

KOREAN PATHOLOGISTS ASSOCIATION OF NORTH AMERICA
Meeting at 2019 USCAP National Harbor

Invasive Breast Cancer Special Types

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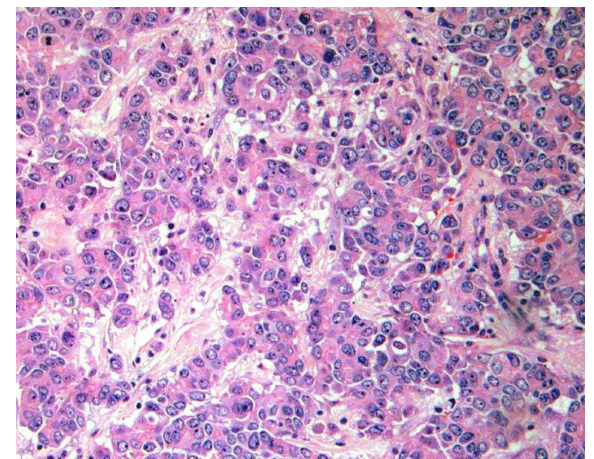
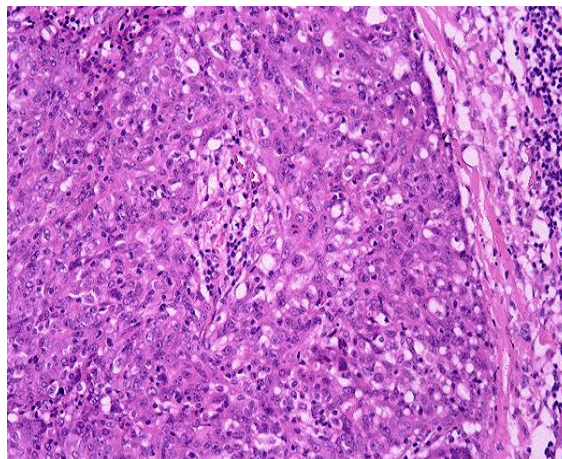
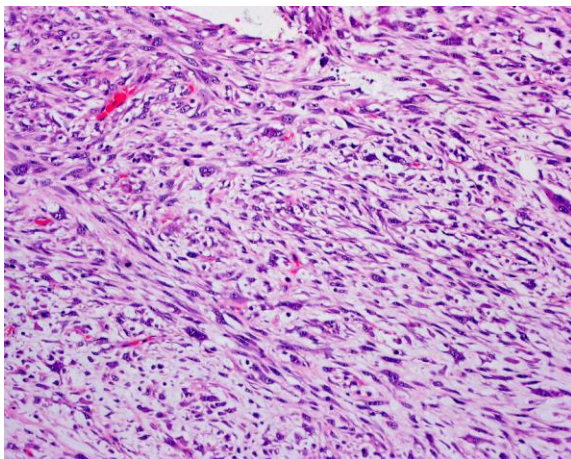
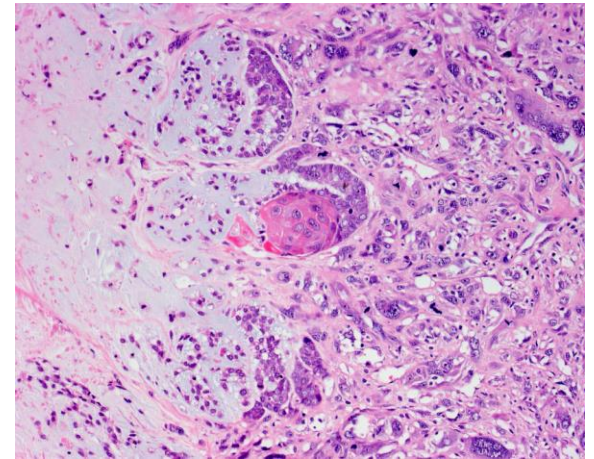
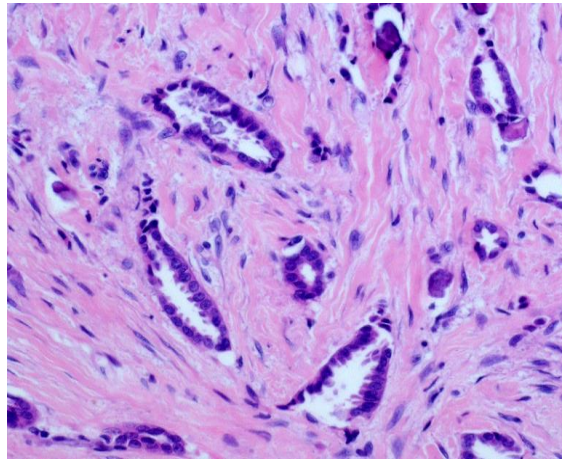
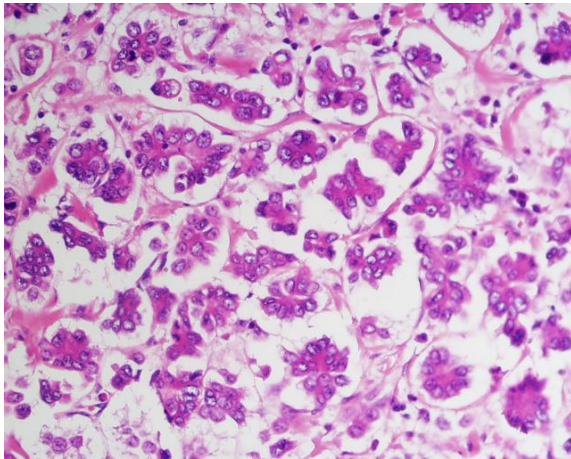
Making Cancer History®

Breast Cancer

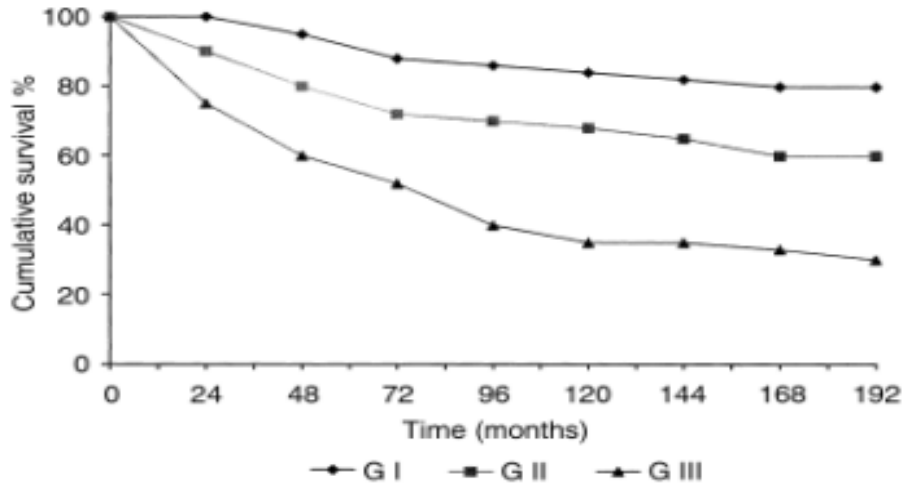
- Complex and multifaceted disease
- Include great variety of entities
- Show considerable variation
 - Clinical
 - Morphologic
 - Molecular

Breast Cancer Morphology

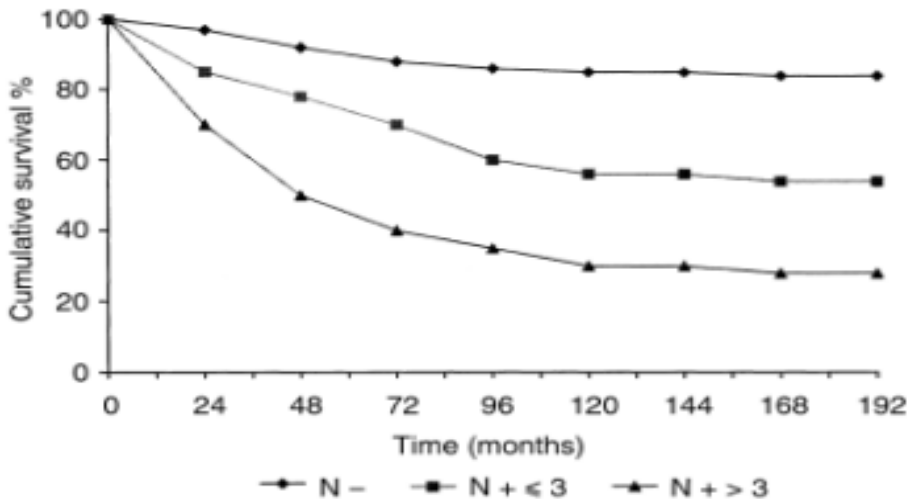
Heterogeneous



Breast Cancer Prognosis



**Grade
1 vs 3**



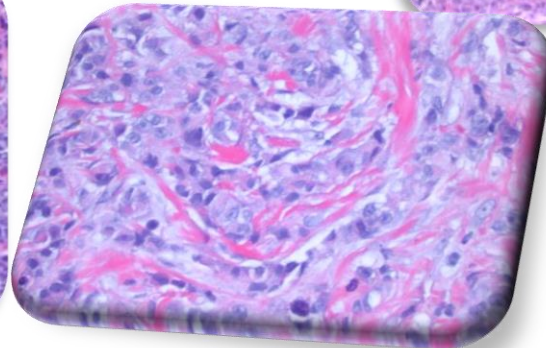
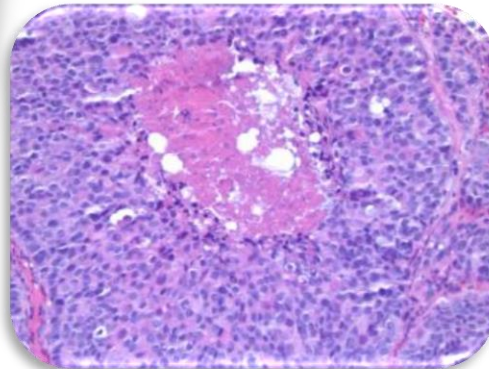
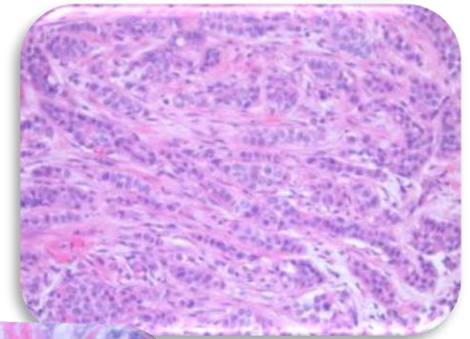
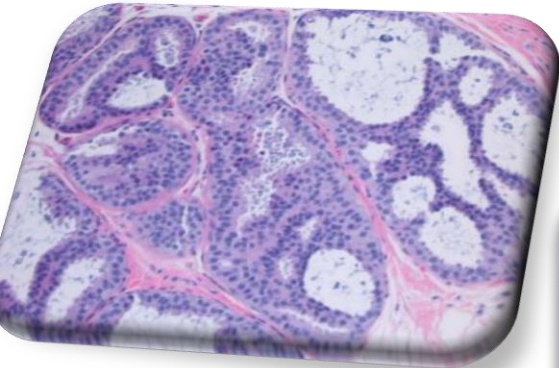
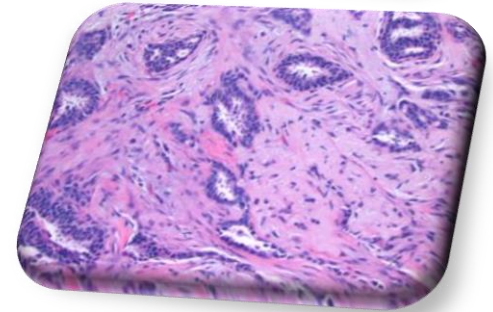
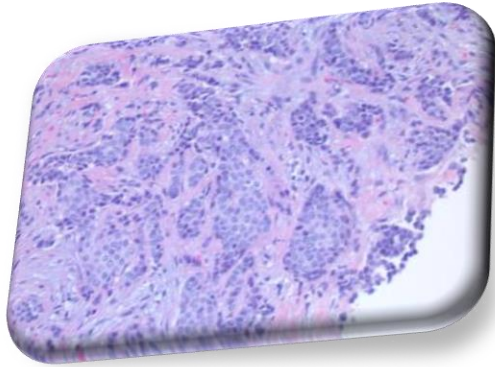
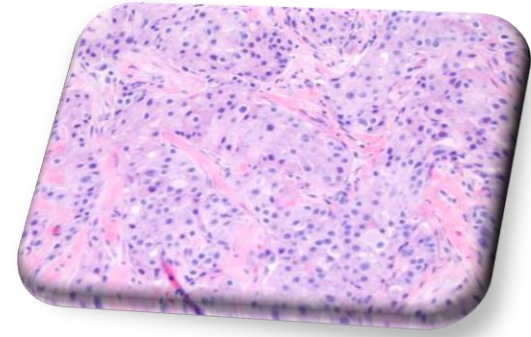
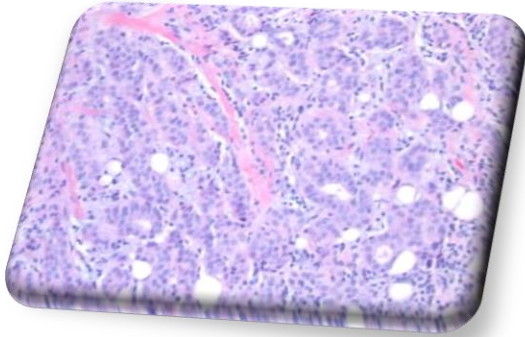
**Stage
size and LN
status**

Problems Remain

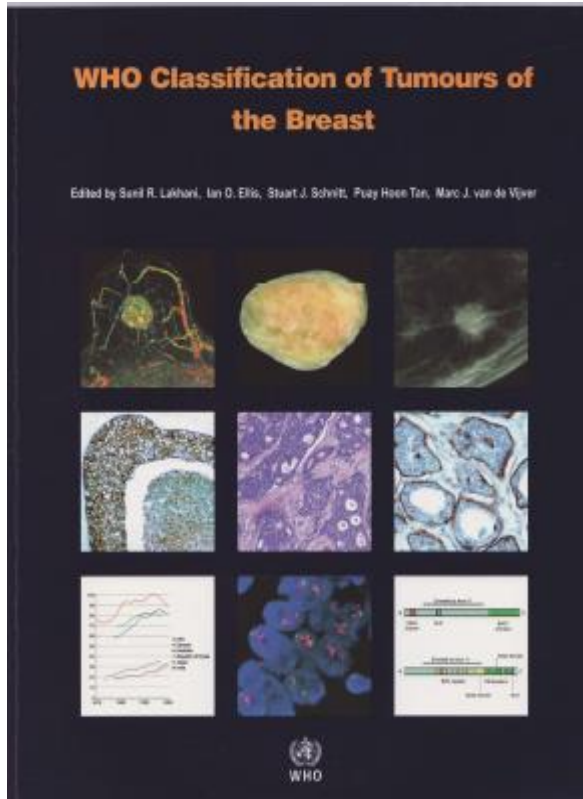
- Same type differing behavior
- Same grade/stage differing behavior
- Same treatment differing response

Classification of BC

- In situ vs Invasive
- Histologic subtype
 - Mostly Ductal, NOS
 - Special subtypes
- Grade



