS cytology). Often ER-, HER2+ or Tripple negative, with complex genetics and a worse prognosis.

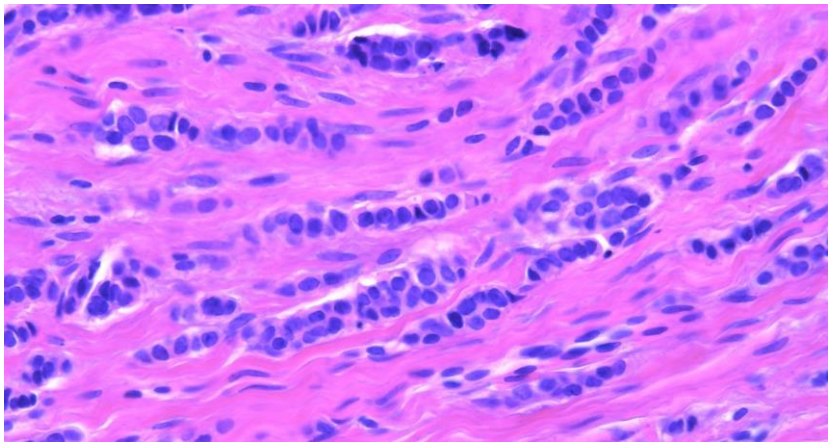


Classic lobular carcinoma



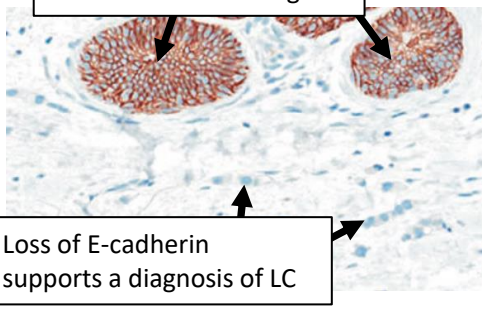
Pleomorphic lobular carcinoma





Virtual Slide 2 3 4

Lobular carcinoma has Loss of E-cadherin complex function: Immunohistochemical stains can confirm loss of E-cadherin and are therefore helpful in confirming the diagnosis. However, intact E-cadherin doesn't exclude the diagnosis of ILC—up to 25% of ILC expresses Ecad (sometimes it is present/positive, but decreased or just not functional). Morphology is most important (more on this on the next page!).



IHC Stain	Normal Epithelium	Lobular Carcinoma	Carcinoma, No Special Type
E-Cadherin	Membrane staining	Negative	Membrane staining
P120 catenin	Membrane staining	Cytoplasmic	Membrane staining
β-catenin	Membrane staining	Absence of membrane staining	Membrane staining

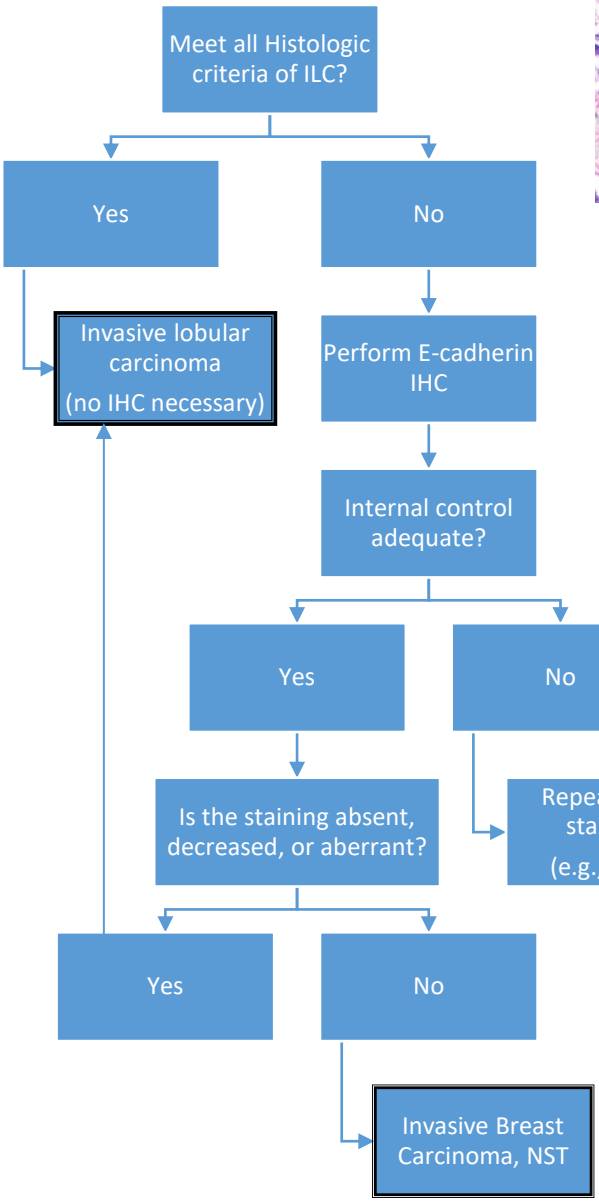
Do I *need* to do an E-Cadherin stain do diagnose lobular carcinoma?

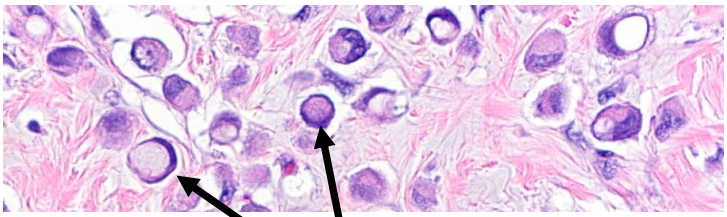
TLDR: If it's morphologically perfect→ No.
If it's not perfect→ Yes, you probably should

Morphology *(is still king)*

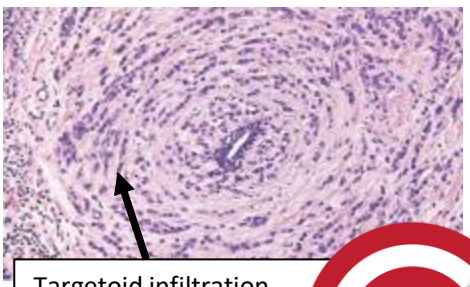
Histologic criteria for diagnosis of classic invasive lobular carcinoma (ILC):

1. Loss of cell cohesion
2. Linear and/or single cell infiltration
3. Circumferential (targetoid) infiltration of cells around ducts (if present)
4. Infiltration of fat without stromal reaction (if fat present)
5. Little host reaction or disturbance of architecture
6. Uniform, round and monomorphic nuclei with a thin rim of cytoplasm
7. Low mitotic score
8. Intracytoplasmic vacuoles ("targetoid cells") or signet ring cells
9. Presence of ALH or LCIS

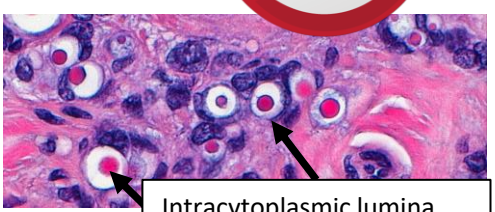




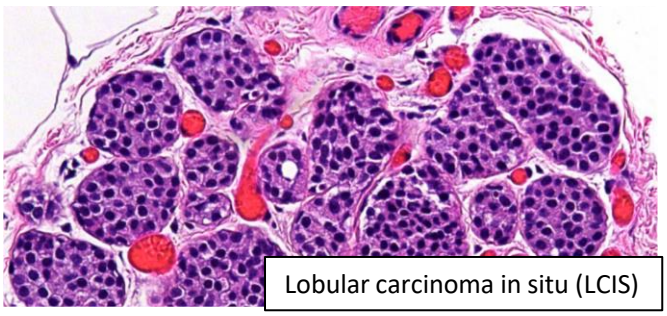
Signet ring cells



Targetoid infiltration around a duct



Intracytoplasmic lumina *(also targetoid)*



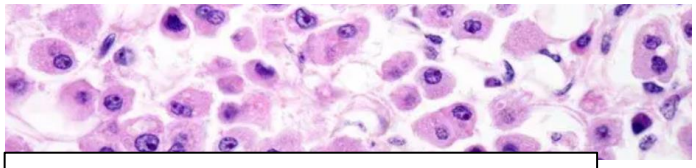
Lobular carcinoma in situ (LCIS)

Modified from: WHO Classification of Tumours of the Breast, 6th Edition.

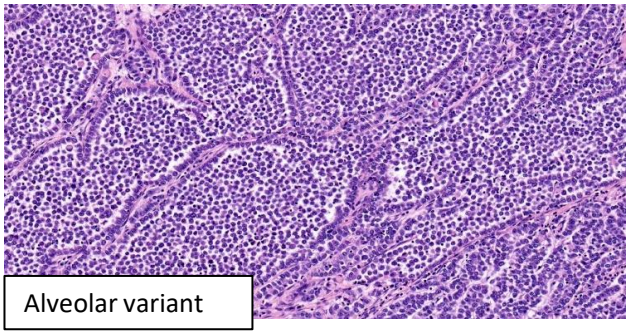
Other Lobular carcinoma variants to know:

ILC can show special architectural patterns – with the most frequently reported being solid, alveolar, and trabecular – and/or special cytological features, including signet ring–cell forms, apocrine, histiocytoid, and pleomorphic. The prognostic relevance of these patterns/appearances is unclear and is likely superseded by histological grade and biomarker profile.

"Tubulolobular carcinoma"—a lobular carcinoma with areas of tubule formation (and loss of E-cadherin in both parts).



Histiocytoid variant
Bland, small cells resembling histiocytes—scary!



Alveolar variant

Tubular Carcinoma

Low-grade invasive carcinoma composed **ovoid or angular tubules with open lumina, lined by a single layer of epithelial cells with small uniform nuclei and low mitotic activity (grade 1)**

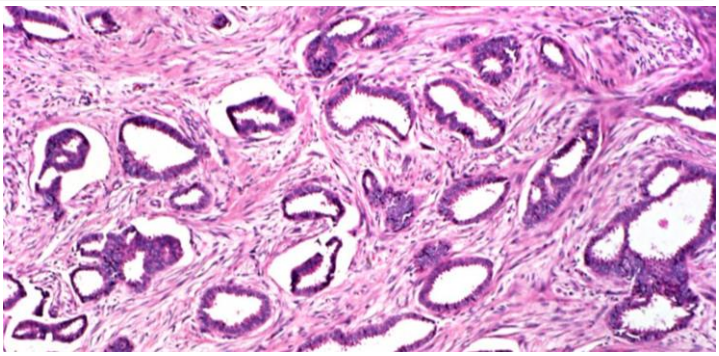
Often old women. ~1.5% of Invasive carcinomas.