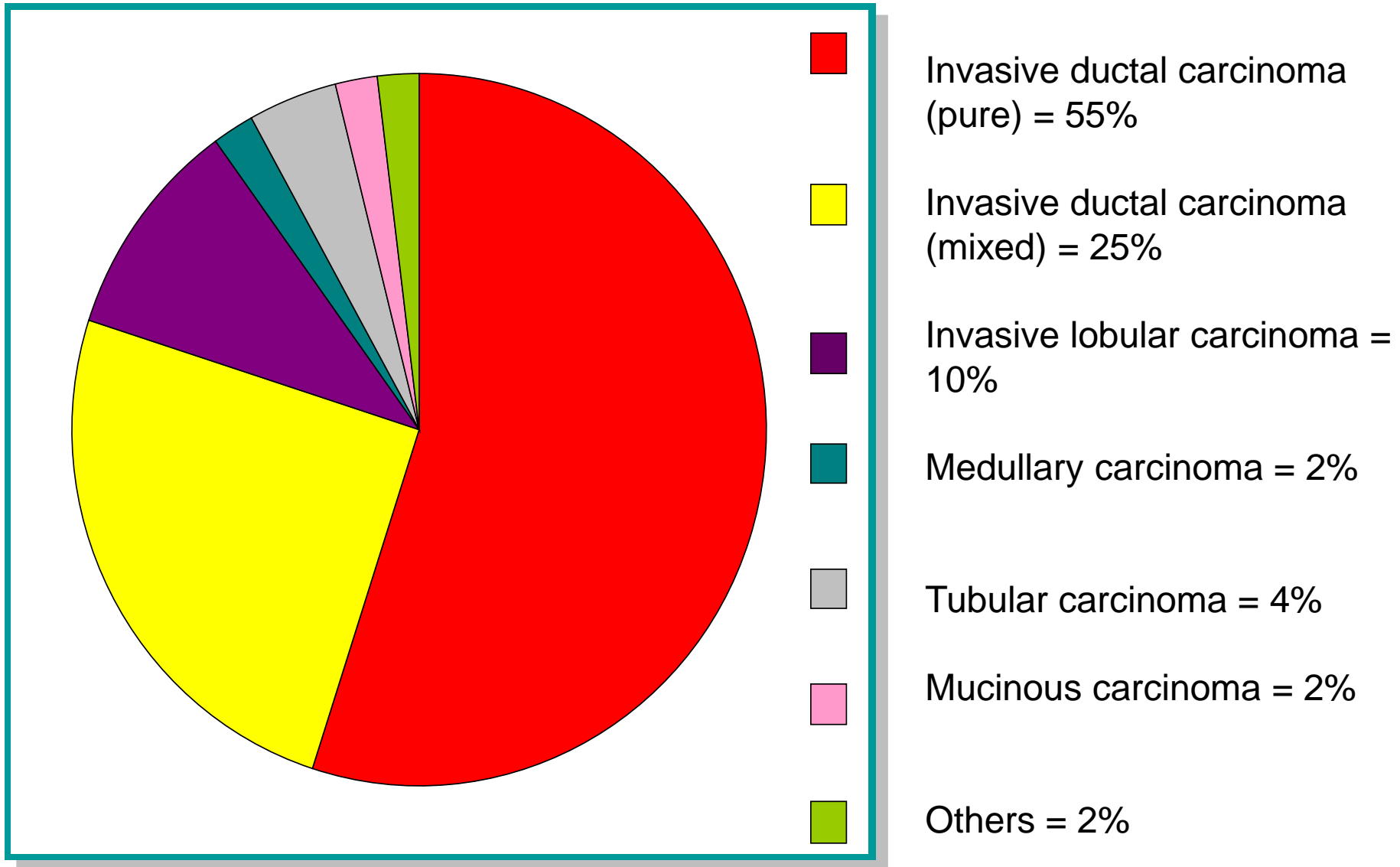
Histologic Types of BC



Ductal
Lobular
Tubular
Cribriform
Medullary
Mucinous
Apocrine
Papillary
Micropapillary

Metaplastic
Secretory
Lipid rich
Oncocytic
Adenoid cystic
Acinar
Clear Cell
Sebaceous
Neuroendocrine

Histologic Types of BC



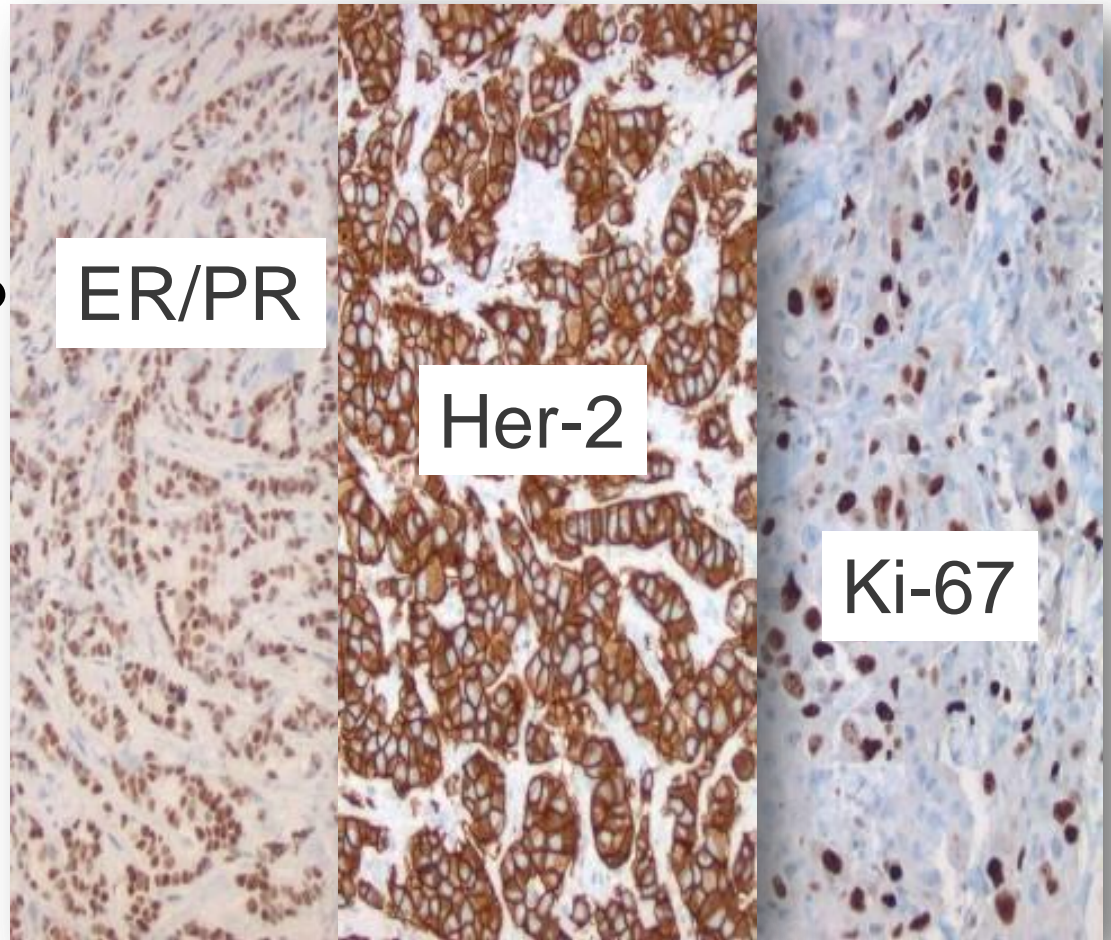
Histologic Types of BC

Categorization of Special Types of Invasive BC Based on Prognosis

| Favorable | Intermediate | Unfavorable |
|----------------|------------------------------------|------------------|
| Tubular | Medullary | HG Metaplastic |
| Cribriform | Secretory | Micropapillary |
| Mucinous | Invasive Lobular (classic type) | Signet Ring Cell |
| Adenoid Cystic | | |

Protein Expression Subtypes

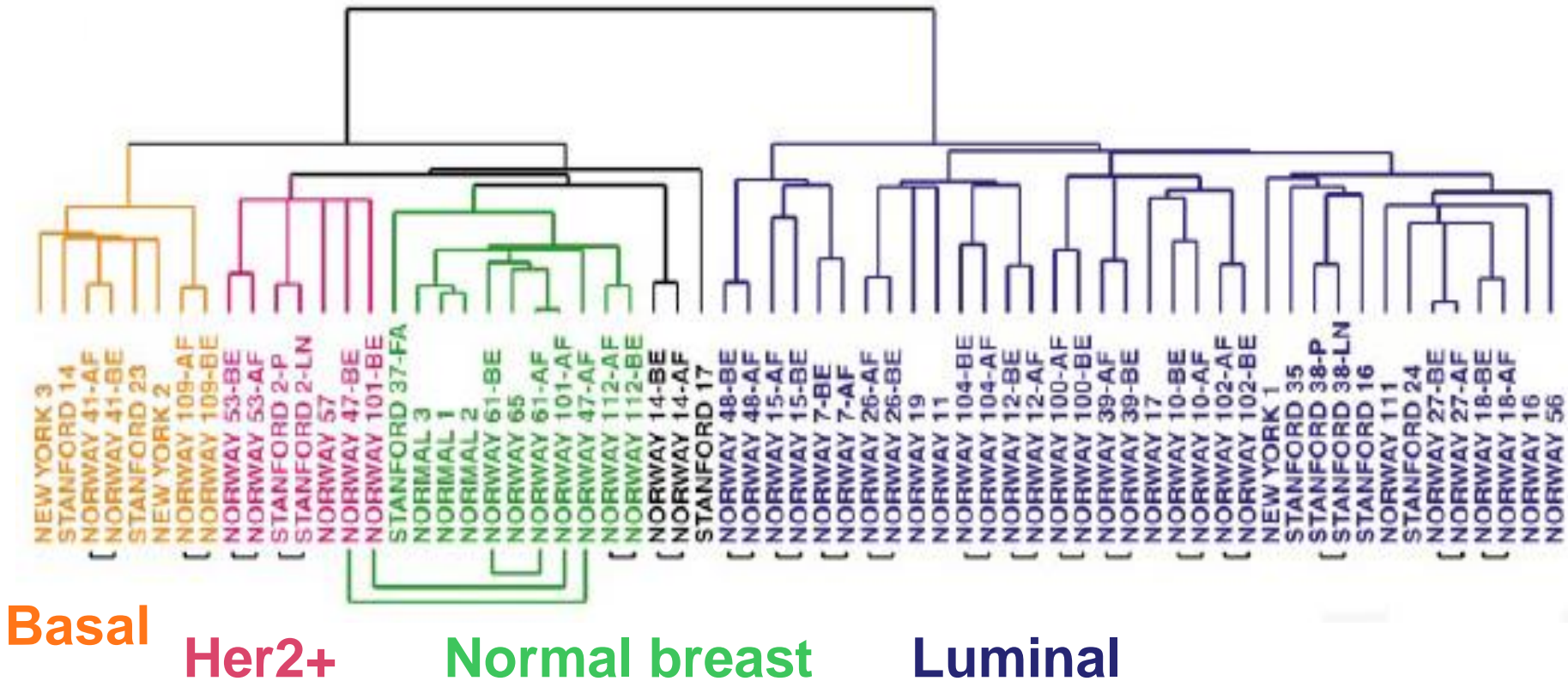
- What proteins does the cancer express in abnormal levels?
- Hormone receptors
- HER2 over-expression
- Proliferation markers

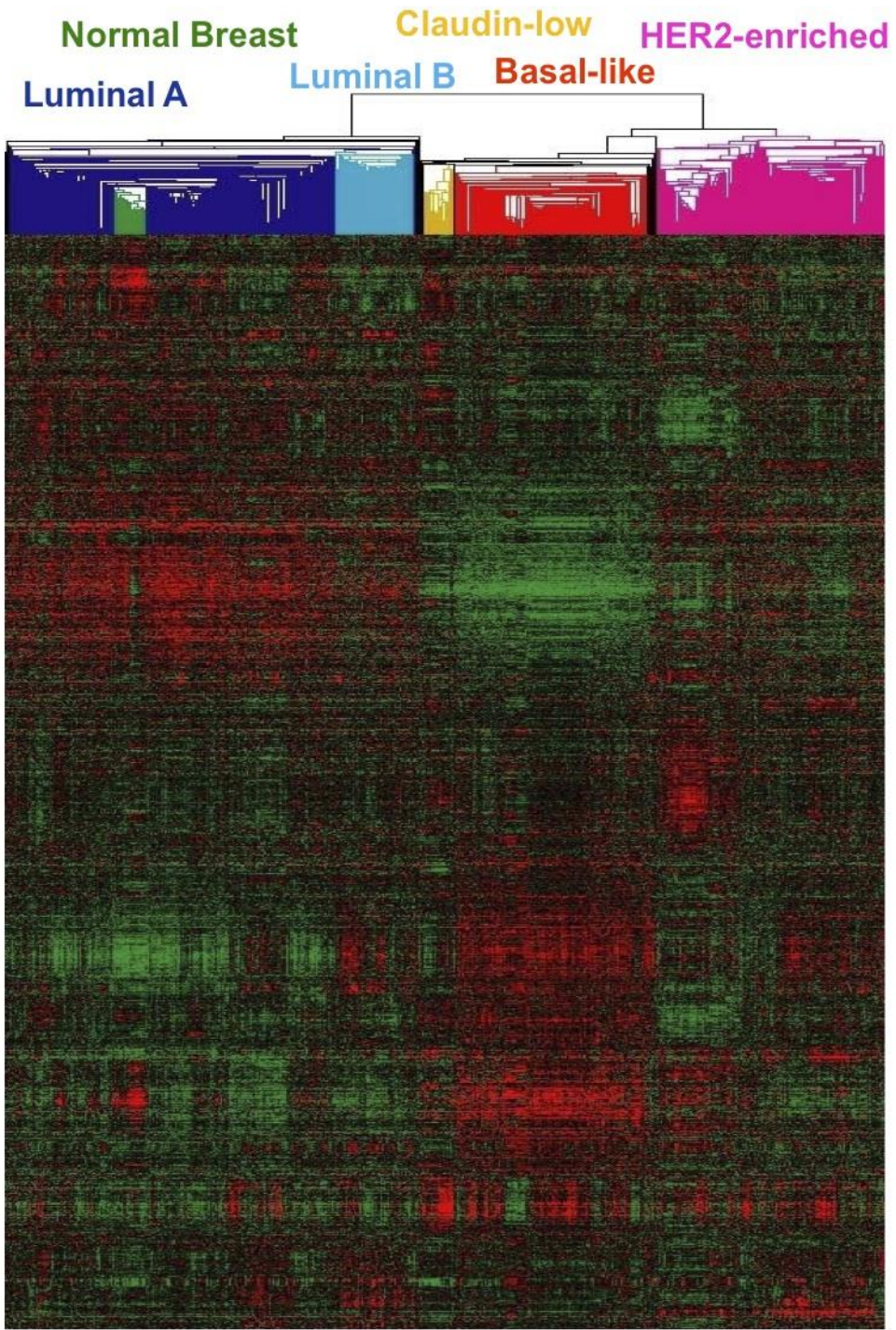


BC Subtypes by Gene Expression Profiling

ER-negative

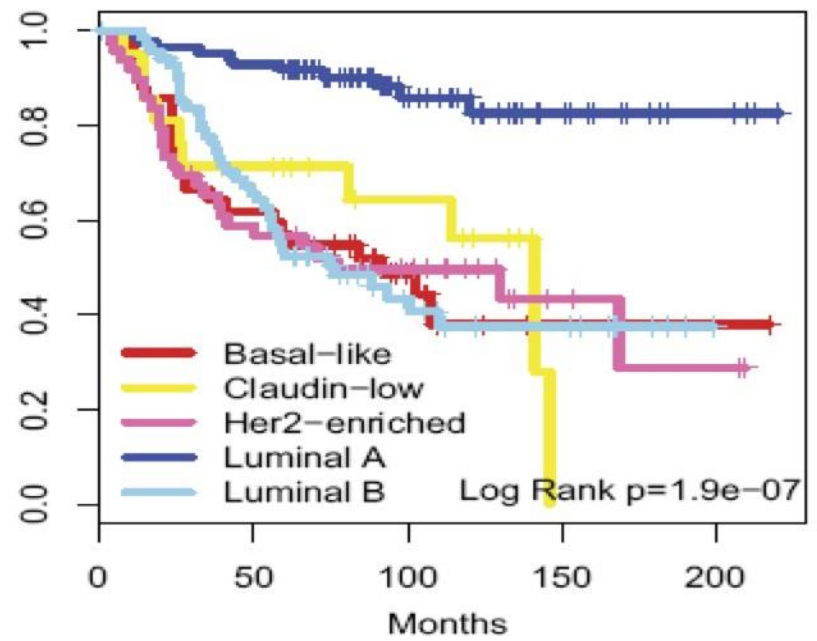
ER-positive





Intrinsic Subtypes

- Perou et al., Nature, 2000
- Sorlie et al., PNAS, 2003
- Usary et al., Oncogene, 2004
- Parker et al., JCO, 2009
- Prat et al., BCR, 2010
- Prat et al., JCO, 2012
- TCGA Network, Nature, 2012
- Dowsett et al., JCO, 2013
- Sestak et al., JNCI, 2013



Luminal Type Carcinomas

Luminal-A

- Good prognosis with endocrine therapy
- Low sensitivity to chemotherapy (pCR=5%)
- >50% are low grade
- Low proliferation rate
- Low p53 mutation rate
- MammaPrint low risk
- Oncotype DX low risk

Luminal-B

- Poor outcome with endocrine therapy alone
- Moderately sensitive to chemotherapy (pCR=20%)
- >50% are high grade
- High proliferation rate
- p53 mutation is common
- MammaPrint high risk
- Oncotype DX high risk

Luminal A

Luminal B

Proliferation:

Low

Higher

PR and FOXA1:

High

Lower

ER:

Similar

Similar

Mutation rate:

Low

Higher

Copy # changes:

Low

Higher

P53 mutations:

Low (12%)

Higher (29%)

GATA3 mutations:

Similar (14%)