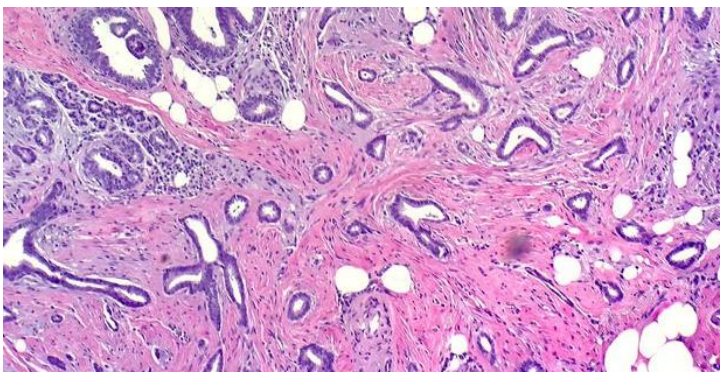
Luminal A subtype (ER and PR positive, HER negative)

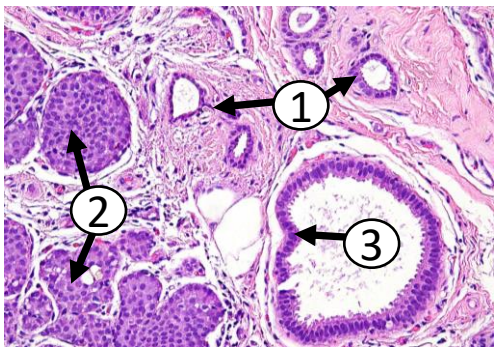
Embedded within a fibrous or fibroelastotic desmoplastic stroma→ Stellate lesion.

>90% of tumor must have this morphology (as is the rule for all special types)

Excellent prognosis ☺







"Rosen's Triad"

= 1) Tubular carcinoma + 2) LCIS + 3) Columnar cell lesions
These three lesions are well-known to occur together, so if you see two of them, look for the third.
All often ER+

Invasive Cribriform Carcinoma

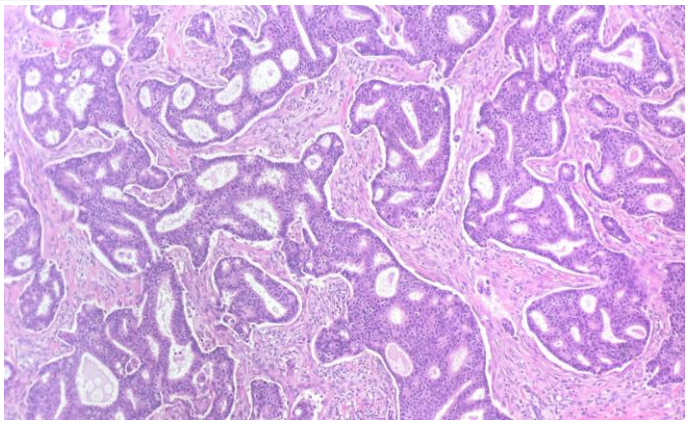
Invasive carcinoma composed of **cribriform islands of epithelial cells with uniform small round nuclei and low mitotic activity (grade 1).**

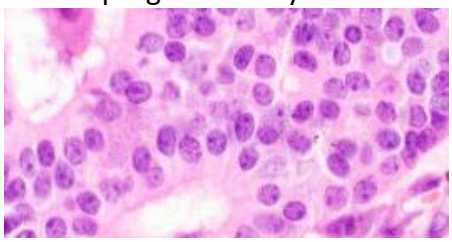
Luminal A subtype (ER and PR positive, HER negative)

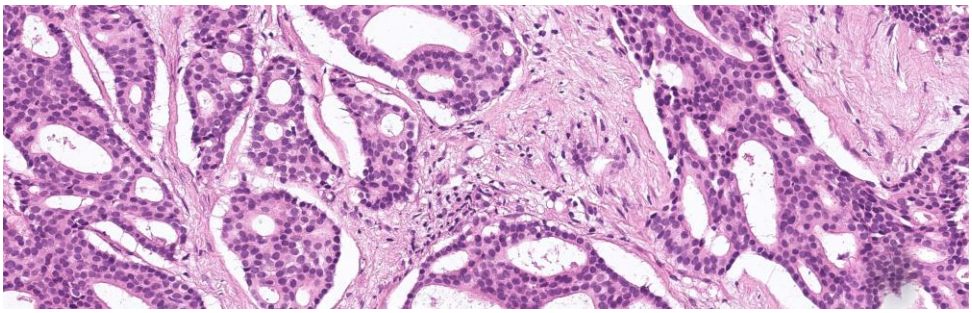
Well-defined rounded to angulated cribriform spaces formed of fused glandular formations (like cribriform DCIS), but without surrounding myoepithelial cells, set in desmoplastic stroma.

Low nuclear grade.

Good prognosis. Very rare







Mucinous Carcinoma

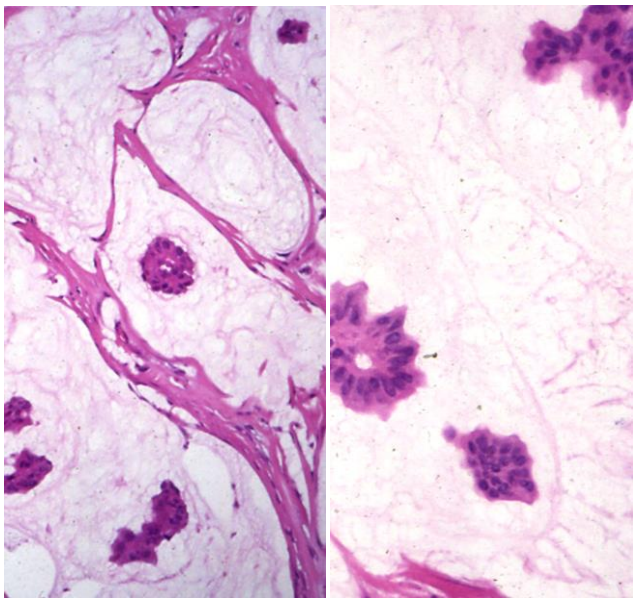
Invasive breast cancer characterized by **clusters of epithelial cells <u>suspended</u> in pools of <u>abundant</u> extracellular mucin**
(and with no features of other IBC types).

Luminal A molecular type (ER & PR +, HER -)
<u>Low to intermediate nuclear grade.</u>

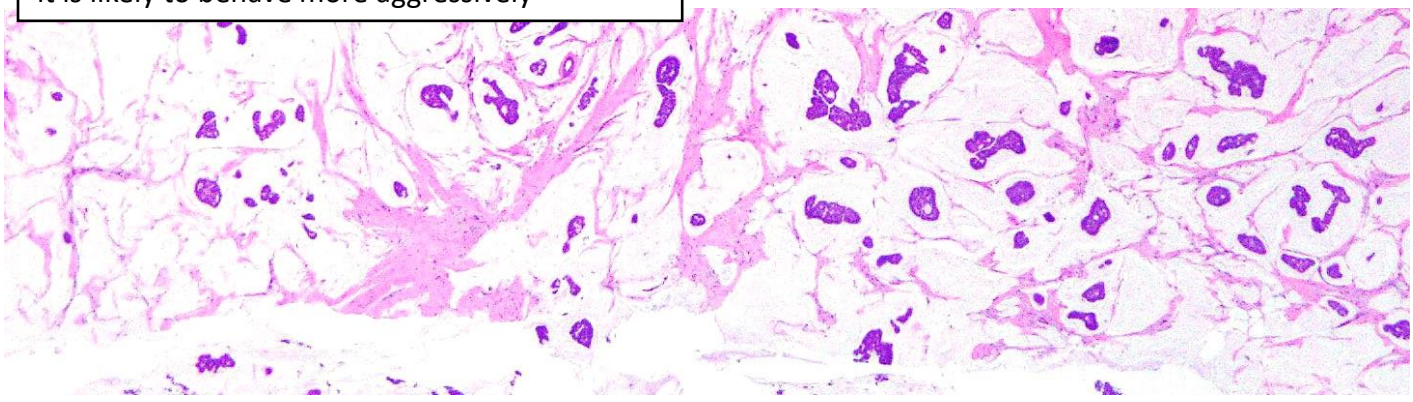
Uncommon.
Well-circumscribed grossly (mimicking benign process).
Frequent neuroendocrine differentiation.

Good prognosis.

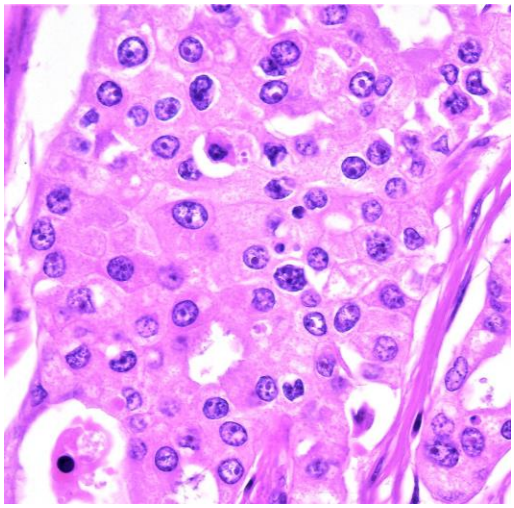
If the tumor is high grade nuclei or HER2+, do NOT use this Dx! Instead, it should be diagnosed as IBC-NST with mucin production, as it is likely to behave more aggressively



Virtual Slide 2



Invasive Apocrine Carcinoma



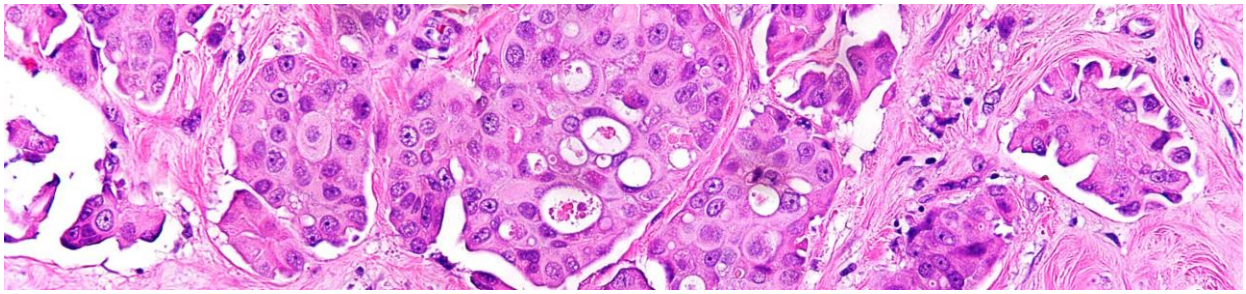
An invasive carcinoma with **large cells with abundant eosinophilic, granular cytoplasm** and large nuclei with prominent nucleoli (resembling apocrine sweat glands) *(and with no features of other IBC types, like lobular).*

Desirable: **GCDFP-15 and Androgen receptor (AR) positivity Most are ER/PR negative.**

Often mostly solid growth with high mitotic index→ Grade 2 or 3

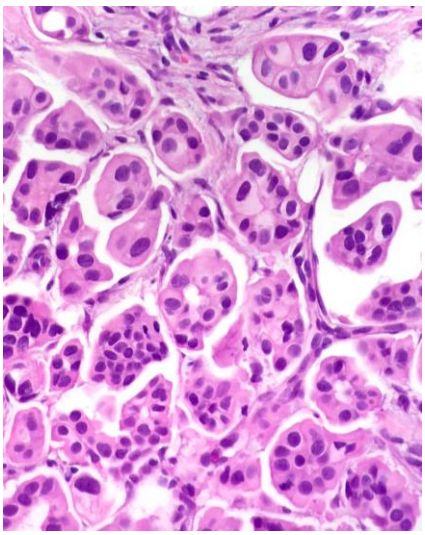
Variable clinical prognosis.
Androgen deprivation therapy a potential treatment option.

If ER+→ consider "apocrine features"



Invasive Micropapillary Carcinoma

Virtual Slide



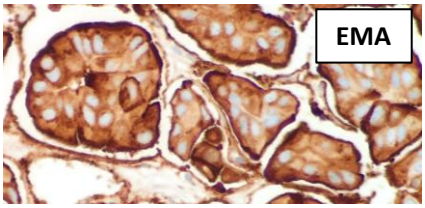
Invasive breast carcinoma composed **of small, hollow, or morula-like clusters of malignant cells, surrounded by clear spaces with inside-out, reversed growth pattern.**

Pure form is uncommon, often mixed with other patterns.
Luminal A or B (ER and PR +, HER – usually)

No fibrovascular cores (as is the case with all micropapillary tumors!)

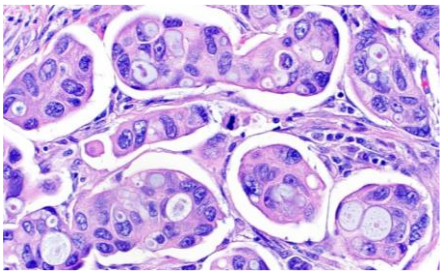
Characteristic empty spaces around cells with delicate stromal framework.

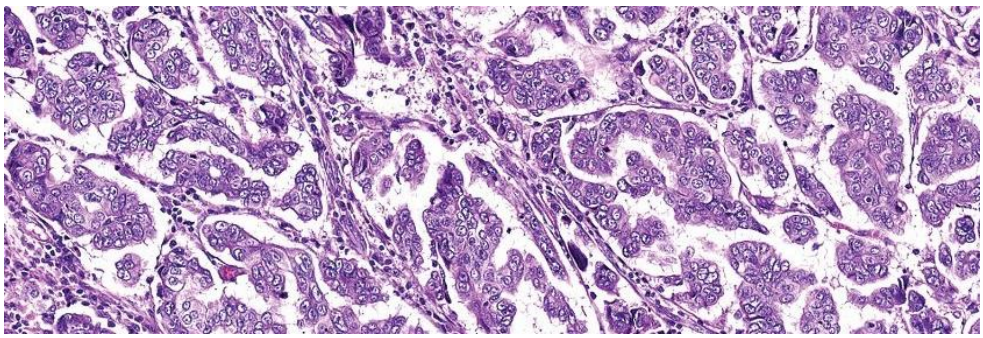
Show **reverse polarity**→ Apical surface faces *outward* stroma (can see on **EMA stain** where it stains the outside more strongly)



Often eosinophilic, granular cytoplasm and intermediate to high-grade nuclei. Cuboidal to columnar cells.

Significantly more lymphovascular invasion and positive lymph nodes, but when stage-matched with NST tumors, not significantly worse survival.





Metaplastic Carcinoma

Invasive Breast Cancers with differentiation of epithelium towards squamous cells and/or mesenchymal elements.

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

Heterogeneous group of tumors, including both low-grade and high-grade tumors with very different prognoses. I like to think of these tumors in these two main groups:

Low-grade	High-grade
Low recurrence risk (no/low metastatic risk)→ *treated with surgery*	**High metastatic risk** → *treated with surgery and chemotherapy*
Low-grade Adenosquamous carcinoma Fibromatosis-like metaplastic carcinoma	High-grade metaplastic carcinomas Spindle cell carcinoma Pure squamous cell carcinoma

IHC: Vast majority **do not express ER, PR, or HER2** (Triple Negative).
However, they do (usually) express some epithelial markers.
Always order a panel on breast spindle cell tumors as staining can be variable!
(+) p63, HMWCKs (e.g., CK5/6, 34βE12), CK AE1/AE3
(-) CK7, CD34,
(+/-) Myoepithelial markers (in tumor cells; e.g. SMA, CD10), Desmin, β-catenin

Pro Tip: CD34 pretty much never stains metaplastic carcinoma, so if it's CD34+, it's likely not metaplastic carcinoma and is instead a fibroepithelial lesion or soft tissue tumor.

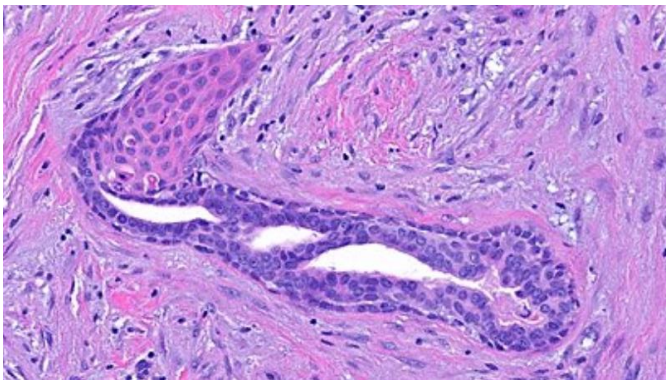
Molecular: Frequent TP53, PIK3CA, and WNT pathway mutations. May be derived from late dedifferentiation or basal-like stem cells.

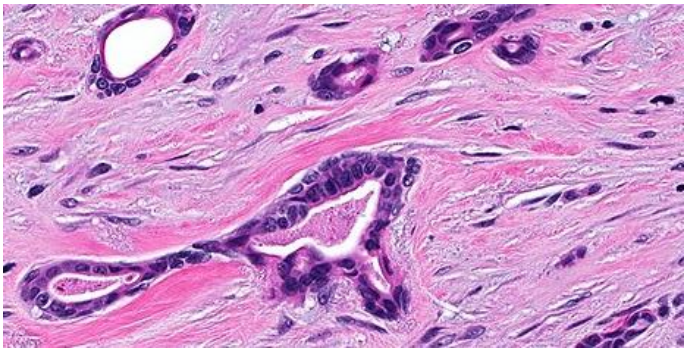
Clinical: Much fewer LN metastases (all types of metaplastic carcinoma).

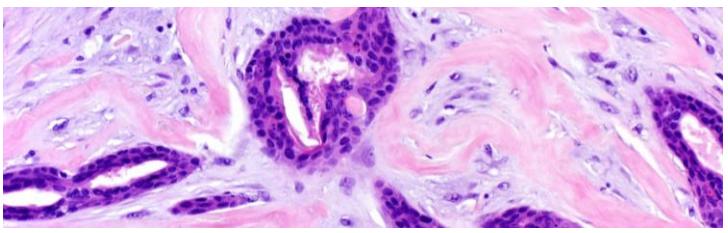
Low-grade Adenosquamous Carcinoma

Well-developed glandular and tubular structures, admixed *with* **nests of squamous cells** that may display squamous pearls and/or squamous cyst formation, **arranged in a haphazard, infiltrative pattern** in a spindle cell background.
Cytological atypia is mild and mitotic activity is low.
Sometimes associated "cannon ball" lymphoid aggregates. Good prognosis.

Inconsistent IHC staining, with frequent patchy and biphasic staining with squamous and myoepithelial markers—be careful not to confuse with a sclerosing lesion! PMID: 22446941

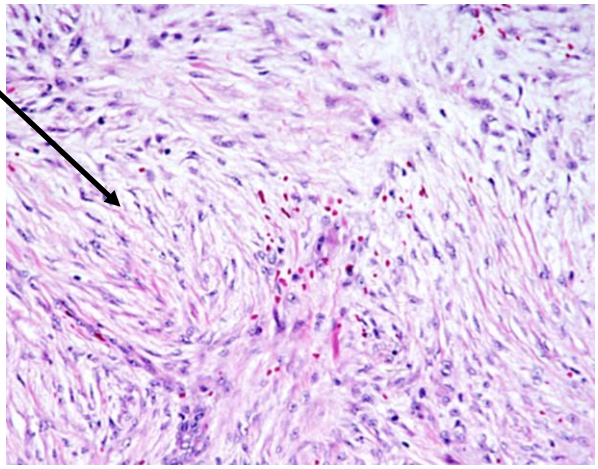






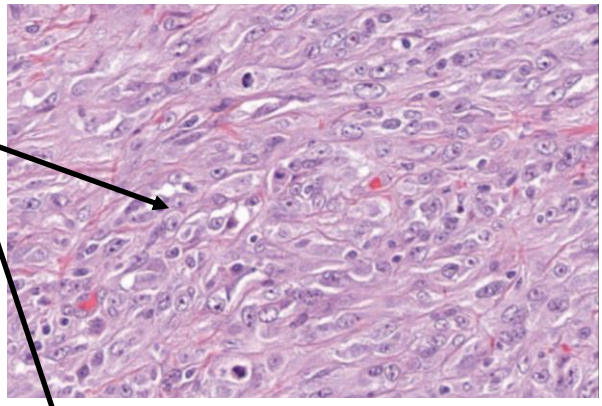
Fibromatosis-like Metaplastic Carcinoma

Bland spindled cells with pale eosinophilic cytoplasm and slender nuclei in stroma with variable collagen. Only mild nuclear atypia. Finely granular chromatin. Often arranged in fascicles.
Usually, gradual transition from plump cells to the spindle cells. Almost always p63-positive; keratins are always expressed, but it can be focal restricted to the/epithelioid cells. Good prognosis.