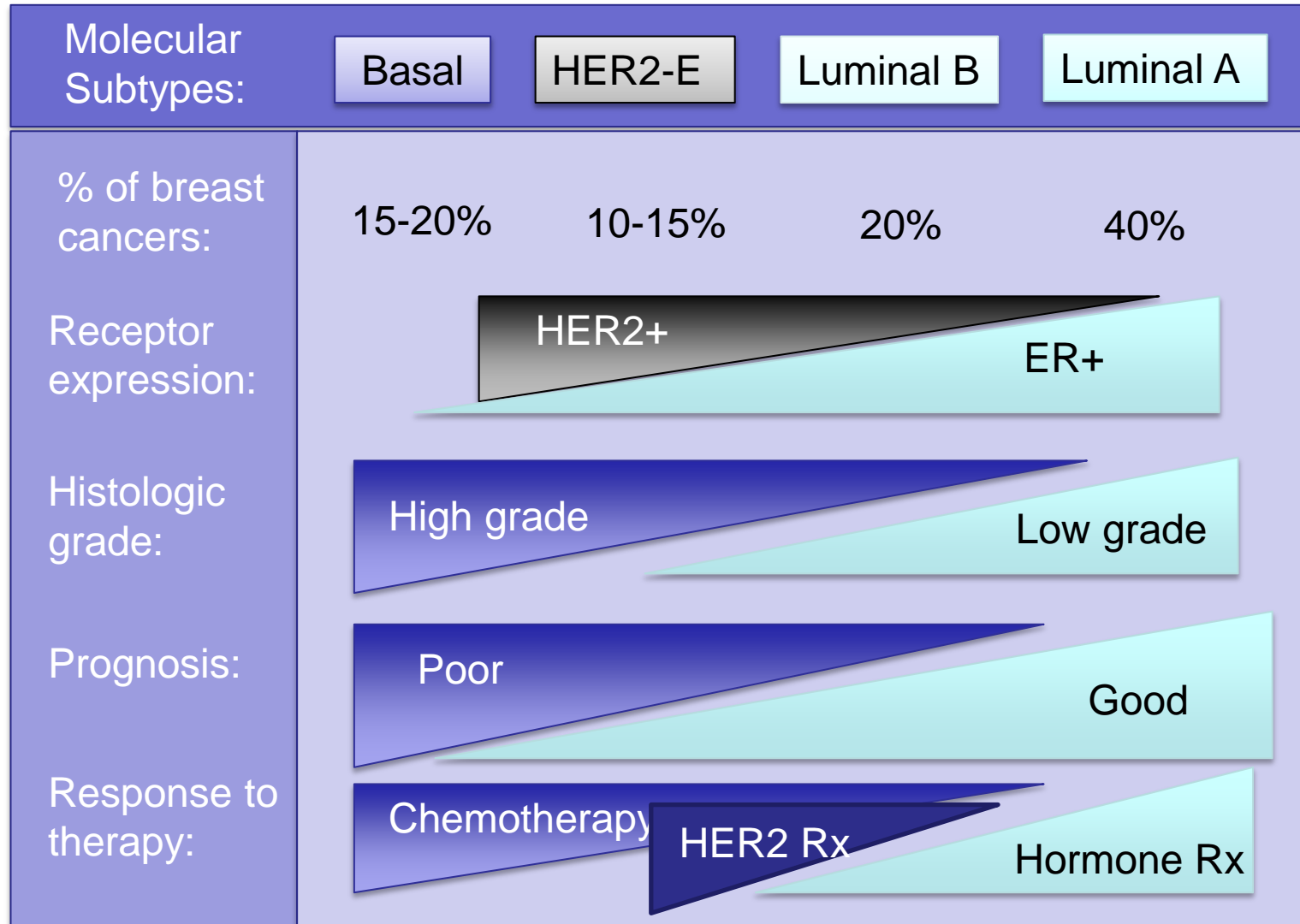
Similar (15%)

PIK3CA mutations:

More (45%)

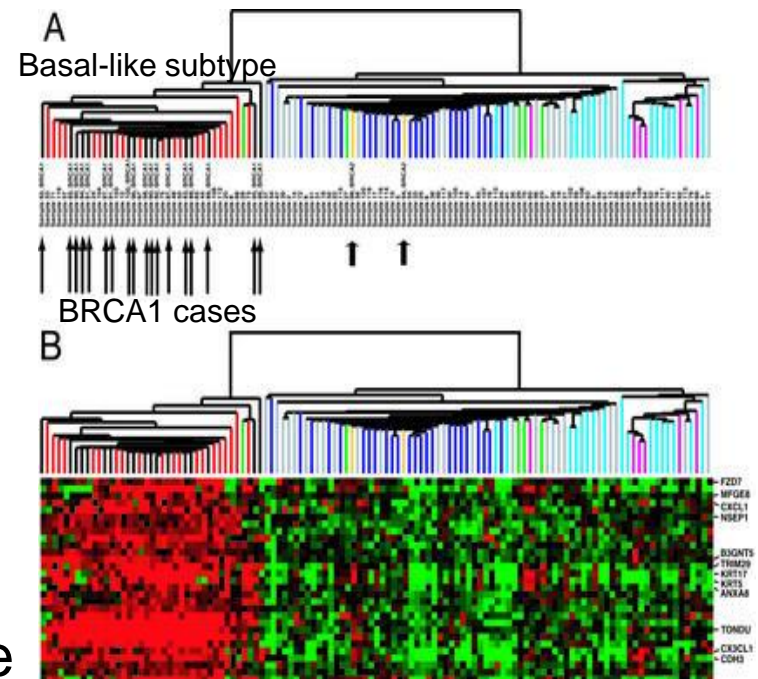
Lower (29%)

Intrinsic Subtype Characteristics



Basal-like Subtype

- Most unique and robust subtype
- More similar to ovarian serous carcinoma than other BC subtypes
- Most frequent subtype in BRCA1+ pts
- Different ethnic distribution = more common in African Americans
- Different age range = younger
- Risk factors: Increased parity, less time breast feeding



Luminal and Basal-like Cancer

Luminal

- 40% of first relapses occur in the bone
- Hazard of recurrence is prolonged over 10-15 years
- Variable grade
- Responds to endocrine thx
- Extreme chemotherapy sensitivity is rare (pCR = 8%-10%)
- Variable proliferative rate

Basal-like

- 8% of first relapses occur in the bone
- Hazard drops steeply after first 3 years
- 85% are high grade
- No response to endocrine thx
- Extreme chemotherapy sensitivity is relatively common (pCR = 25%-35%)
- High proliferative rate

Basal-like Breast Cancer

- Heterogeneous group of tumors
- 12-20% of all BCs
- Some special histologic types of BC consistently display basal like phenotype

Basal-like Breast Cancer

BL1: Basal-like 1

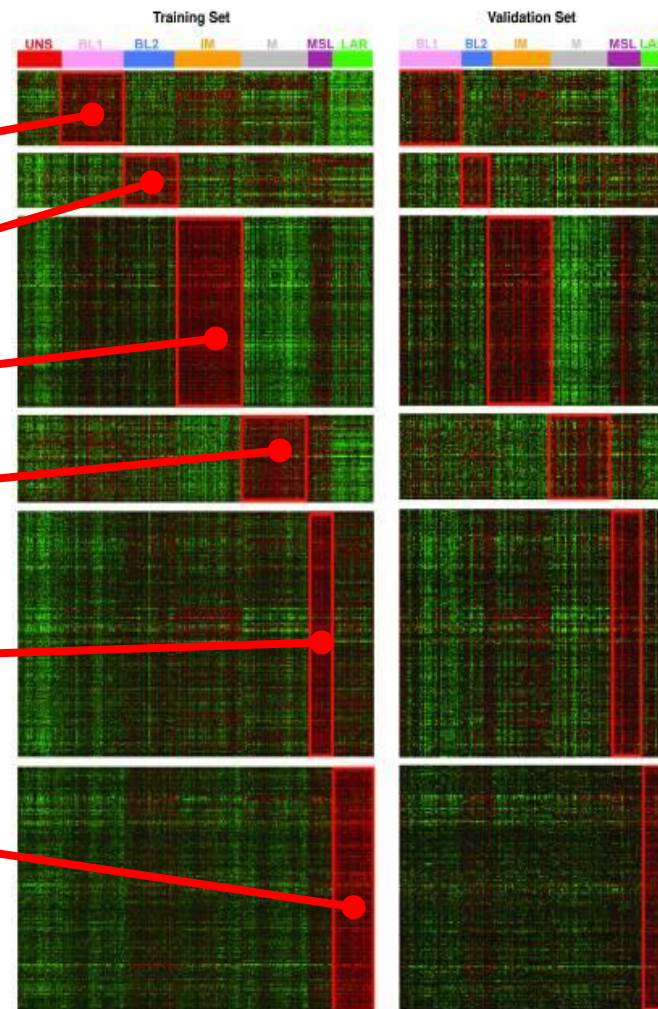
BL2: Basal-like 2

IM: Immunomodulatory

M: Mesenchymal-like

MSL: Mesenchymal Stem Like

LAR: Luminal; Androgen Receptor



Basal-like Breast Cancer

- Clinical features
 - Younger patients (47-55 yrs)
 - African American women
 - ? Hispanic women
 - Interval cancers
 - BRCA-1 mutations
 - Prevalence of brain and lung metastases
 - Early metastases (2-3 yrs)

Basal-like Breast Cancer

- More aggressive
 - Higher rate of relapse
 - Decreased OS in metastatic disease
- Subsets of pts respond well to standard chemotherapy
- Pts achieve pCR after NAC have survival rates similar to those with non-TNBC

BRCA1 and Sporadic BLBC

- Most BC in BRCA1 mutation carriers are basal-like
- Most basal-like BC are not in BRCA1 mutation carriers
- Defects in Homologous Recombination
 - 30-40% of TNBC without BRCA mutation

Basal-like Breast Cancer

BL-1: cell cycle, DNA repair and proliferation genes

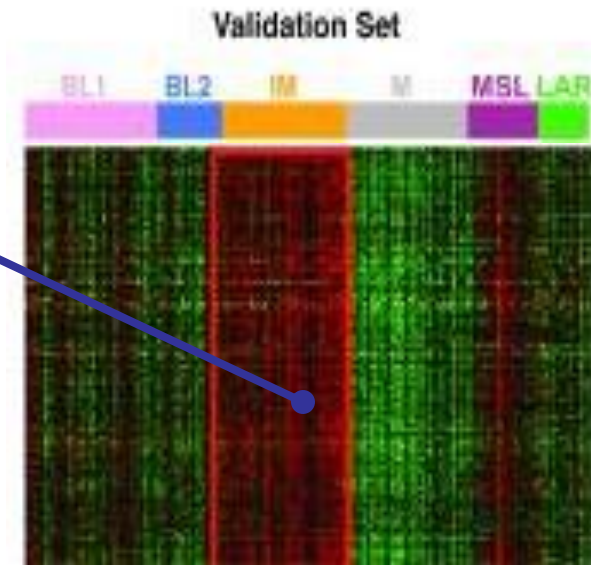
BL-2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)



- 40-60% of BLBCs
- EGFR pathway activation
- IGF1R pathway activation
- ?BRCA1 carriers?
- p53 mutant
- Highly proliferative

Immunomodulatory Basal-Like BC

IM: immune cell Processes

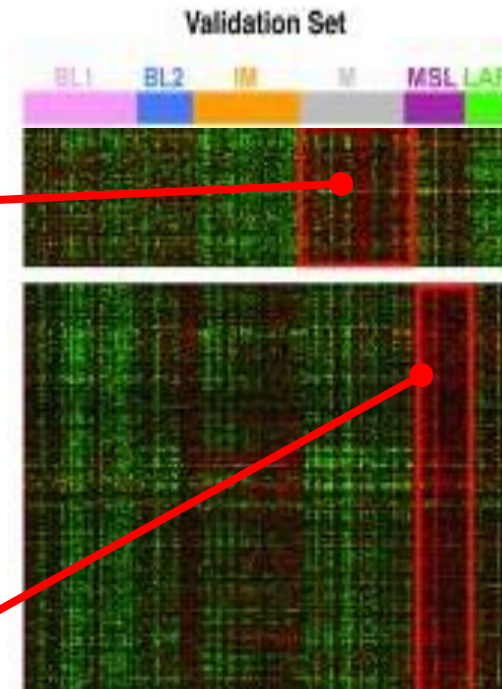


- 10-15% of BLBC
- enriched in immune cell processes
- medullary BC
- ?BRCA1 carriers
- p53 mutant

Mesenchymal-like Subtypes

M: Cell motility and differentiation, EMT processes

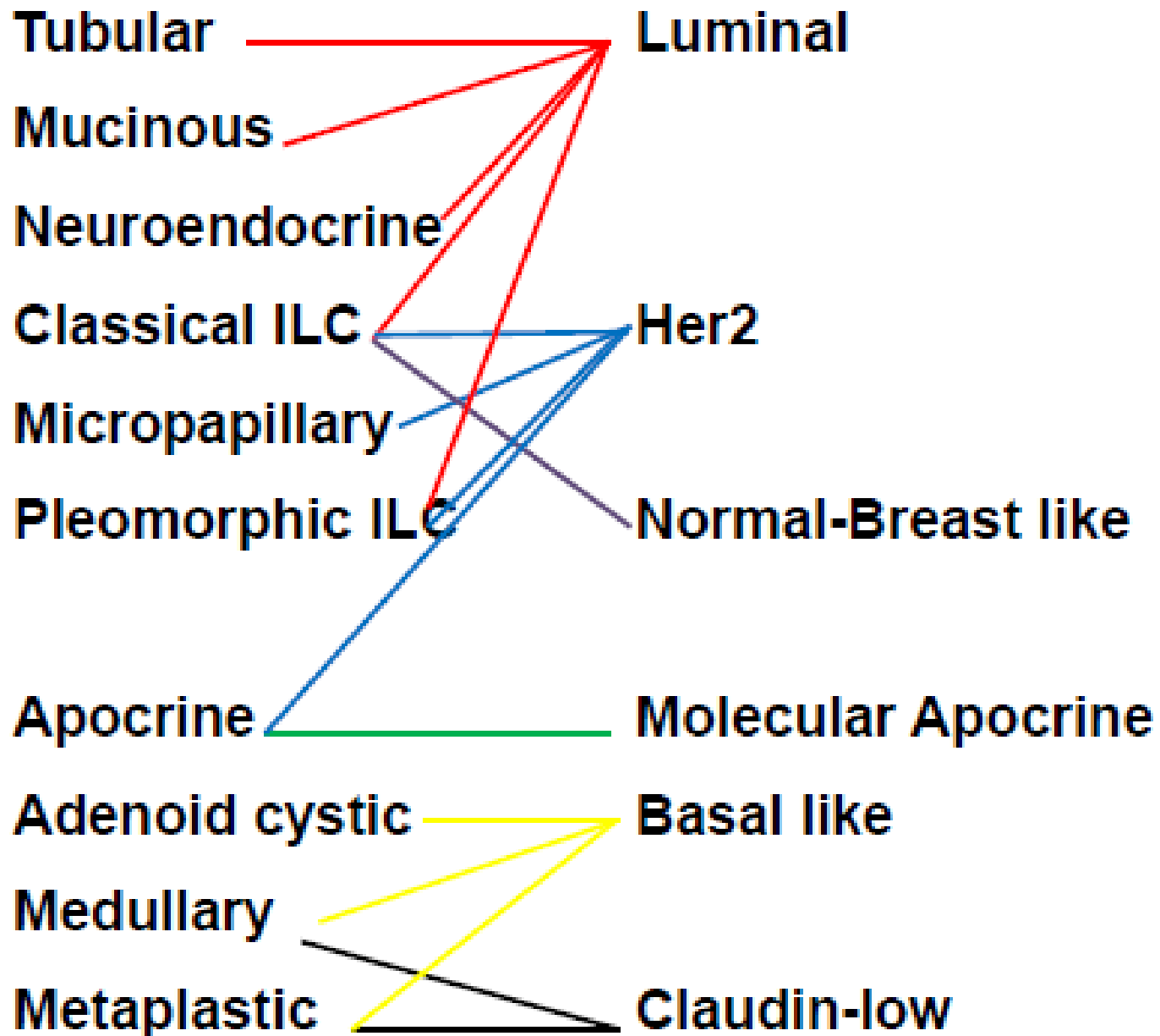
MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)



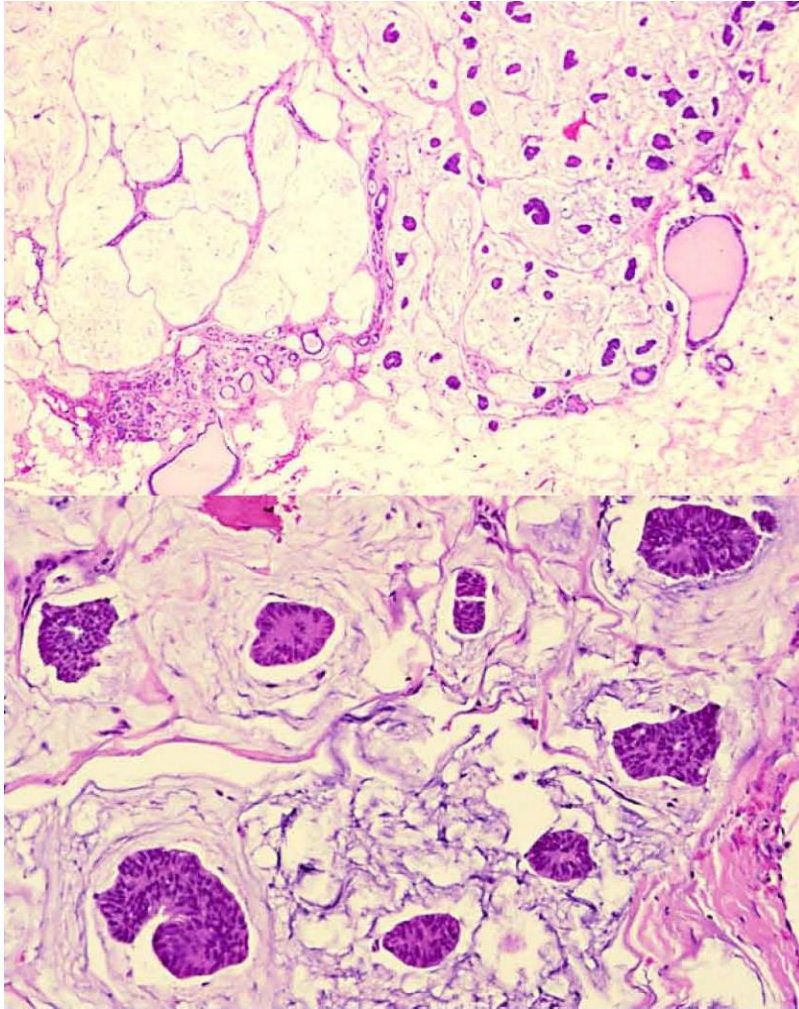
- 20-30% of BLBCs
- cell motility
- EMT
- angiogenesis
- BRCA1 carriers?
- p53 mutant
- PIK3CA mutations
- MSL- low expression of proliferation genes