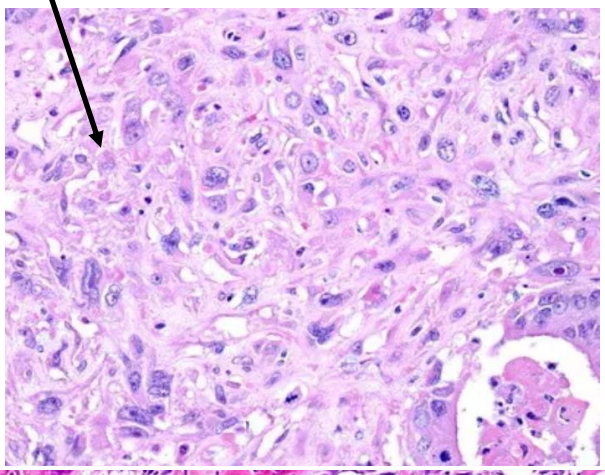
Spindle Cell Carcinoma

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.



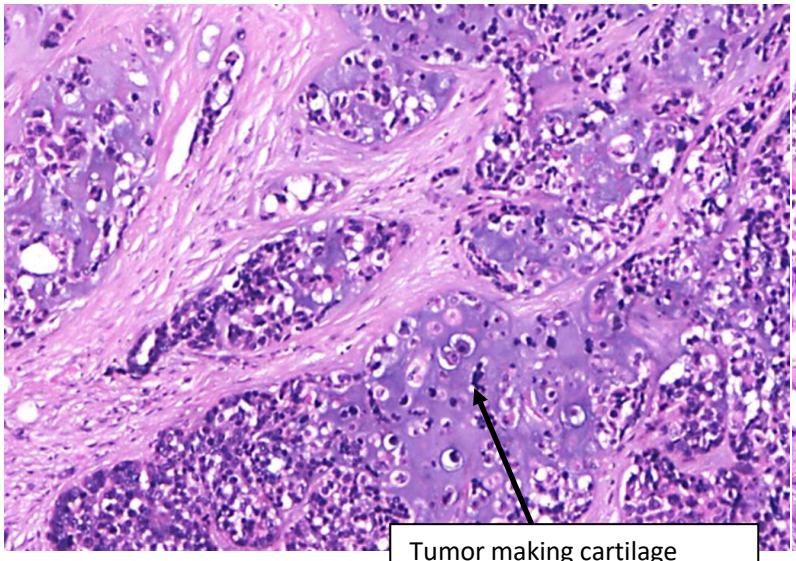
Squamous Cell Carcinoma

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

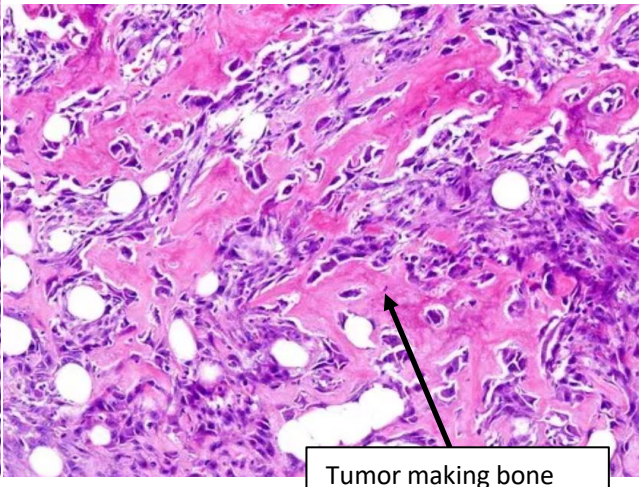


Metaplastic Carcinoma with Heterologous Mesenchymal Differentiation

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).



Tumor making cartilage



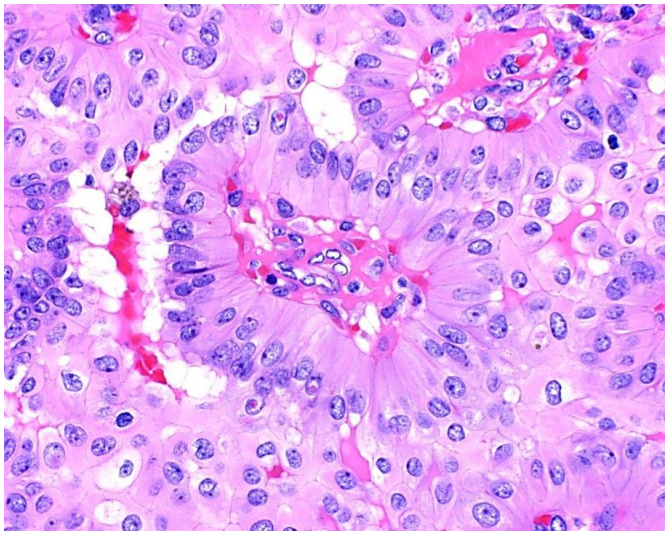
Tumor making bone

Rare Types

All of these tumors are usually triple negative, but usually have a **good prognosis**.

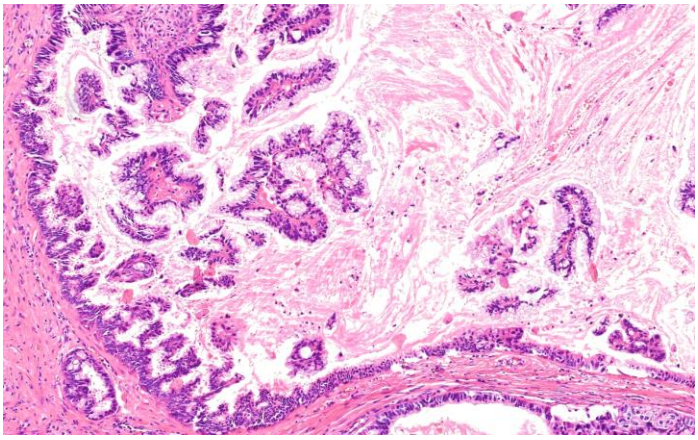
Tall Cell Carcinoma with Reverse Polarity:
Invasive breast carcinoma with the neoplastic cell nests arranged in a predominantly solid papillary pattern, composed of columnar epithelial cells showing reversed polarity of the nuclei.
Eosinophilic cytoplasm. Nuclear grooves and inclusions. (Resembles tall cell papillary thyroid carcinoma).

Desirable: Expression of both low- and high-molecular-weight cytokeratins; a triple-negative or weakly hormone receptor–positive phenotype.
Often (+)Calretinin, GATA3; (-)TTF1, thyroglobulin
Frequent IDH2 p.Arg172 hotspot mutations.



Mucinous cystadenocarcinoma
Extremely rare.
Invasive breast carcinoma with large cystic spaces containing mucin and lined by atypical columnar cells with intracytoplasmic mucin. Resembles pancreatobiliary, ovarian, or gastrointestinal tumors.

Desirable: ER-negative and PR-negative (typically); adjacent DCIS; CK7-positive, CK20-negative, and CDX2-negative



Salivary gland tumors

Most salivary gland tumors can occur in the breast, where there are usually relatively more indolent than their head and neck counterparts. They are often triple-negative.

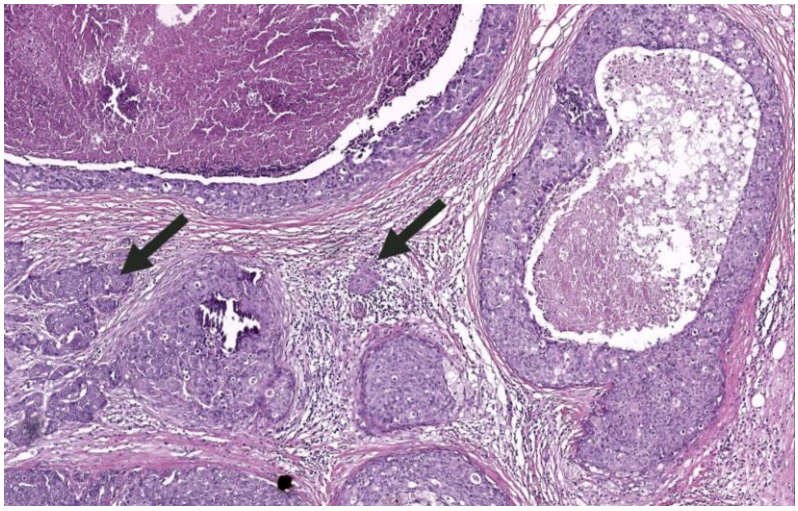
Acinic Cell-like Carcinoma: Invasive breast carcinoma composed of granular and clear epithelial cells, some of which contain intracytoplasmic zymogen granules, with various architectural patterns ranging from microglandular to solid. IHC: (+) S100, EMA, lysozyme, and α1-antichymotrypsin. Triple negative. Complex genetics (TP53 mts). Likely arises from Microglandular adenosis. Intermediate behavior.

Adenoid Cystic Carcinoma: An invasive carcinoma composed of epithelial and myoepithelial cells arranged in tubules, cribriform, and solid patterns associated with basophilic matrix and basement membrane material. Frequent MYB-NFIB fusions. Triple negative, but generally good prognosis (unlike in head and neck), cured by surgery alone. Virtual Slide 2

Secretory Carcinoma: Polygonal tumor cells with eosinophilic granular or vacuolated cytoplasm and round to oval nuclei arranged in microcystic/honeycomb, solid, tubular, or papillary growth patterns with intracytoplasmic and extracellular secretions. Frequent ETV6-NTRK3 fusions. Triple negative. IHC: (+) S100, GATA3, SOX10, Mammaglobin, PanTRK, MUC4. ER low or negative. Generally indolent.

Mucoepidermoid Carcinoma: Composed of a mixture of 1) mucinous cells, 2) epidermoid/squamoid cells, and 3) “intermediate” cells, arranged in a solid and cystic pattern. Absence of true keratinization. Frequent MAML2 fusions. Triple negative. Good prognosis if low-grade.

Microinvasive Carcinoma



Invasive breast carcinoma **≤1mm in size**
Usually **adjacent to a dominant area of DCIS**, often high-grade DCIS.
Stage as **pT1mi**

Earliest recognizable form of invasive carcinoma

- Invasion beyond myoepithelium
- Small, angulated clusters of tumor cells infiltrating stroma
- Often desmoplastic stromal changes

Better prognosis than larger invasive tumors

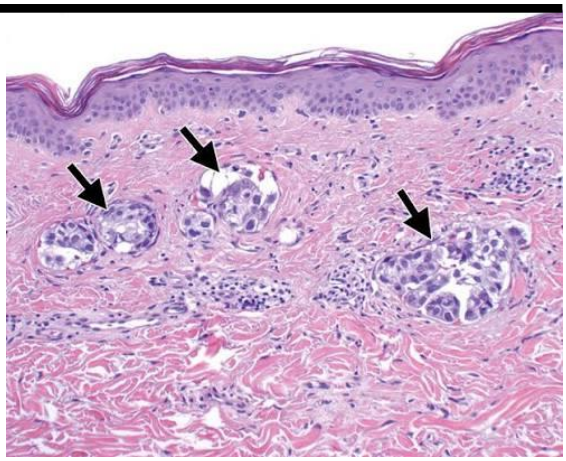
Often multifocal→ if any single invasive focus is larger than 1 mm→ invasive carcinoma (not micro)
Pragmatically, deposits < 5 mm apart are best considered as a single invasive tumor deposit (as opposed to multiple separate foci)

Be cautious diagnosing this on core biopsy, as could be more invasion on excision. Often good to get levels to exclude larger foci of invasion

Clinical **types of Cancer**

These are types of cancer that are defined by certain clinical metrics (not by histology), but are important to know about nonetheless.

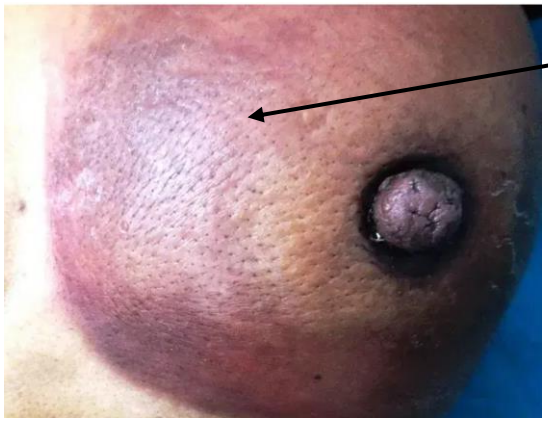
Inflammatory Carcinoma



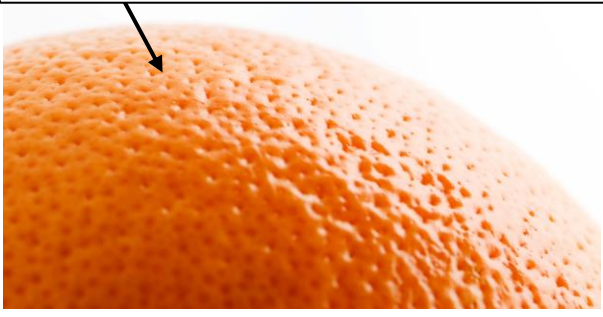
Clinically defined by**: "p'eau d'orange" diffuse erythema and edema involving one-third or more of the breast.**

Staged by definition as **pT4d**

Histologically, this manifests as cancer in the dermal lymphatic spaces, but this finding alone is insufficient to make the diagnosis (although it is still a poor prognostic indicator)

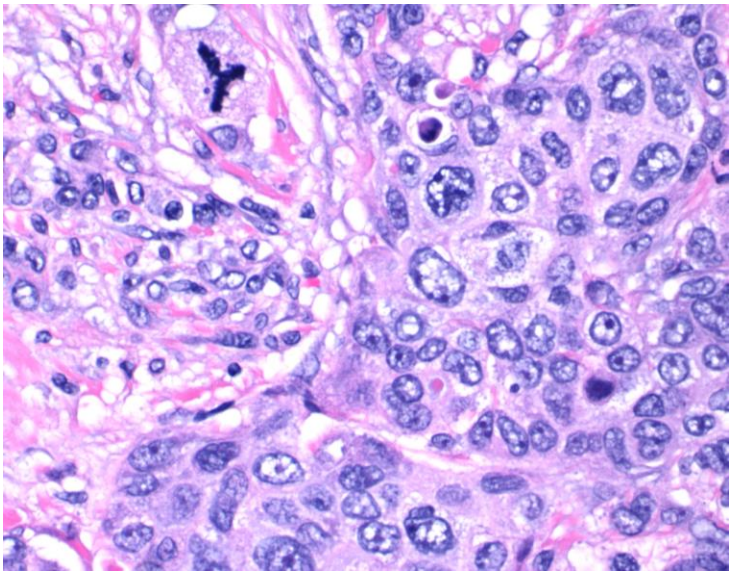


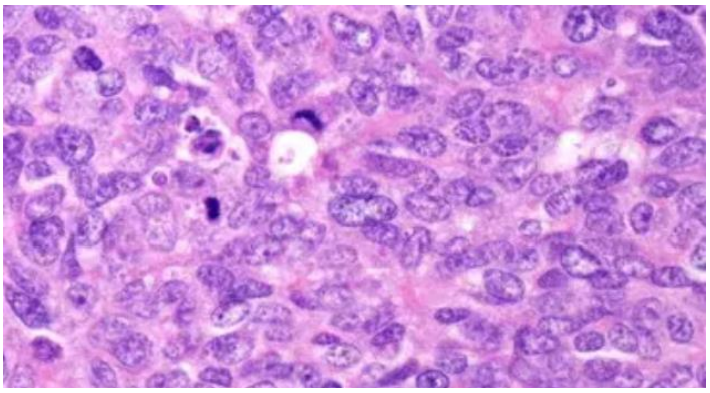
"p'eau d'orange" refers to the cutaneous changes caused by lymphedema secondary to widespread carcinomatous emboli within dermal lymphatic channels.



Tripple Negative Breast Cancer

ER/PR- (<1%) and HER2- *aka "**TNBC**"*





About 15% of breast cancers.
Most are High-grade "No special type," and "Basal-like."→ Often treated with Neoadjuvant therapy.

"Basal-like" cancers express basal/myoepithelial markers (e.g., CK5/6). They have complex genetics with frequent TP53 mutations.
Often younger and more often African-American.
Associated with BRCA1 mutations.

Usual morphology:
Solid growth,
high nuclear grade,
lots of mitoses,
lots of tumor infiltrating lymphocytes (**TILs**).

Several "special types" of cancer are also TNBC:
Metaplastic carcinoma, Apocrine carcinoma, Tall cell carcinoma with reverse polarity, Salivary gland-type tumors

When should I question a TNBC diagnosis?

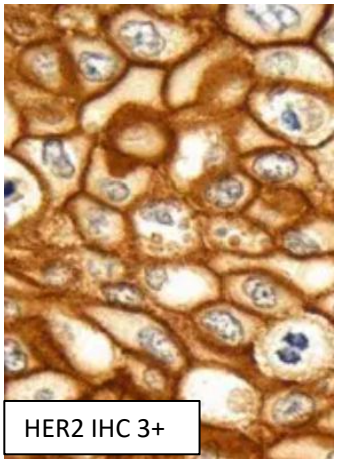
1. **Unusual morphology** (Not "basal-like" with solid growth, high nuclear grade, and TILs)
2. **No in situ component**
3. **History of other malignancy**

If there is a question as to if this is TNBC, consider getting an IHC panel to exclude lymphoma or a metastasis (e.g., melanoma, lung cancer, etc…).

Possible panel: CK AE1/AE3, GATA3, TRPS1, SOX10 (often, all of these are positive in TNBC)

HER2-Positive Breast Cancer

Driven by **HER2 overexpression** usually due to *ERBB2* amplification
Usually, intermediate to high histological grade "NST" cancers.
Very pleomorphic nuclei and more-abundant eosinophilic cytoplasm (vaguely apocrine appearance).
Frequently associated with high-grade comedo DCIS.
Numerous genomic gains and losses, along with frequent mutations in TP53
Ki-67 proliferation rates in the 20–60% range.
Treated neoadjuvantly with HER2-targeted therapies→ Ok prognosis.
(Prior to HER2-targeted therapies, these tumors had the worst prognosis of all breast cancers)



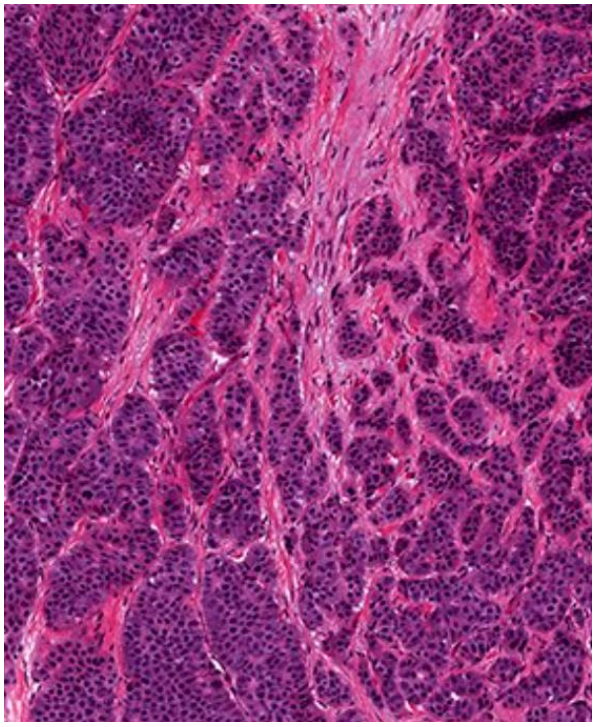
HER2 IHC 3+

Neuroendocrine Lesions

Neuroendocrine (NE) breast lesions are hard! They have somewhat poorly-defined criteria.
As there is currently no conclusive clinical relevance of neuroendocrine differentiation, routine staining of IBC-NST for neuroendocrine markers is not recommended. Only do NE stains if it *looks* NE on H&E.

Generally, to consider these NE diagnoses below, you want to see strong, diffuse staining with NE markers, including Synaptophysin, Chromograning, and/or INSM1

Neuroendocrine Tumors



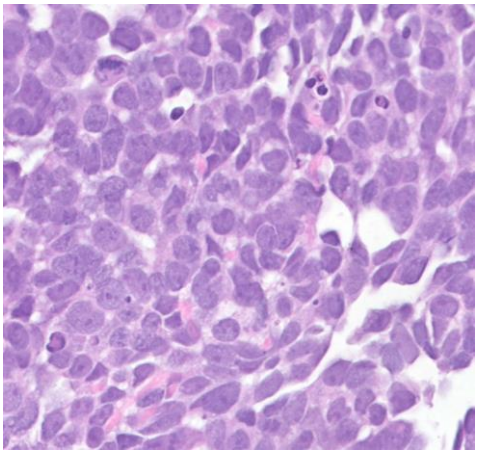
Primary NETs of the breast are extremely rare (and may even not exist according to some!)

Can be diagnosed only if has the typical morphology of a NET, similar to other anatomical sites, and display strong, diffuse expression of neuroendocrine markers.
Solid, nesting, or trabecular architecture.
Monomorphic polygonal cells.
Round, regular nuclei with dispersed, granular, salt-and-pepper chromatin
It is essential that metastatic NET, solid papillary carcinoma, and invasive carcinoma NST with neuroendocrine differentiation have been excluded.
Desirable: coexisting ductal carcinoma in situ.