Breast Cancer Classification

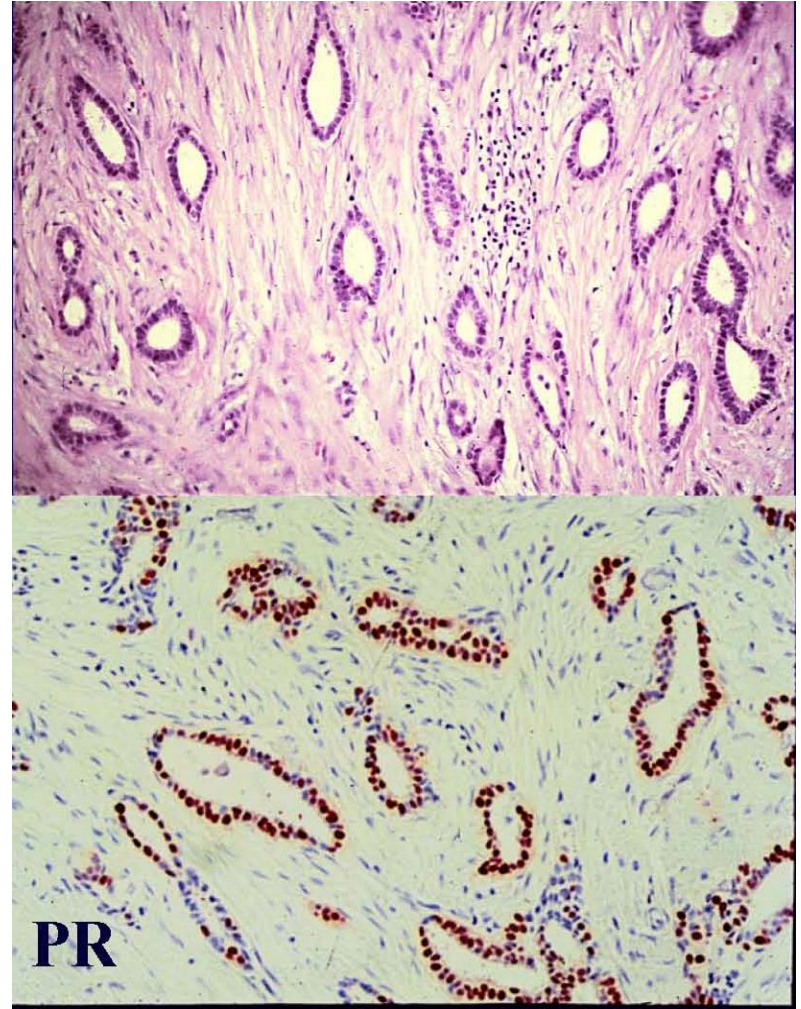
How do conventional histologic classes relate to molecular subtypes?



Breast Carcinoma



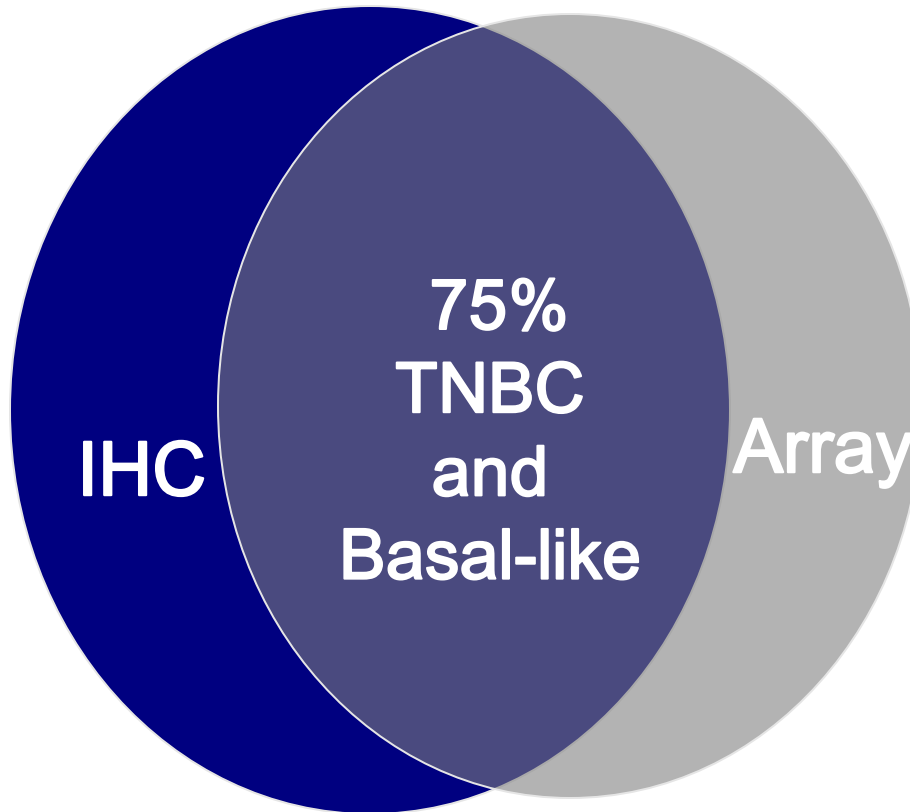
Mucinous Ca



Tubular Ca

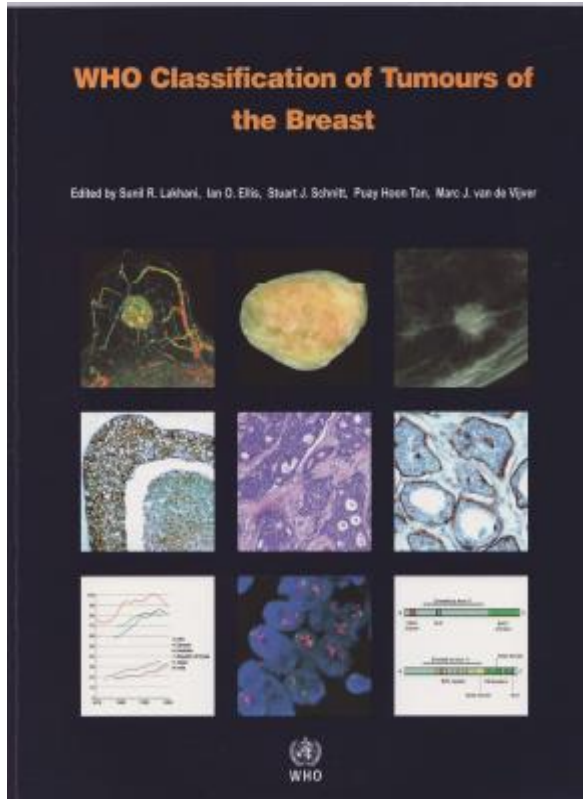
TNBCC and Basal-like Breast Ca

Triple
negative
but not
basal
10-30%



Basal but not
triple negative
15-30% are
ER+, PR+, or
HER2+

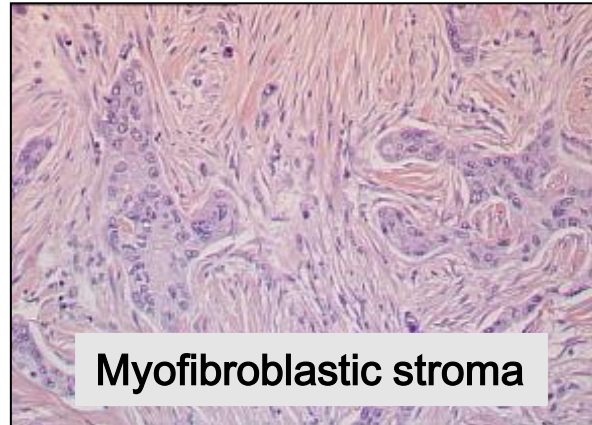
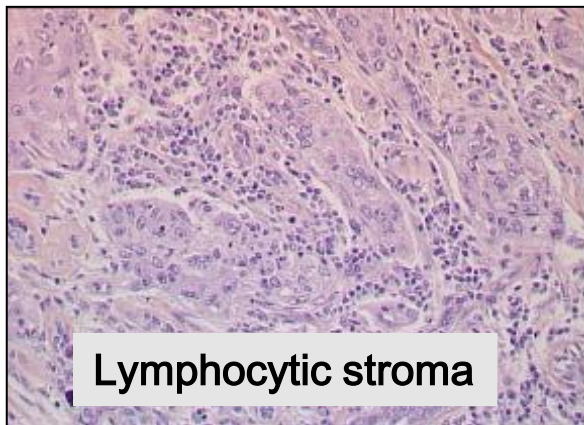
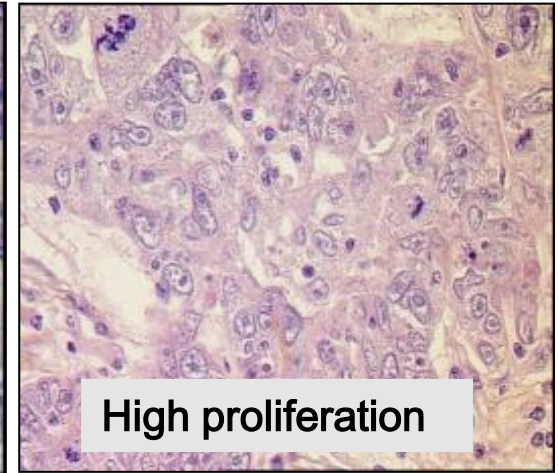
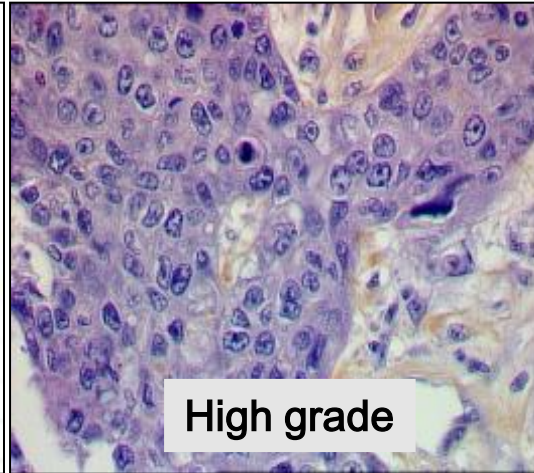
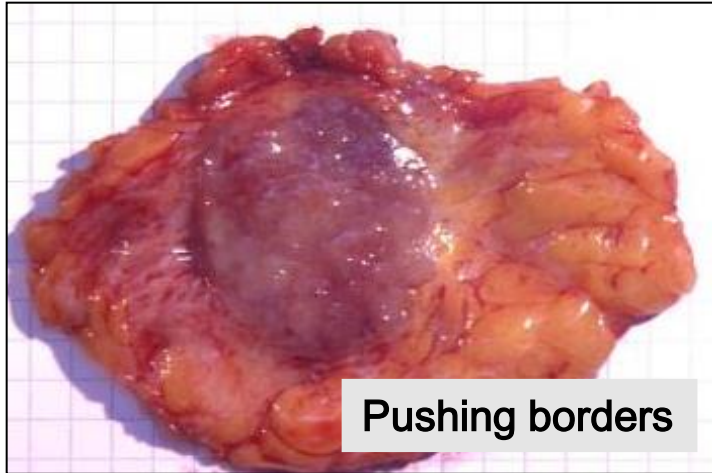
Histopathologic Types of BC



Ductal
Lobular
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Medullary
Mucinous
Apocrine
Papillary
Micropapillary

Metaplastic
Secretory
Lipid rich
Oncocytic
Adenoid cystic
Acinic cell
Clear Cell
Sebaceous
Neuroendocrine

T N B C: Histopathologic Features



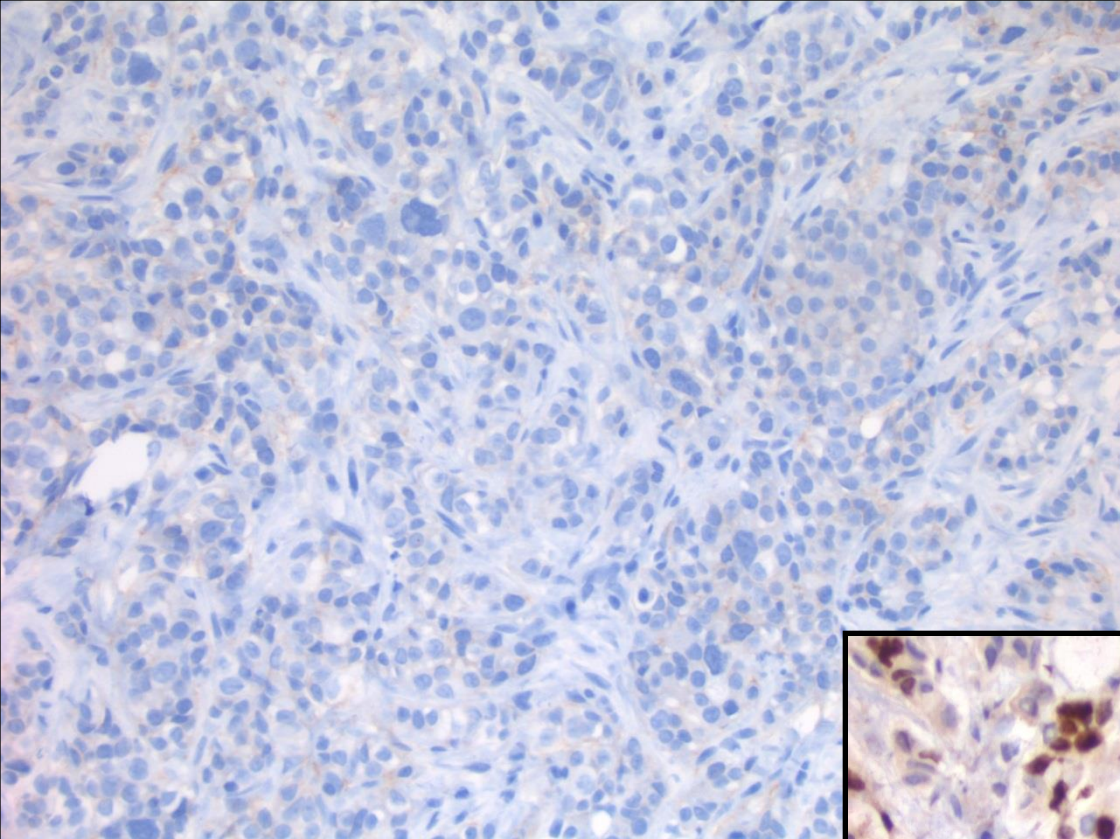
T N B C: Histopathologic Features

- Expansile/pushing margins
- Poorly differentiated
- Solid architecture
- Absence of tubules and glands
- Lymphocytic infiltrate
- High mitotic index
- Geographic necrosis
- Central fibrotic, acellular zones

Immunoprofile of T N B C

- ER-, PR-, HER2-
- Expression of basal keratin
 - CK14, CK17, CK5/6
- EGFR and c-kit expression
- Vimentin +

These are also features of the normal myoepithelial cells and tumors with myoepithelial differentiation