Still grade using Nottingham grading system.
Treated similar to IBC-NST and have similar outcomes.

IHC: Low Ki67; (+)ER, GATA3, TRPS1, SOX10;
(+/-) AR, GCDFP-15,
(-)CDX2, TTF1,

Small Cell Carcinoma



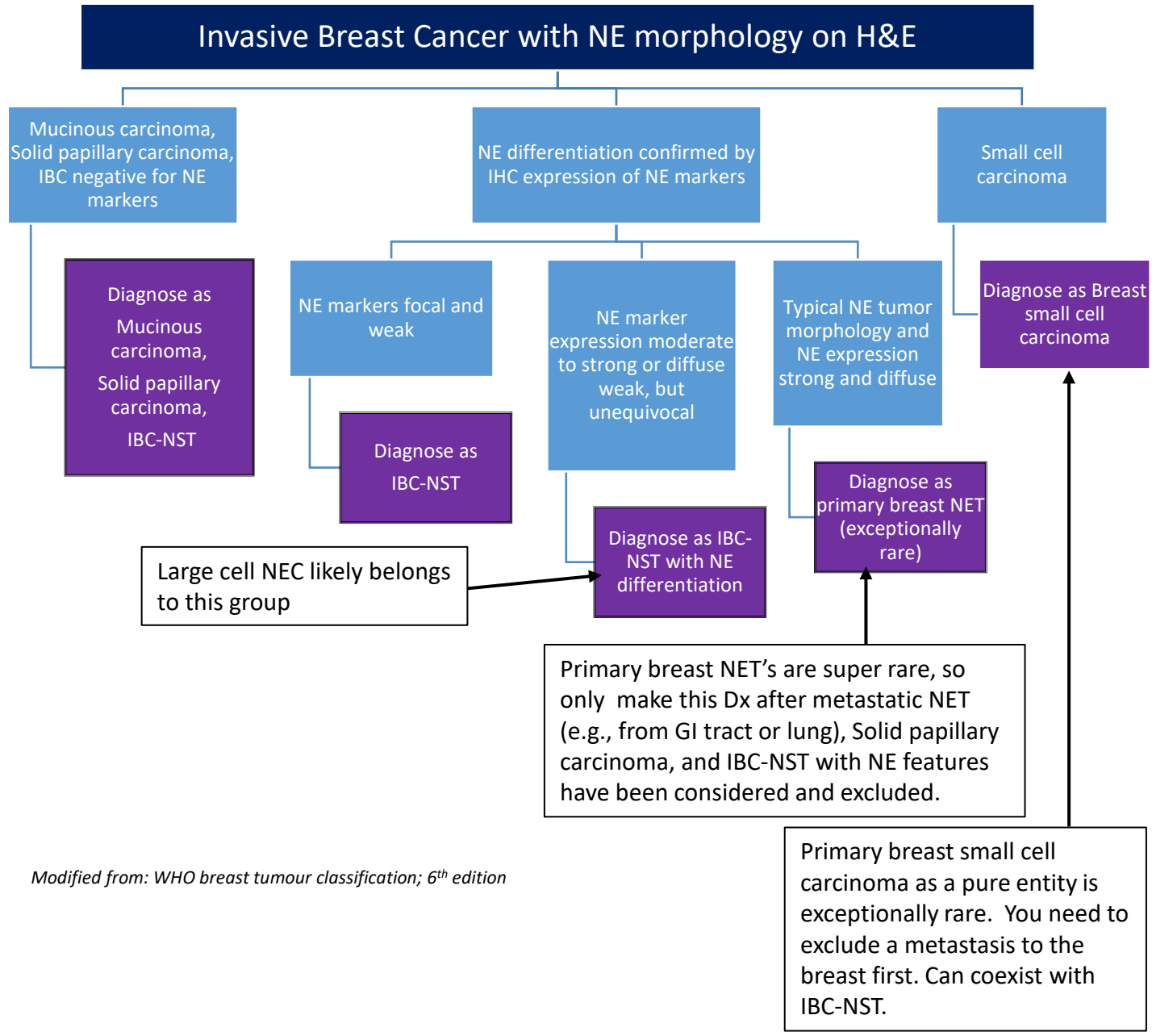
Identical to in the lung! Need to exclude a metastasis, which is best done clinically.

Densely packed, fairly uniform, small, dark hyperchromatic cells.
High N:C ratio, scant cytoplasm, inconspicuous nucleoli.
High mitotic and proliferation indexes;

Can be mixed with other types of breast cancer or DCIS.

Large Cell Neuroendocrine Carcinoma

Large cell NEC (LCNEC) in the breast is best classified as invasive breast carcinoma of no special type (NST) with neuroendocrine differentiation.



Modified from: WHO breast tumour classification; 6th edition

Metastases to the Breast

The most common non-breast primary neoplasm to involve the breast is **lymphoma**.
The most common solid tumor to metastasize to the breast is **melanoma**.

Important times to consider a metastasis:

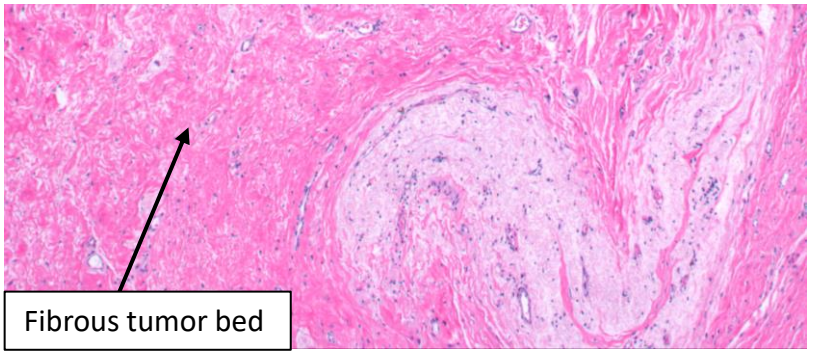
- High-grade, triple-negative tumor that lacks an associated in situ component
- Low- to intermediate-grade adenocarcinoma that is ER-negative.
- Cytoplasmic pigment (consider melanoma specifically)
- Papillary and micropapillary architecture in an invasive tumor (consider metastatic HG serous of tubo-ovarian origin)

Post-therapy findings

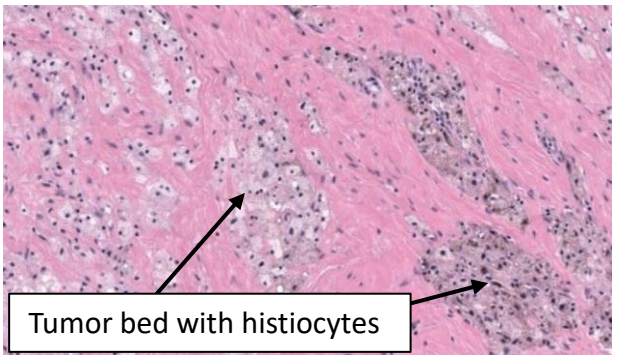
Some tumors (particularly big and/or high-grade ones) are treated with **Neoadjuvant Therapy (NAT)**. The staging of these specimens is challenging, so I'll direct you to the CAP protocol for that.

Here are some important things to be able to recognize and know though:

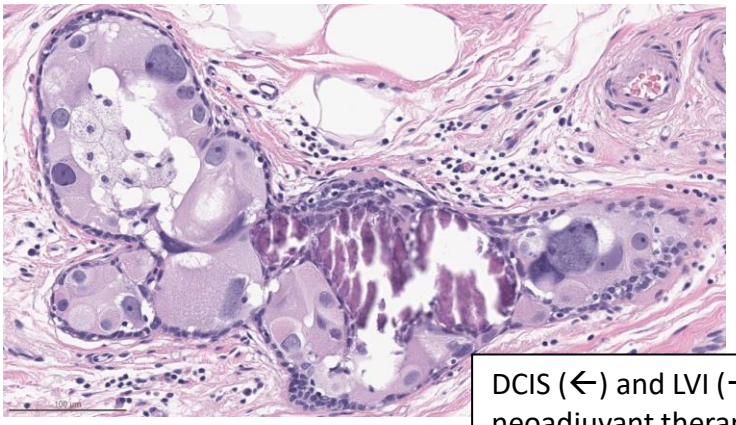
The **tumor bed** should *not* look like normal breast.
Look for: dense fibrosis/elastosis, histiocytes, lymphocytes, hemosiderin-laden macrophages, calcifications, fewer epithelial elements, prominent vessels.
With complete response, this is all you see.

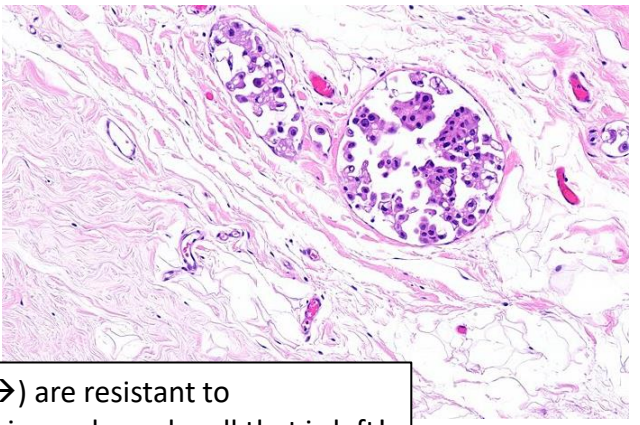


Fibrous tumor bed

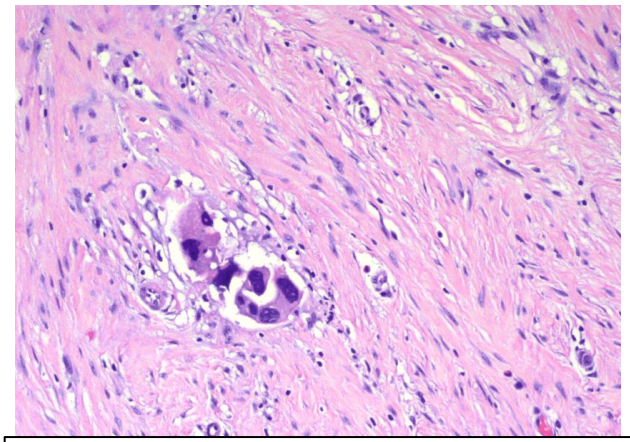


Tumor bed with histiocytes

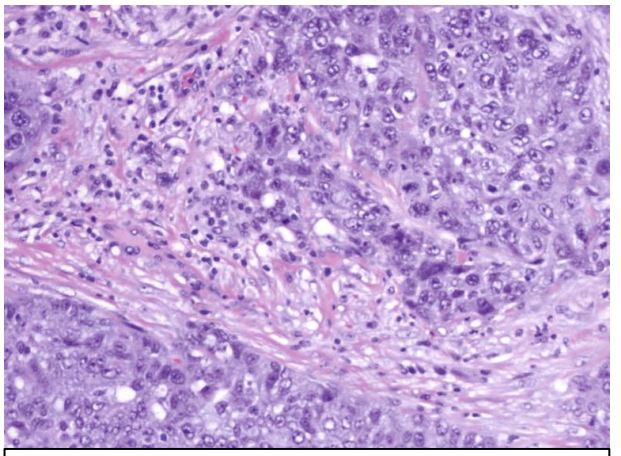




DCIS (←) and LVI (→) are resistant to neoadjuvant therapies and may be all that is left!