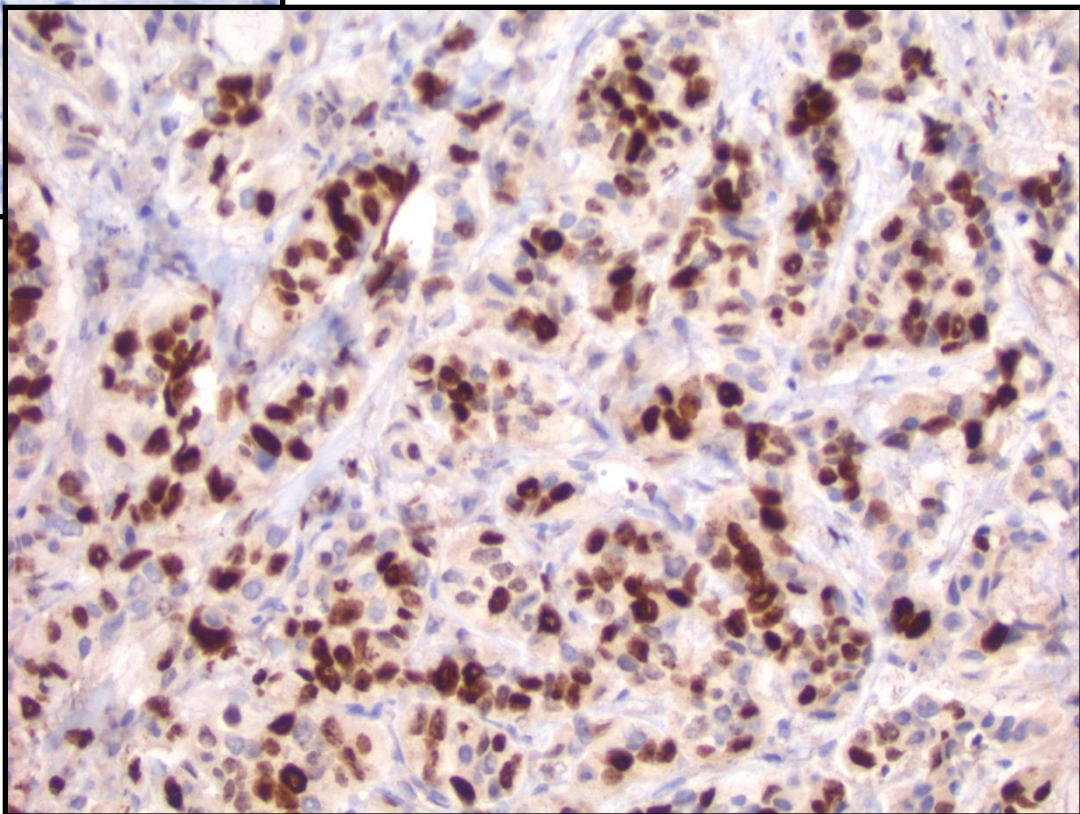


“Triple Negative
Immunophenotype”:

ER –

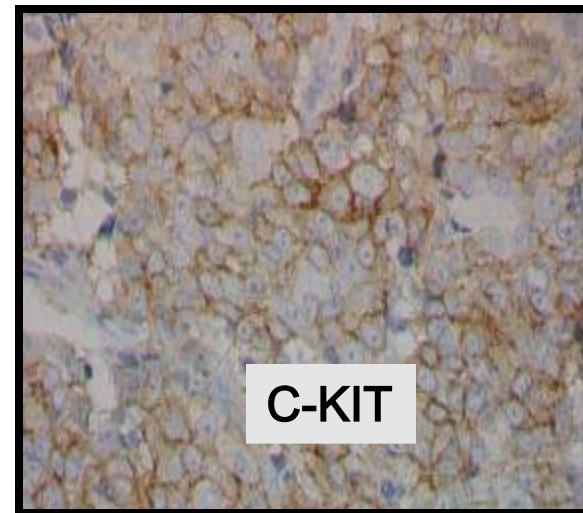
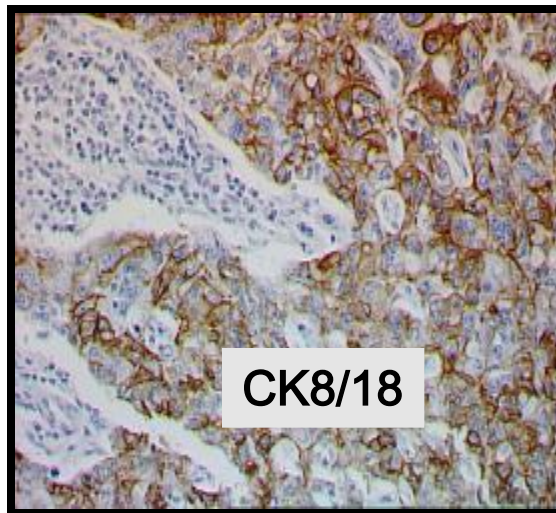
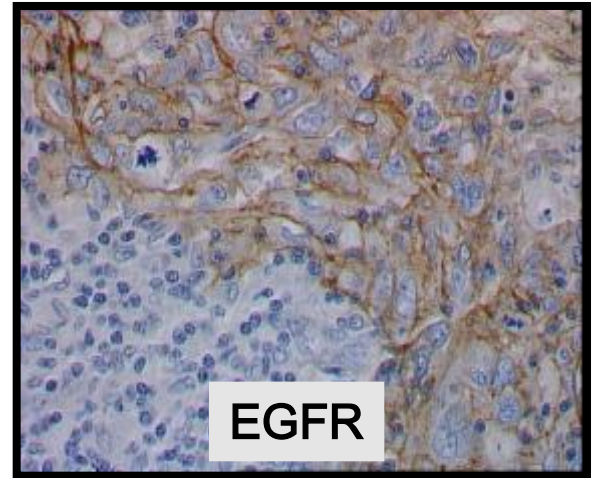
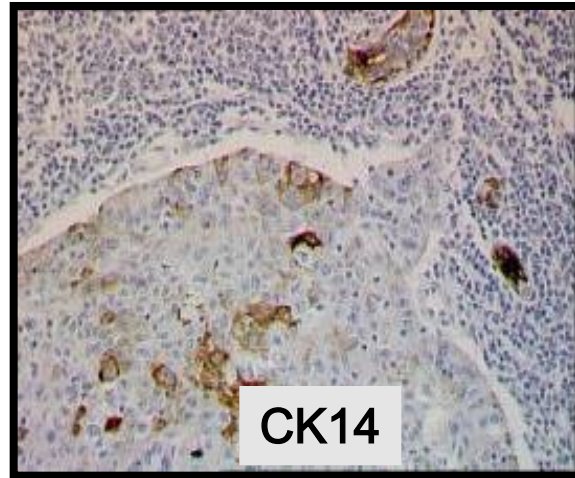
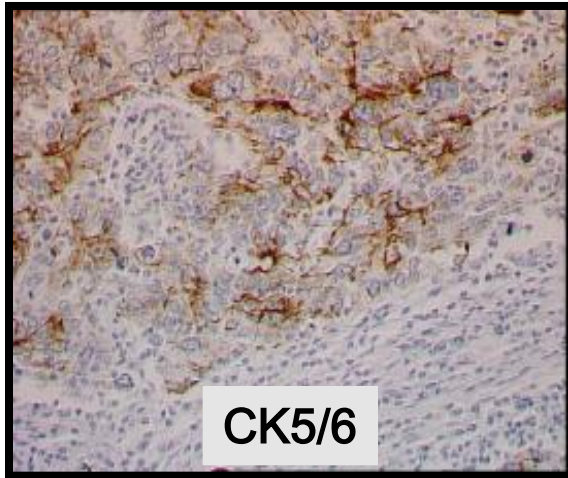
PR –

Her2 –



Ki67 index HIGH

T N B C: IHC Features



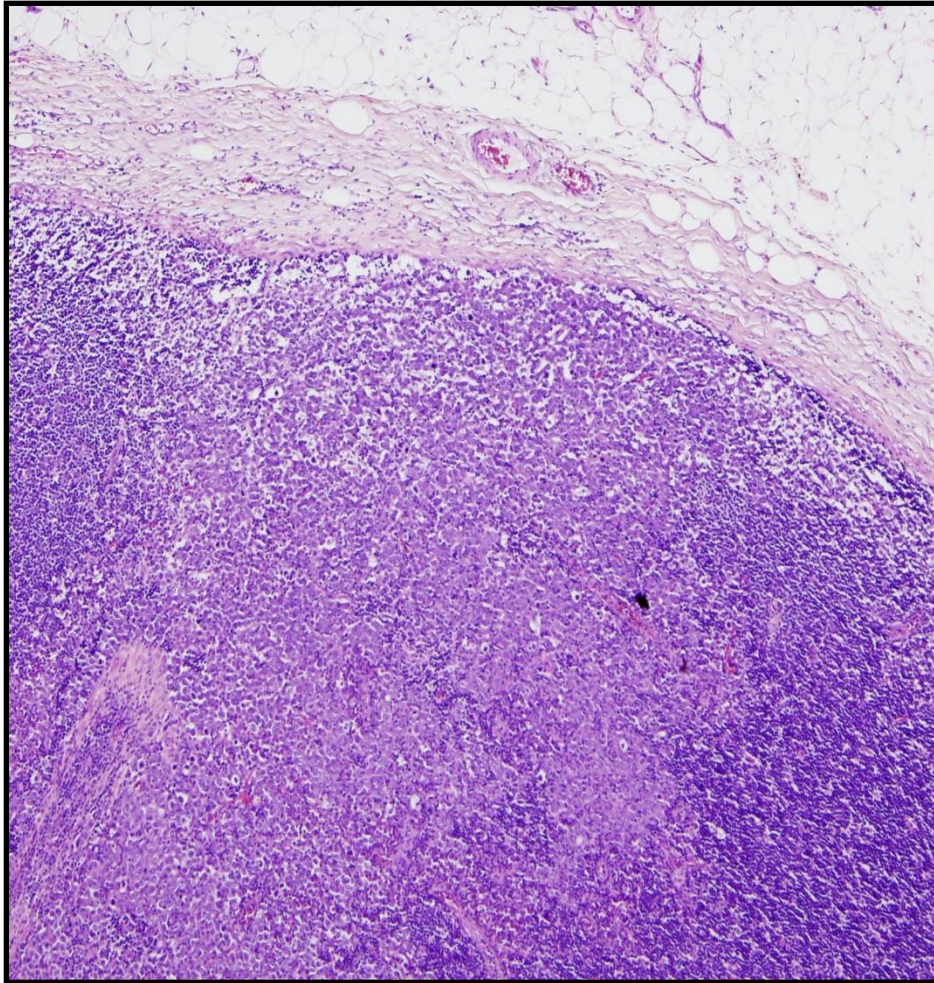
TNBC Are Heterogeneous

- IDC NOS, high grade
- ILC high grade, pleomorphic
- High grade metaplastic
- High grade myoepithelial carcinoma
- High-grade (oat-cell) neuroendocrine
- Apocrine
- Medullary
- Adenoid-cystic/Acinic cell
- Secretory
- Metaplastic, low grade
 - Low-grade adenosquamous
 - Fibromatosis-like

**Poor
prognosis**

**Good
prognosis**

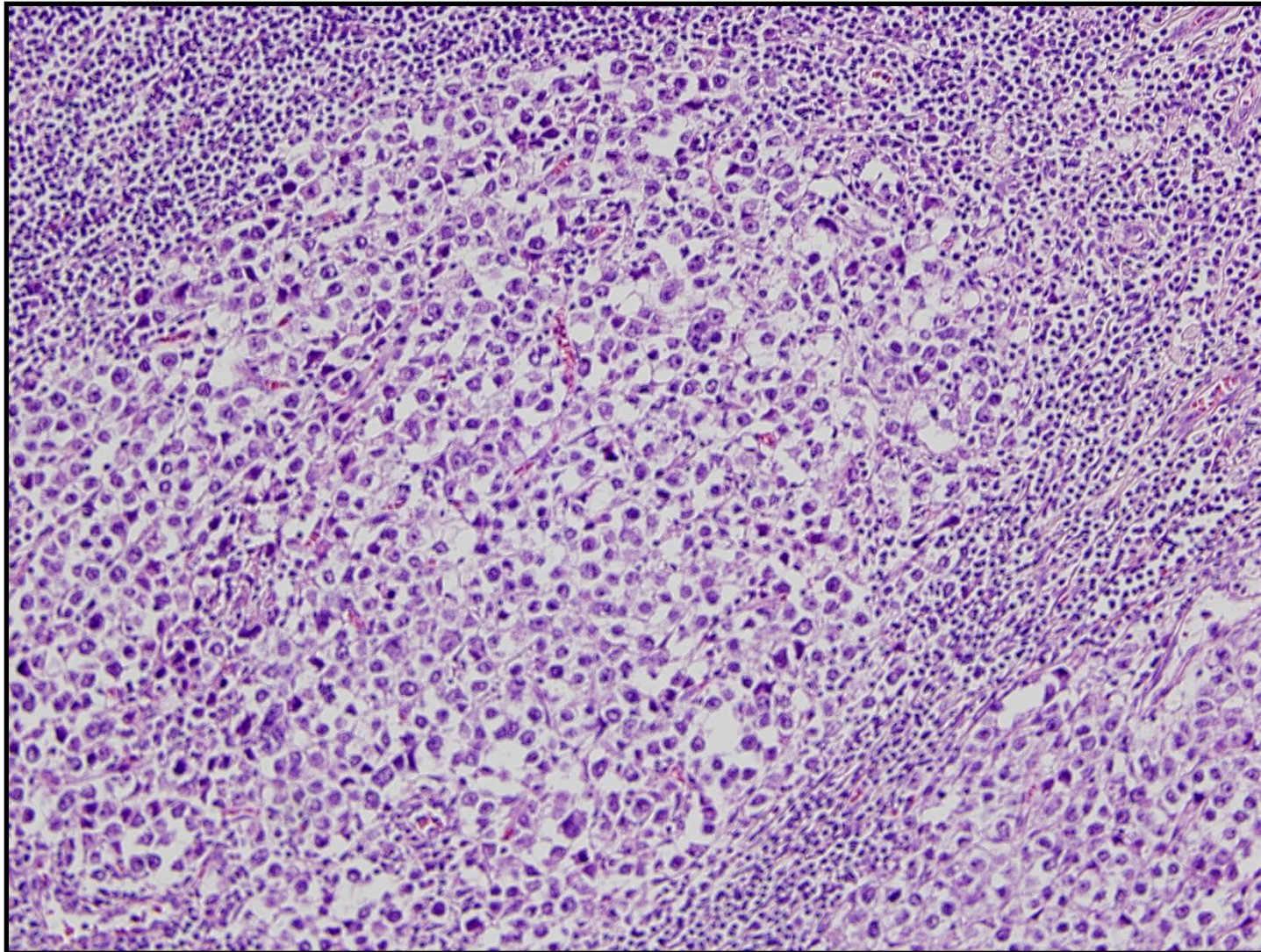
Medullary Carcinoma



Morphological Criteria

- Good limitation
- Solid growth > 75%
- Lack of tubular structures
- Atypical nuclei
- High mitotic rate
- Moderate to marked inflammatory infiltrate

Medullary Carcinoma

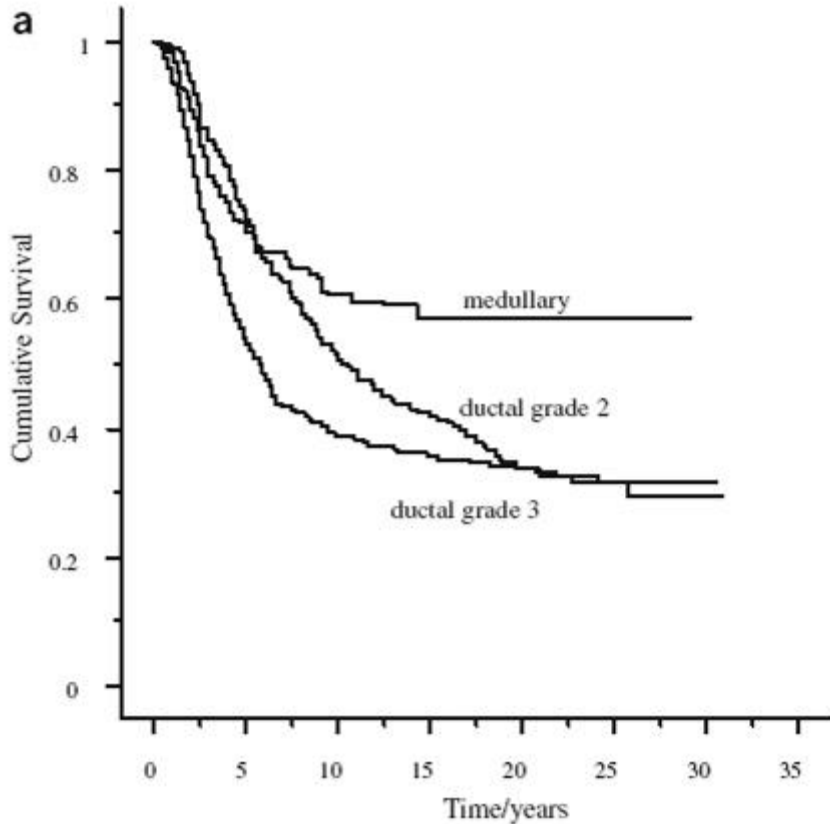


Medullary Carcinoma

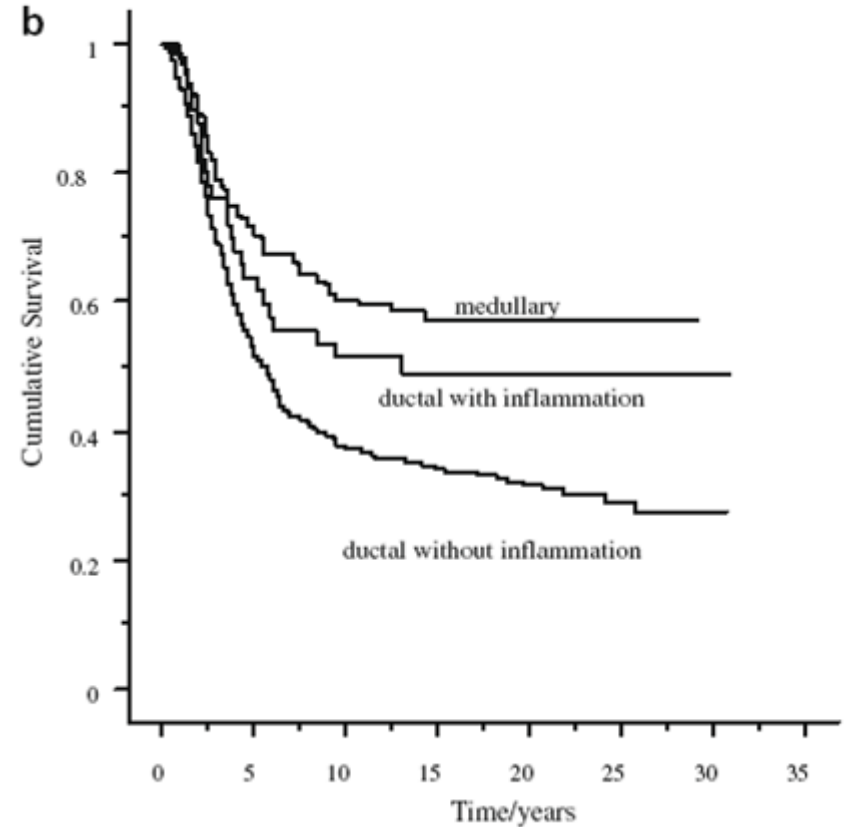
- Women with BRCA1 mutation: 30% MBC
- 15% of MBC occur BRCA1+
- Prognosis better than high grade IDC
- 10-year survival from 50 to 90%
- 90% MBC are N0
- Very good chemo and radiosensitivity

Medullary Carcinoma

Overall survival depending on the type and histological grade



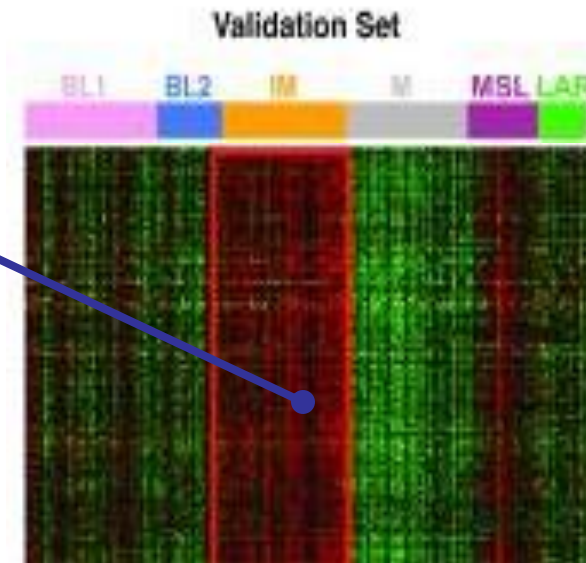
Overall survival in grade III tumors depending on the type and stromal inflammation



1579 patients operated on between 1974 and 1988 - No adjuvant treatment

Immunomodulatory Basal-Like BC

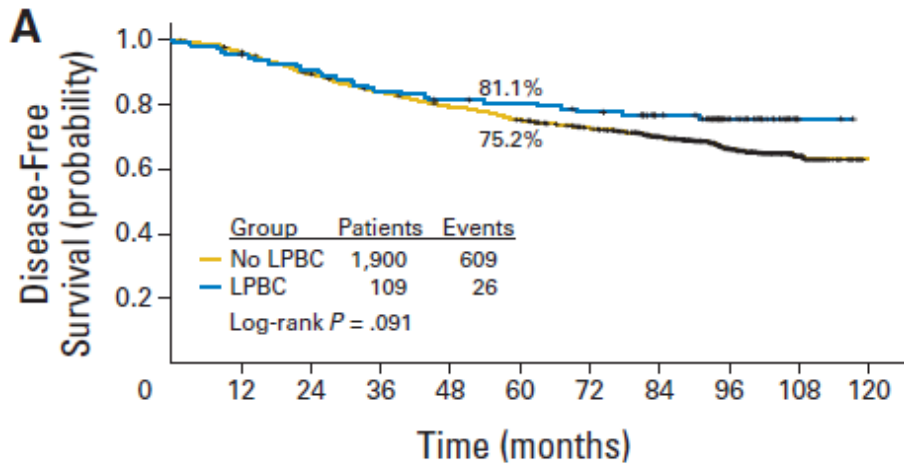
IM: immune cell Processes



- 10-15% of BLBC
- enriched in immune cell processes
- **medullary BC**
- ?BRCA1 carriers
- p53 mutant

Prognostic Value of TILs

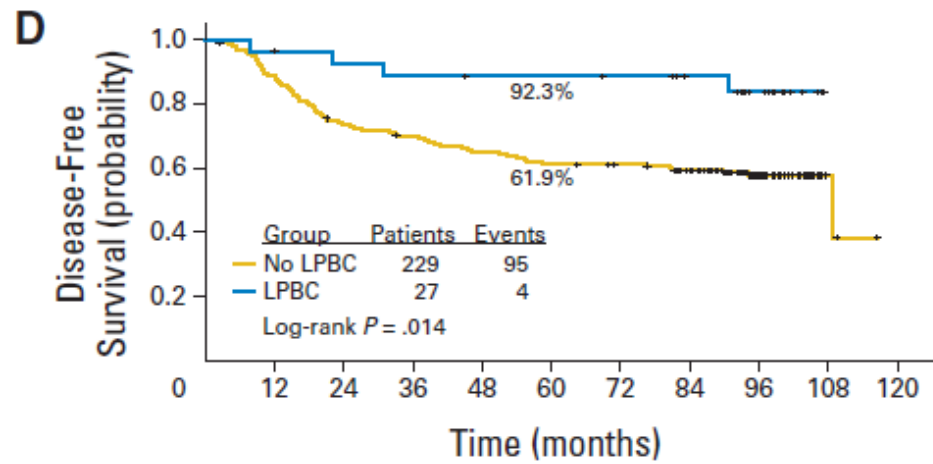
All Patients



No. at risk

| | | | | | | | | | | | |
|---------|-------|-------|-------|-------|-------|-------|-------|-------|-----|----|---|
| No LPBC | 1,900 | 1,824 | 1,687 | 1,570 | 1,482 | 1,394 | 1,314 | 1,062 | 430 | 67 | 4 |
| LPBC | 109 | 104 | 98 | 91 | 86 | 84 | 80 | 69 | 34 | 2 | 0 |

TNBC

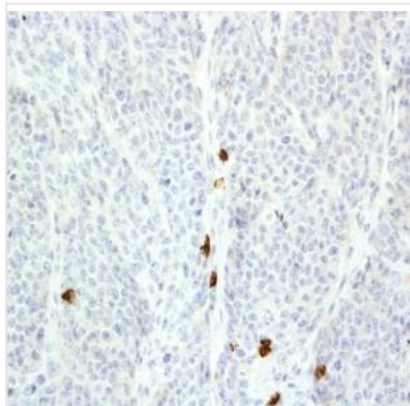
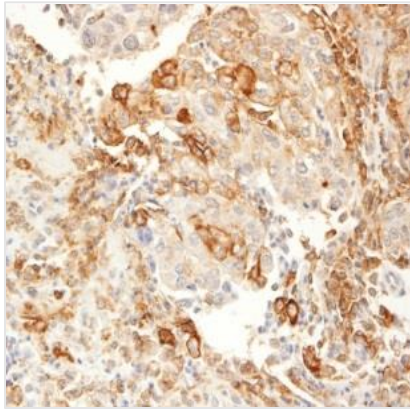


No. at risk

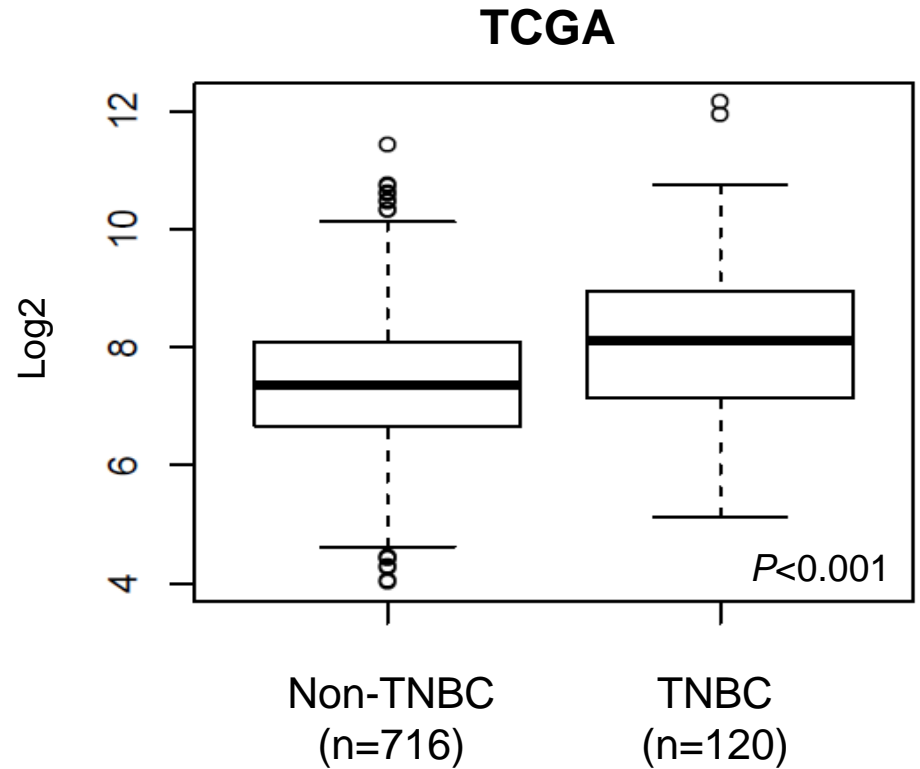
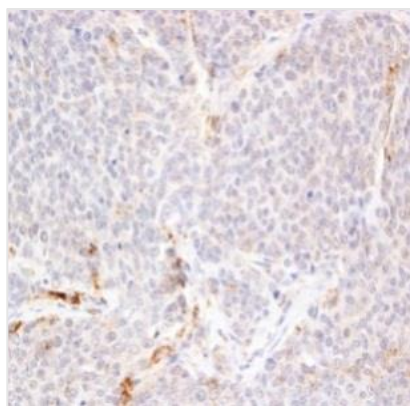
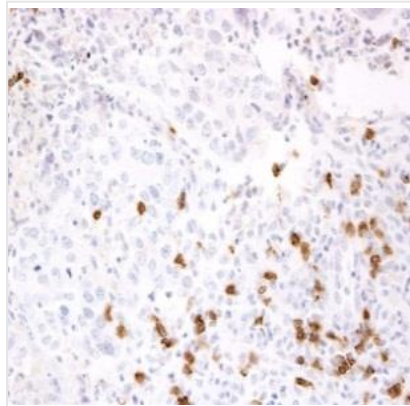
| | | | | | | | | | | | |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|----|---|---|
| No LPBC | 229 | 202 | 167 | 156 | 146 | 138 | 134 | 116 | 41 | 3 | 0 |
| LPBC | 27 | 26 | 24 | 23 | 22 | 22 | 21 | 18 | 11 | 0 | 0 |

PD-L1 in TNBC

PD-L1



CD8⁺ T cells



Metaplastic Carcinoma

Heterogeneous group of tumors

pure epithelial form

squamous/adenosquamous ca

ca with spindle cell metaplasia

mucoepidermoid ca

mixed forms (epithelial/mesenchymal)

ca with chondroid or osseous differentiation

matrix producing ca

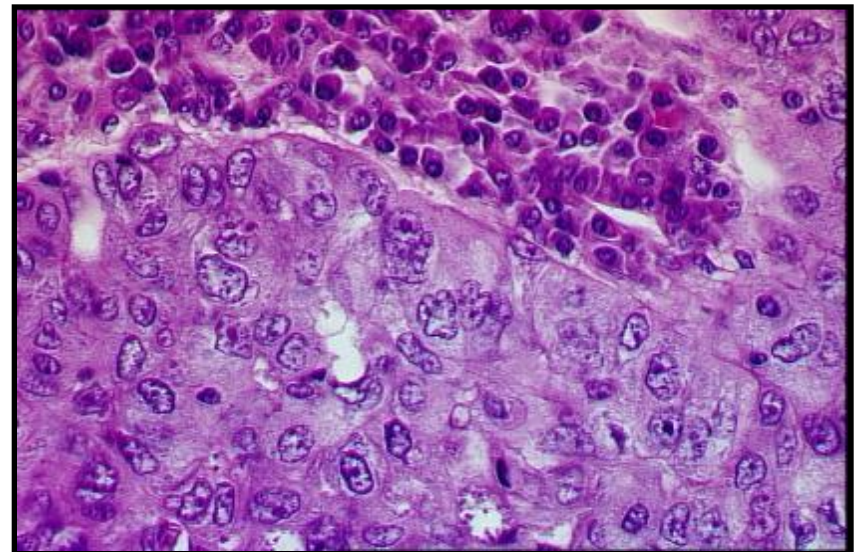
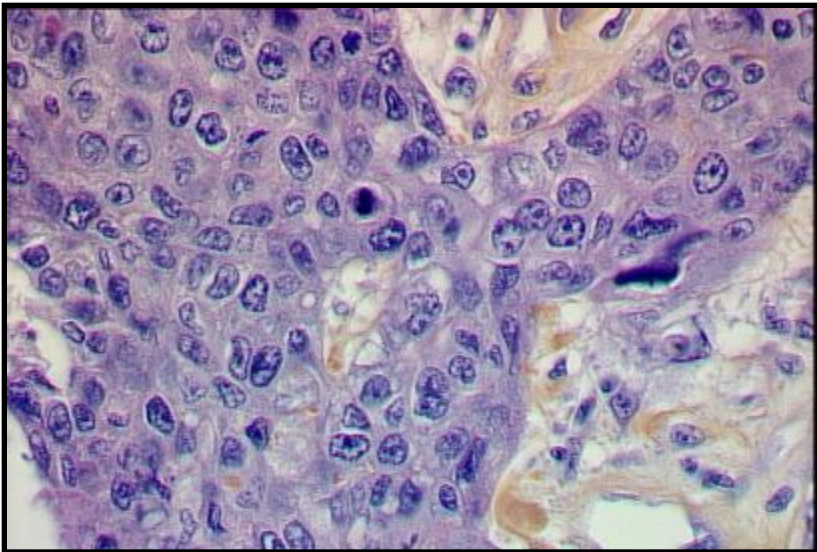
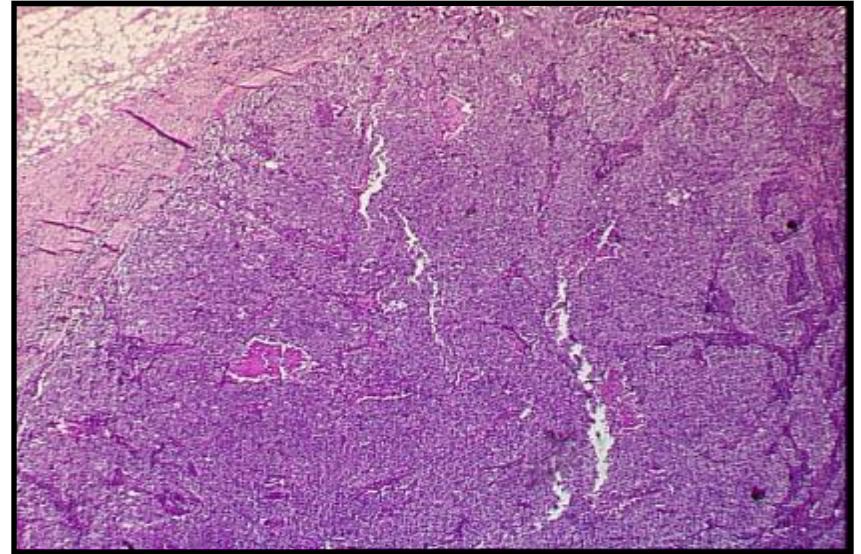
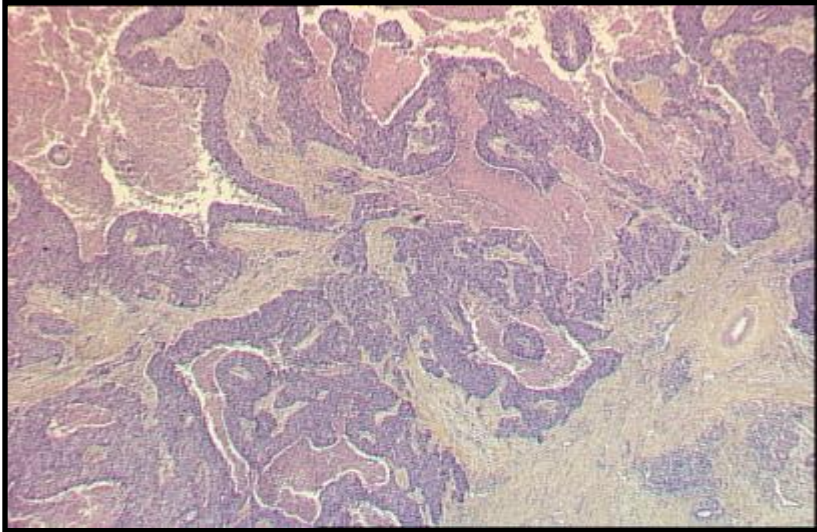
carcinosarcoma