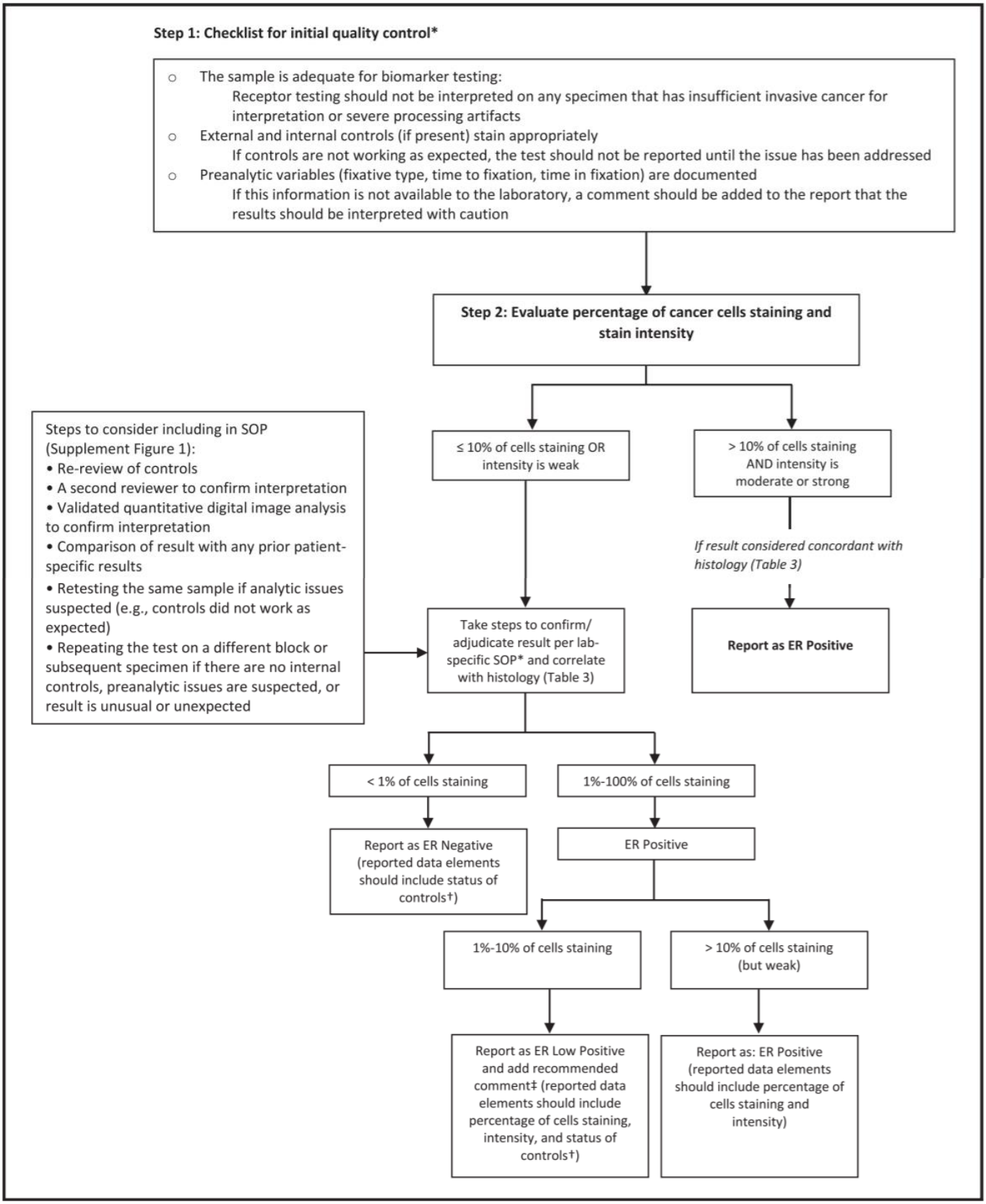
Partial response: the tumor shows decreased cellularity and may be present as multiple foci of invasion scattered over a larger tumor bed.



No definite response: there is extensive residual tumor

Prognostic Markers Testing

Estrogen Receptor (ER)



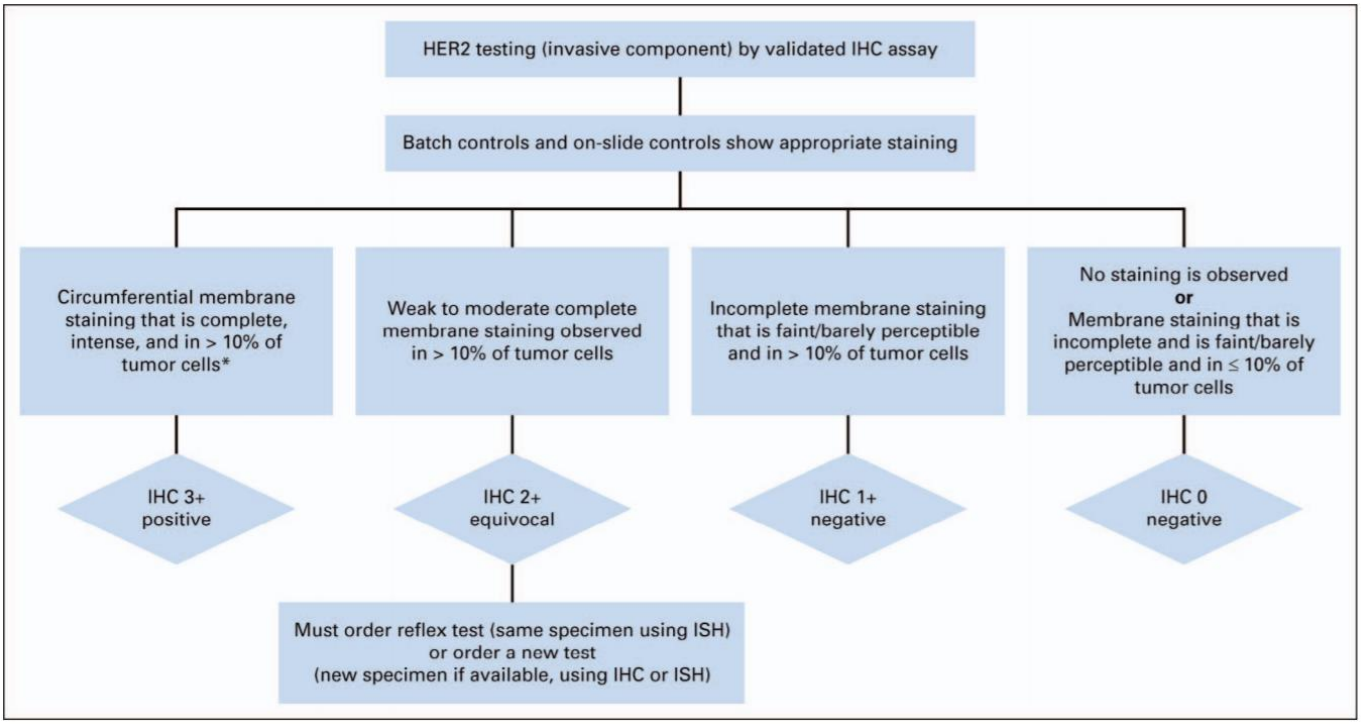
From: Allison KH et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med. 2020 May;144(5):545-563.

Table 3. Invasive Breast Cancer Histopathologic Concordance With ER Staining	
Highly Unusual ER-Negative Results	**Highly Unusual ER-Positive Results**
Low-grade invasive carcinomas of no special type (also known as invasive ductal carcinoma)	Metaplastic carcinomas of all subtypes
Lobular carcinomas (classic type)	Adenoid cystic carcinomas and other salivary gland–like carcinomas of the breast
Pure tubular, cribriform, or mucinous carcinomas	Secretory carcinoma
Encapsulated papillary and solid papillary carcinomas	Carcinomas with apocrine differentiation

NOTE. If a result is considered highly unusual/discordant, additional steps should be taken to check the accuracy of the histologic type or grade as well as the preanalytic and analytic testing factors. This workup may include second reviews and repeat testing. If all results appear valid, the result can be reported with a comment noting that the findings are highly unusual and testing of additional samples may be of value to confirm the findings.

From: Allison KH et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med. 2020 May;144(5):545-563.

HER2



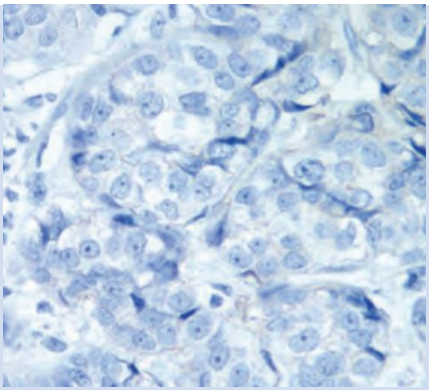
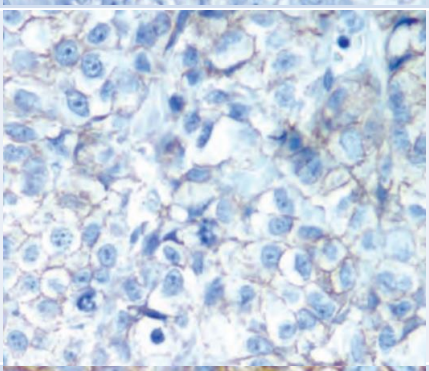
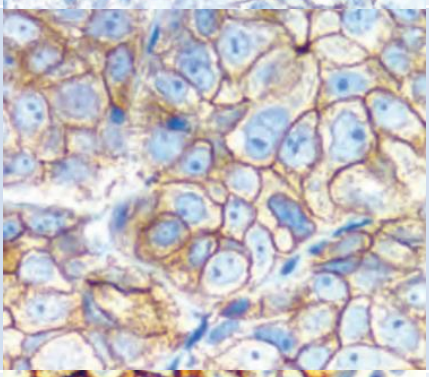
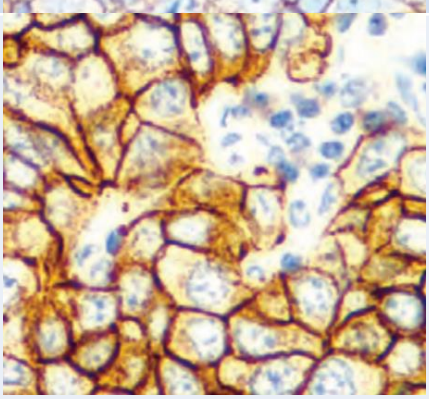
Wolf et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018 Nov;142(11):1364-1382.