high grade sarcomatoid ca

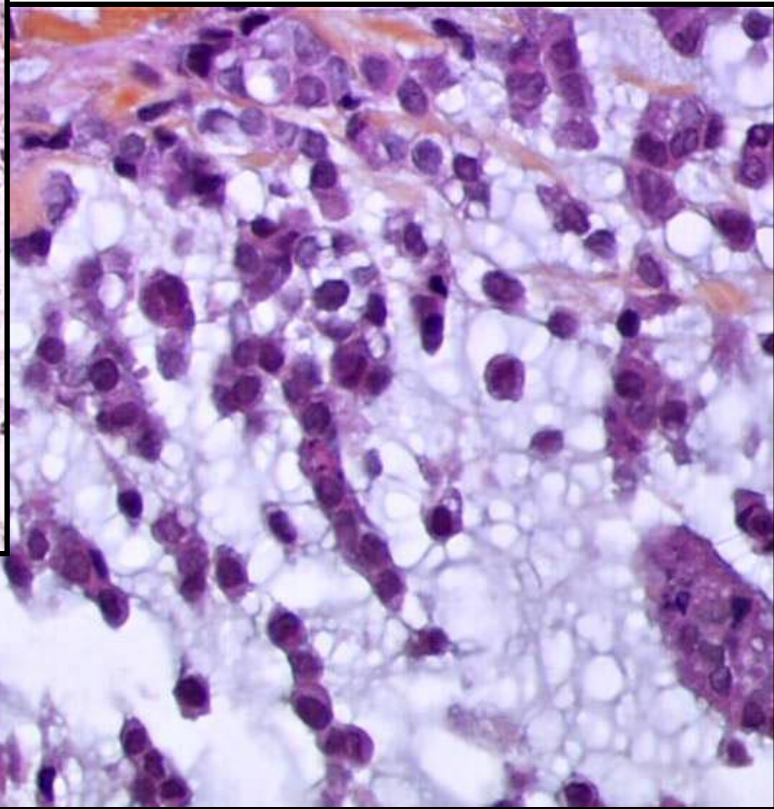
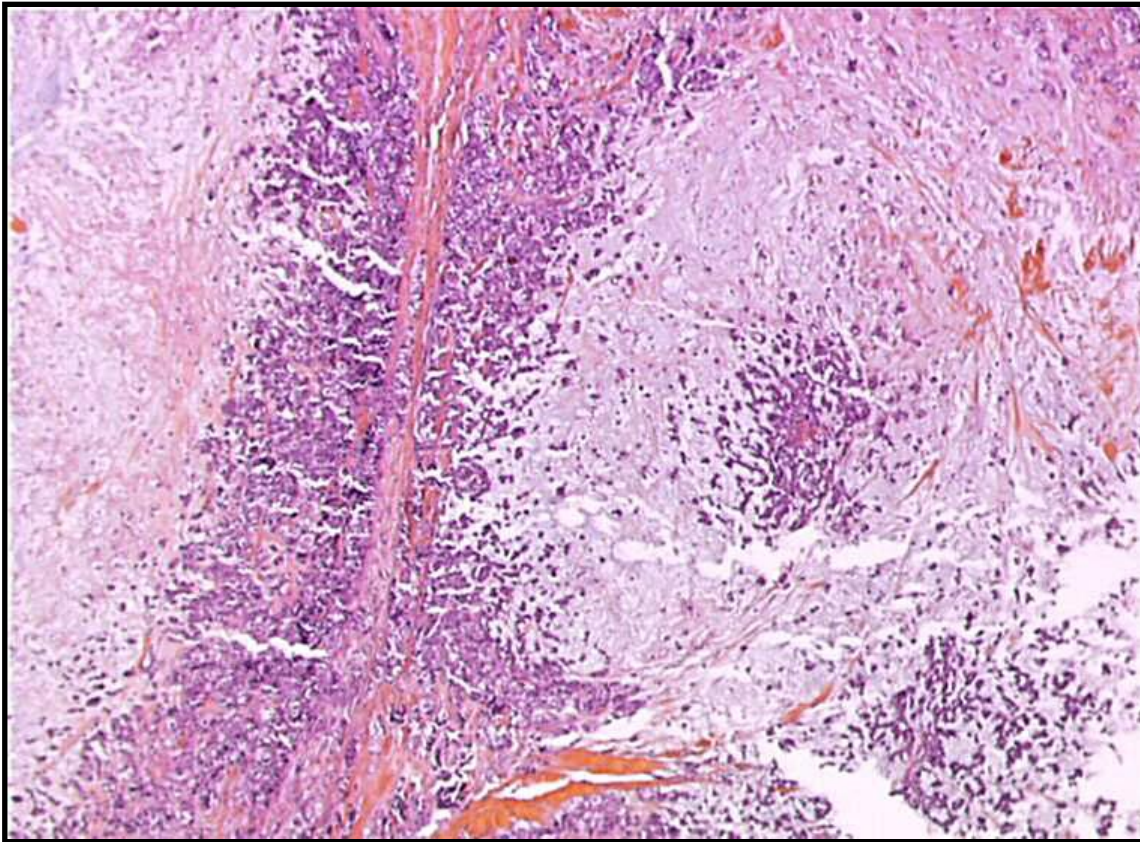
Metaplastic Carcinoma

- 1% of breast ca
- Large tumors, often rapid growth
- EGFR activation, wnt pathway activation, BRCA methylation
- Low rate of lymph node involvement
- Poor overall survival
 - 70% at 3 years
 - 55% at 5 years

Metaplastic Carcinoma

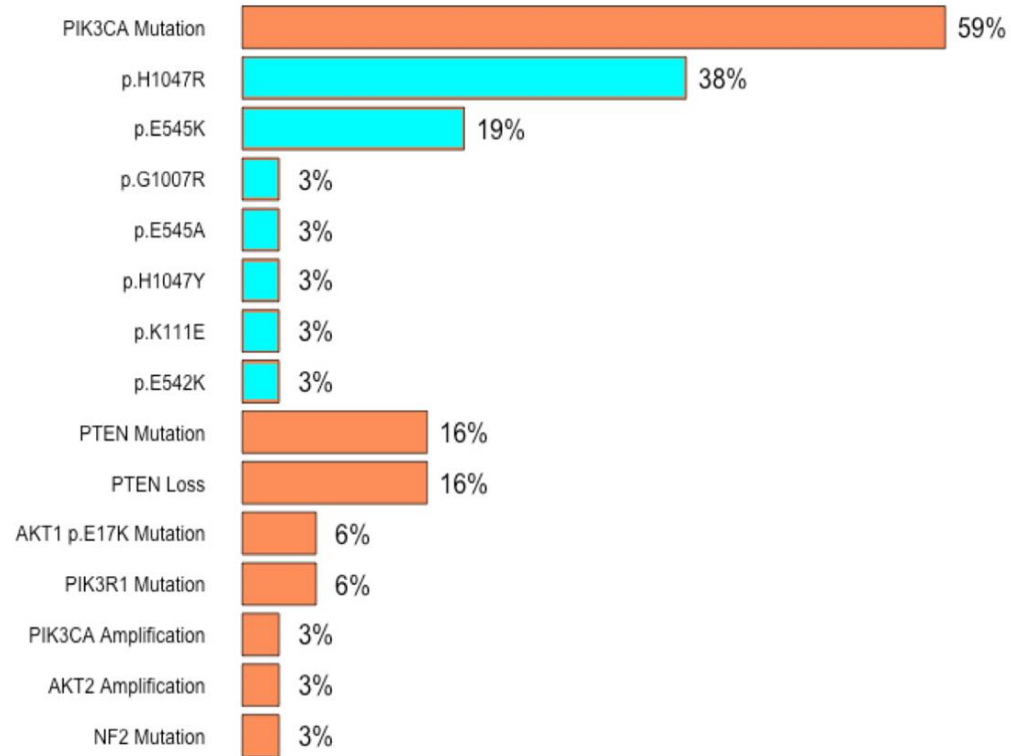


Metaplastic Carcinoma



PI3K Aberrations

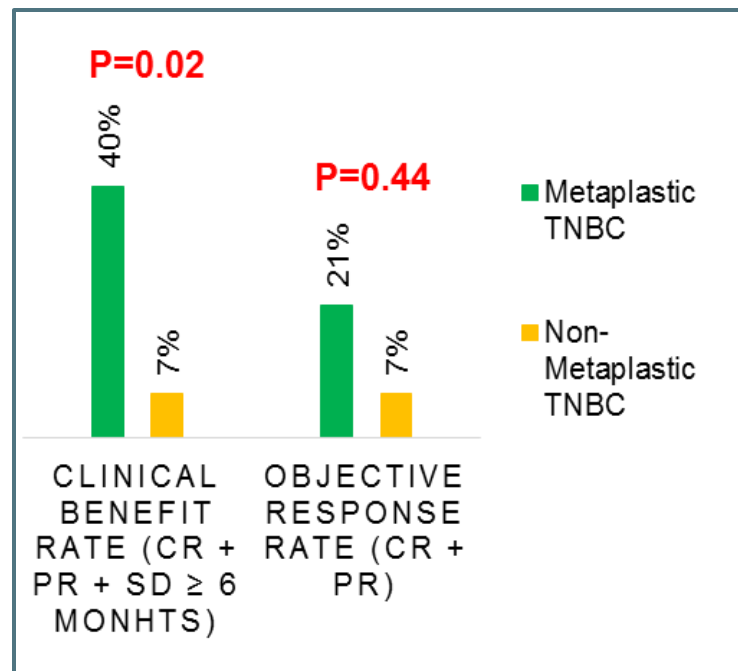
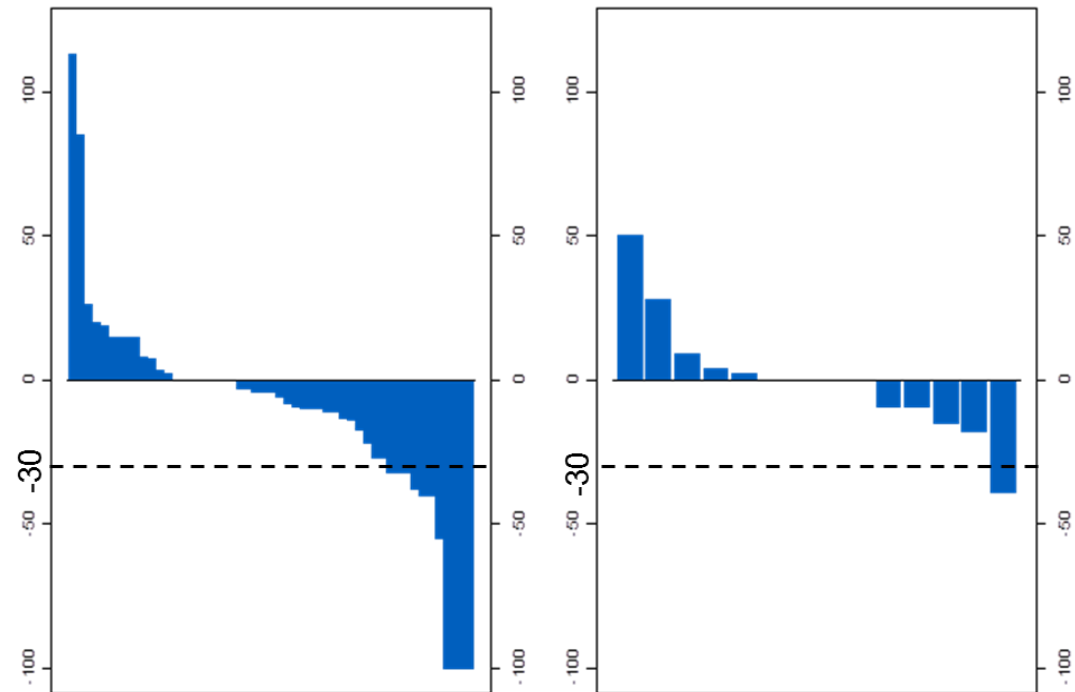
- High incidence of PIK3 pathway activating aberrations
- VEGF/HIF1- α production



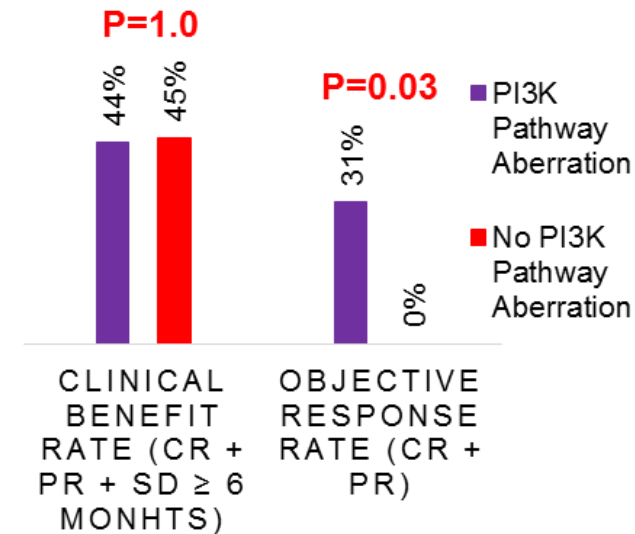
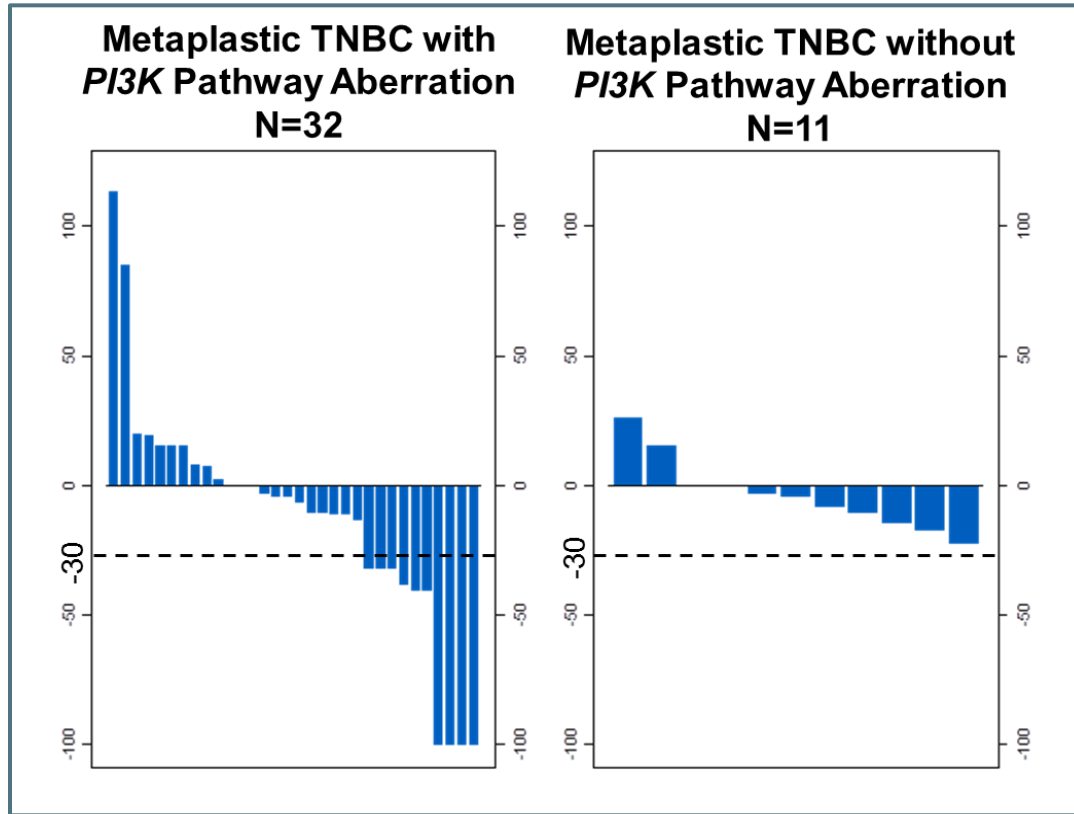
Better Response in Metaplastic TNBC