General Testing recommendations

Core biopsies are preferred for ER, PR, and HER2 testing because they have short ischemic times and better fixation than surgical specimens. However, if the resection specimen has a different tumor type in terms of morphology or grade, a new test may be advisable to rule out heterogeneity in biomarker expression.

Laboratories and pathologists assessing ER, PR, and HER2 should participate in external quality assurance processes to ensure the accuracy of results. In the US, this is usually done through CAP.

HER2 Grading:

Score	Interpretation	Staining Pattern	Think	
0	Negative	No staining is observed, or membrane staining is observed in <10% of tumor cells	Essentially nothing, like an eraser 	
1+	Negative	A faint/barely perceptible membrane staining is detected in >10% of tumor cells. The cells exhibit incomplete membrane staining	Slight pencil tracing 	
2+	Equivocal (order FISH)	A weak to moderate ***complete, circumfirential*** **membrane staining** is observed in >10% of tumor cells.	Ballpoint pen 	
3+	Positive	A **strong *complete* membrane staining** is observed in >10% of tumor cells.	Sharpie marker 	

Modified from: HercepTest Interpretation Manual Breast Cancer. Dako.

Familial Syndromes

Breast cancer shows more familial clustering than most tumors.

BRCA1/2

BRCA-genes are tumor suppressors involved in the homologous recombination repair pathway (repairs DNA breaks using sister chromatids as a template) → mutations in BRCA → genomic instability → oncogenesis

Highest risks: **Breast and ovarian cancer**
~3.5% of all breast cancers; More common in certain populations, like Ashkenazi Jews

Treatment: patients may opt for **prophylactic bilateral mastectomy and salpingo-oophorectomy** before 40 yrs → Must submit entire FT and ovary looking for STIC
Carcinomas can be treated with **PARP inhibitors** (PARP helps with single-strand DNA breaks, so when combined with BRCA mutations → cancer cells can't repair breaks at all→ "synthetic lethality")

Characteristic	BRCA1	BRCA2
Risk of breast cancer	40-90%	45-85%
Risk of ovarian/fallopian tube high-grade serous carcinoma	40-50%	10-20%
Male breast cancer risk	Lower	Higher
Other Cancer risk	Possibly pancreatic and colon	Pancreatic cancer, prostate cancer
Morphology	Circumscribed growth pattern with pushing borders, dense lymphocytic infiltrate. High-grade.	Variable morphology and grade
Molecular cancer type	Basal-like (triple-negative)	Luminal A (ER/PR +; HER2 -)

Li Fraumeni Syndrome

Autosomal dominant TP53 mutation (one of the most prominent tumor suppressors)
Early onset of a broad spectrum of cancers. Most common is breast (>90% lifetime risk), but also soft tissue, brain (esp. choroid plexus carcinoma), adrenal cortical, bone, etc…

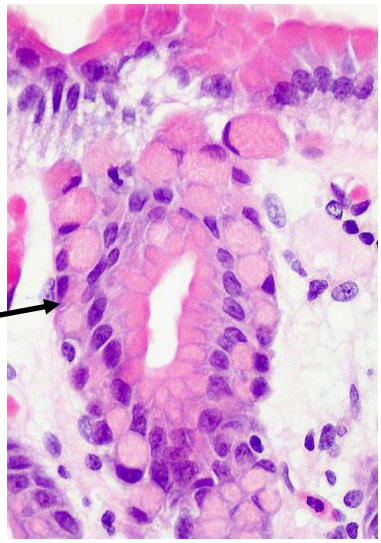
CHEK2-related hereditary (breast) cancer predisposition syndrome

Germline mutations in CHECK2, moderately penetrant. CHECK2 is a tumor suppressor activated by double strand DNA breaks (upstream of TP53 and BRCA1). Mutation→ disrupt DNA repair→ more errors → carcinogenesis. ~30% lifetime risk of breast cancer. Also increased risk of a variety of cancers.

Peutz-Jeghers Syndrome

Autosomal dominant polyp and cancer syndrome. Germline mutations in tumor suppressor STK11.
Characteristic hamartomatous polyps in >95% of patients, often in small bowel.
Also frequent mucocutaneous melanin pigmentation.
Increased risk of many cancers including Breast, colon, stomach, pancreas, ovary (SCTATs), etc…

CDH1-associated Breast Cancer



Inactivating germline mutations in **CDH1 (gene for E-cadherin)** resulting in characteristic **lobular carcinoma** of the breast.

Most (but not all) CDH1 mutations are associated with **Hereditary diffuse gastric cancer (HDGC)**, which also has germline mutations in CDH1 and can have lobular carcinoma of the breast also.

E-cadherin is important for cell adhesion and tumor suppression

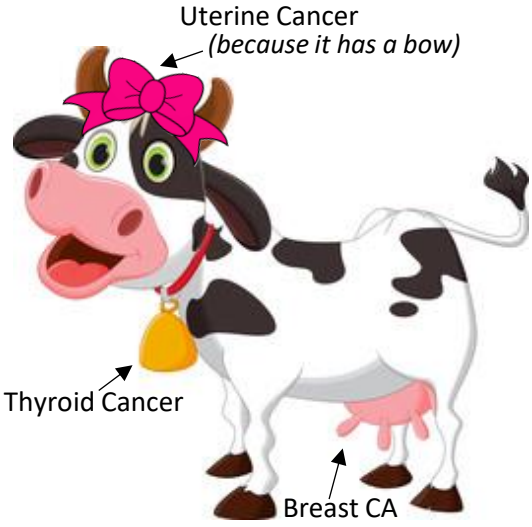
Classic HDGC finding: **Signet ring carcinoma in situ**
- Signet ring cells above basement membrane
- Pagetoid spread
- Can then progress to invasive, diffuse gastric cancer
- **Often Multifocal**

Ataxia-Telangiectasia

Autosomal recessive disorder with progressive cerebellar ataxia, oculocutaneous telangiectasia, variable immunodeficiency, sterility, and sinopulmonary infections.
Mutations in ATM gene (tumor suppressor)→ phosphorylates p53 and BRCA1 in response to DNA double-strand breaks
High risk of malignancy and sensitivity to ionizing radiation
Homozygotes have full disorder
Heterozygotes have a risk of breast cancer at a young age.

PTEN hamartoma tumor syndrome

PTEN mutation. Autosomal dominant
Old name: *Cow*den's syndrome — *Think of this cow*
- Tumor suppressor → lots of different tumors
  - *Other PTEN syndromes subtypes include: Bannayan-Riley Ruvalcaba syndrome and Lhermitte-Duclos disease*



At risk for:
Breast Cancer *(highest risk)*
Multiple **hamartomas** (mouth, GI tract)
Thyroid carcinoma (usually Follicular)
Endometrial Cancer
Trichile*MMOOOOO*mas
Lipomas

Esophagus: Glycogen acanthosis

Stomach: Polyps that often resemble **HP's**

Colon: **Stroma-rich polyps** with cystically dilated glands
- Can mimic JP's.
- Can contain **Adipocytes** in lamina propria (relatively unique)
- Can get **ganlgioneuromatous** polyps

Treatment Basics

Disclaimer: This is a very simplified (pathologist's) way of thinking of treatment for breast cancer. For more complete information, please consult the NCCN guidelines for breast cancer treatment.

Pre-operative Work up

Patients should get imaging of the breast and axilla (e.g., ultrasound or MRI) to map extent of disease and possible nodal involvement.

Imaging for staging (e.g. PET, Bone scan) is reserved for those with symptoms of metastatic disease or that are high risk.

Neoadjuvant therapy

The following are frequent candidates for Preoperative chemotherapy:
Patient's with not currently operable cancer: **bulky/extensive nodal disease, cT4 tumors**.
Select operable tumors: **HER2+ and Triple-negative cancers**, **Big tumors** in patients that desire breast conservation therapy

Surgery

The two main surgical approaches are:
Lumpectomy—a localized, breast-conserving excision. Frequently additionally treated with radiation.
Mastectomy—removal of all of breast glandular tissue

Lymph node sampling:
It is generally recommended that patients undergo sentinel lymph node sampling (exceptions include older patients with ER+/HER2- tumors). If positive, an axillary dissection may be recommended depending on tumor size and chemo/radiation plan.

Desired margins:
DCIS: Generally want > 2 mm
Invasive tumor: "No ink on tumor"

Post-surgical therapy

For DCIS: Patients may receive Endocrine therapy (e.g., Tamoxifen) and/or Radiation therapy.

For Invasive cancer, the following patients often receive adjuvant (postsurgical) chemotherapy:
Tumors with advanced stage (big tumors and/or multiple positive lymph nodes)
HER2+ or Triple negative tumors
ER+/HER2- tumors that are deemed to have a higher risk of recurrence based on a RT-PCR panel like Oncotype Dx.

What's this about HER2 *"Low"* and *"Ultra low"*?!

With new mediations, like Trastuzumab-Deruxtecan (Enhertu), clinical trails that even individuals with low-level HER2 IHC expression derive clinical benefit (i.e., not just 3+). This is an "evolving" area with lots of controversy.

First, as of 2026, CAP-ASCO have affirmed the 2018 recommendations (so everything preceding is still what is recommended by our professional organizations).

That said, drug companies are very eager to test for "low" HER2 levels (and sell their expensive medications ;-). The problem is, the HER2 IHC assay was developed to identify HER2 amplified (by FISH) cancers and has poor reproducibility for low levels of expression (0 to 1+) as it is at the low end of detection. Essentially, the IHC stain wasn't designed or optimized for the type of low-level testing they want to use it for (it's not "fit for purpose").

Drug companies use the following definitions (not currently recommended by CAP-ASCO):
HER2 Positive: IHC 3+
HER2-Low: IHC 1+ or 2+
HER2-ultralow: IHC 0 with some membranous staining
HER2-Null/Negative: Absent membranous staining