Metaplastic TNBC

Non-Metaplastic TNBC



Response Higher in Metaplastic Cancers with PI3K Aberrations



Secretory Carcinoma

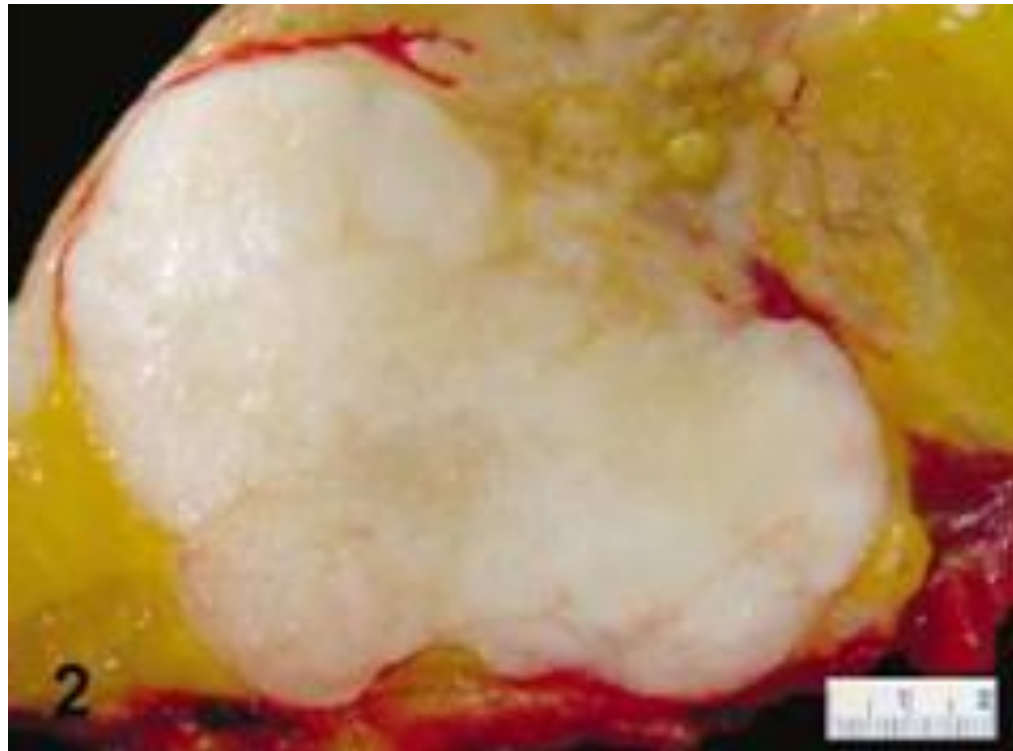
- <1% of breast ca
- 1/3 children and teens
- 2/3 between 20 and 50yrs
- Good prognosis
- Specific molecular alteration
t (12;15) (ETV6; NTRK3)

Secretory Carcinoma

- Rare variant of invasive ductal carcinoma
- First described in children as “juvenile carcinoma”
- A wide range of ages (3-87 years), most of pts are adults (mean age, 25)

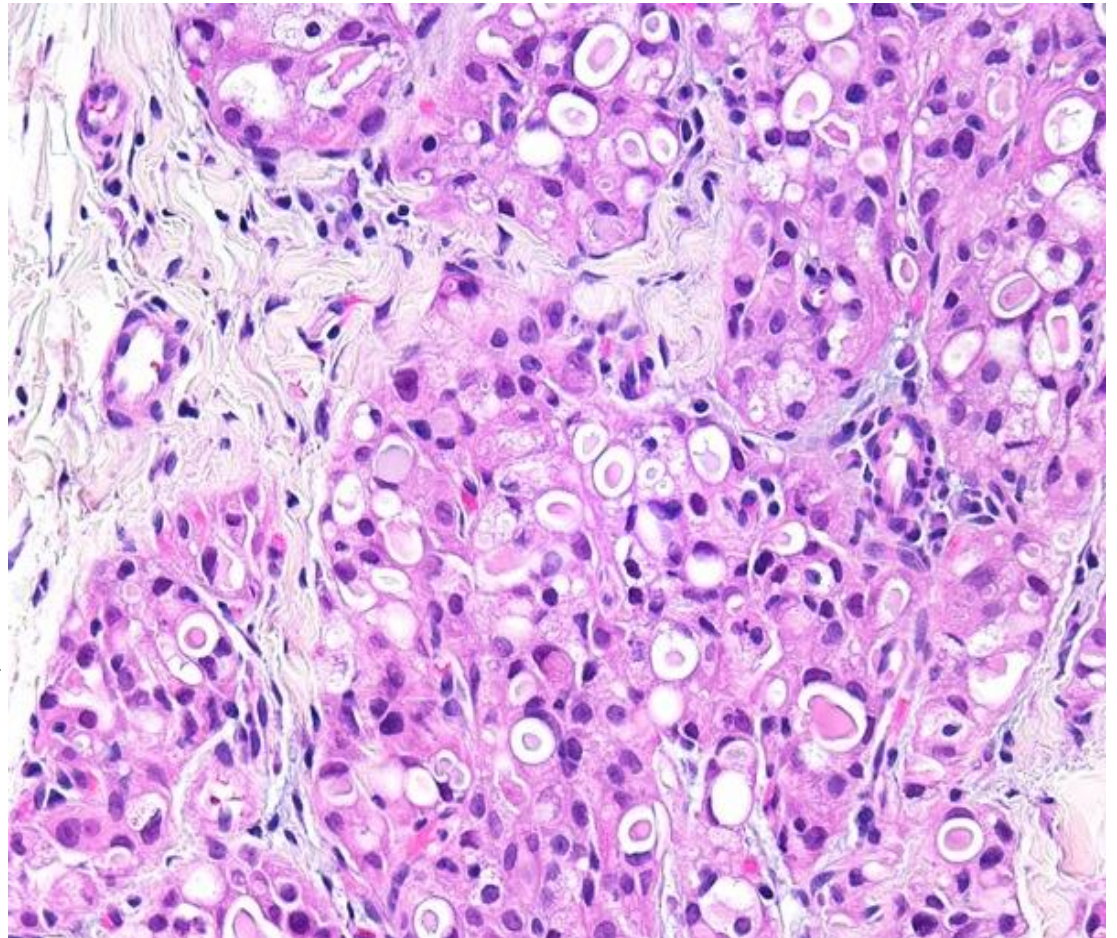
Secretory Carcinoma

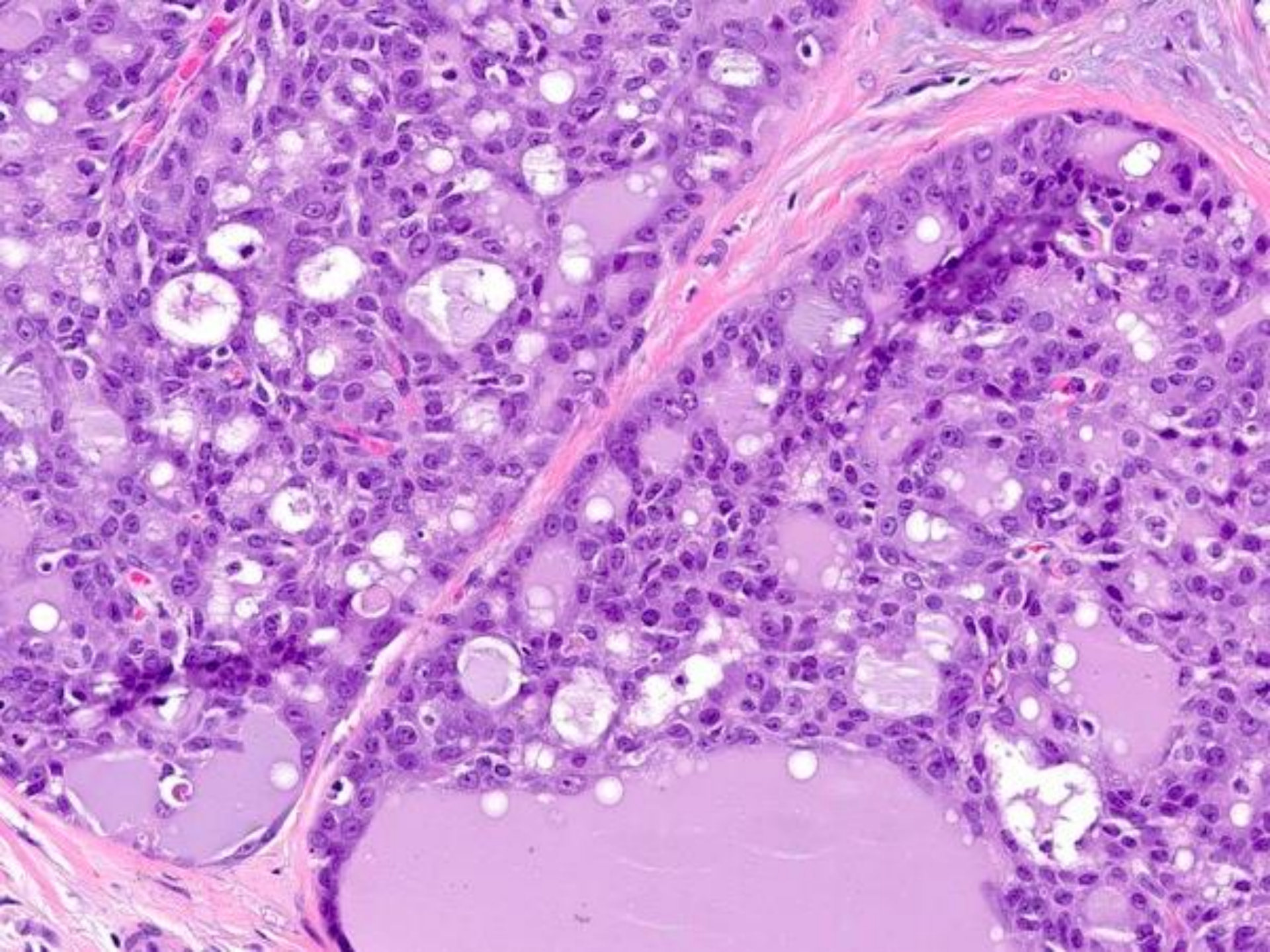
- Well circumscribed slow-growing mobile mass with lobulated margins and white-to-tan cut surface
- size ranges from 1-12 cm (median, 3 cm)

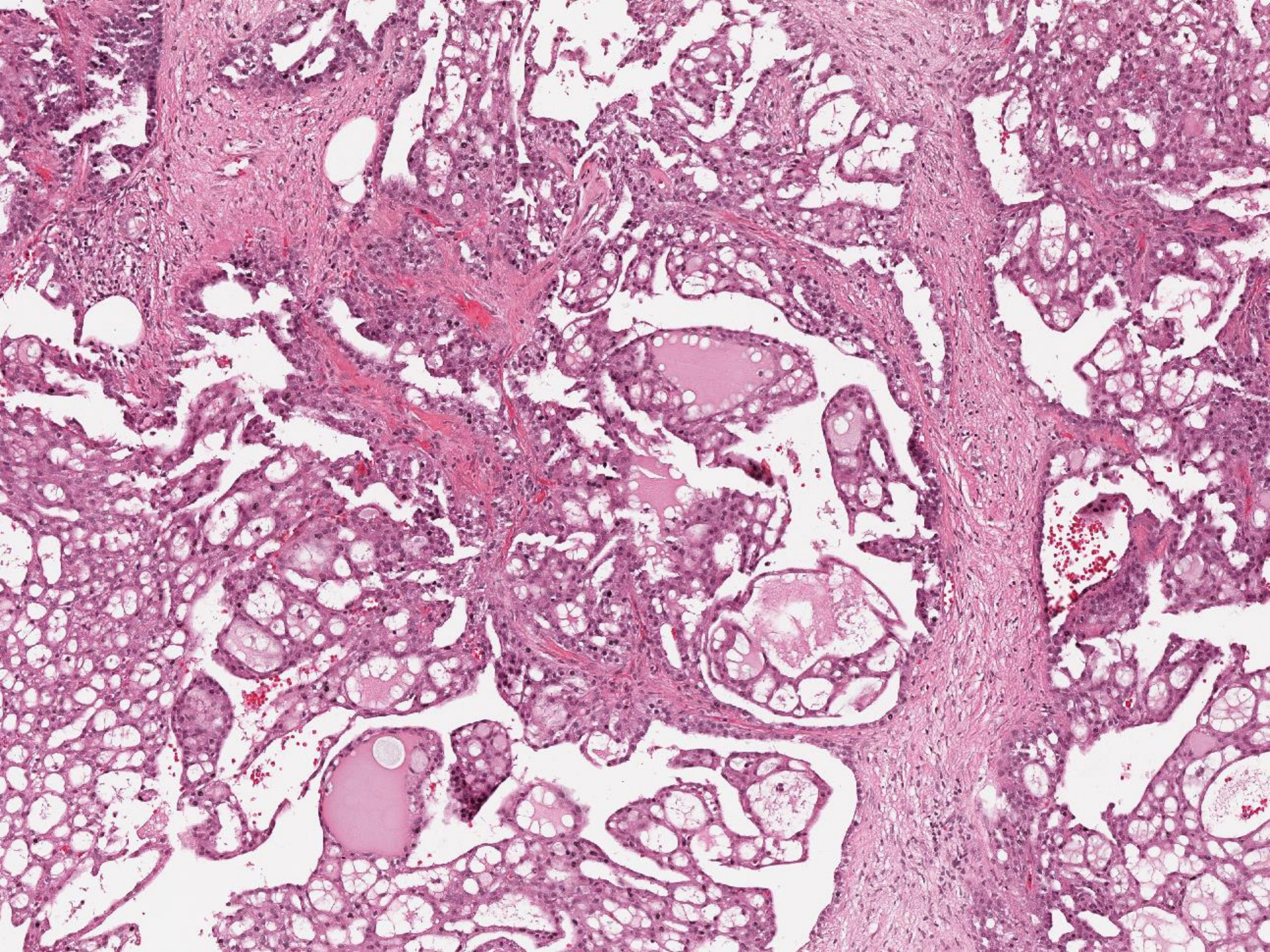


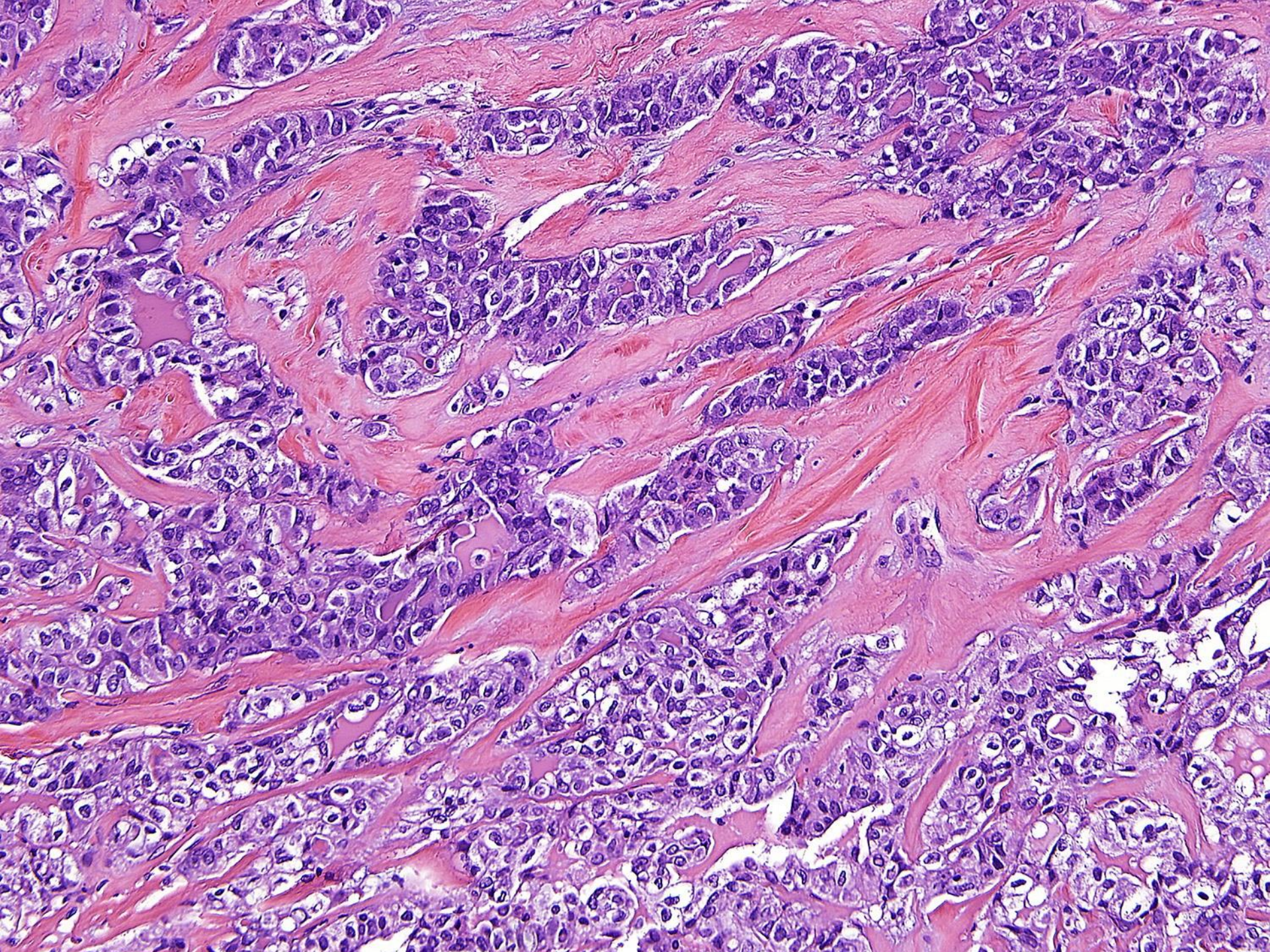
Secretory Carcinoma

- Abundant intracellular and extracellular secretions
- Growth patterns:
 - Nested cysts
 - Cribriform
 - Papillary
 - Solid
 - Trabecular
 - Glandular/tubular

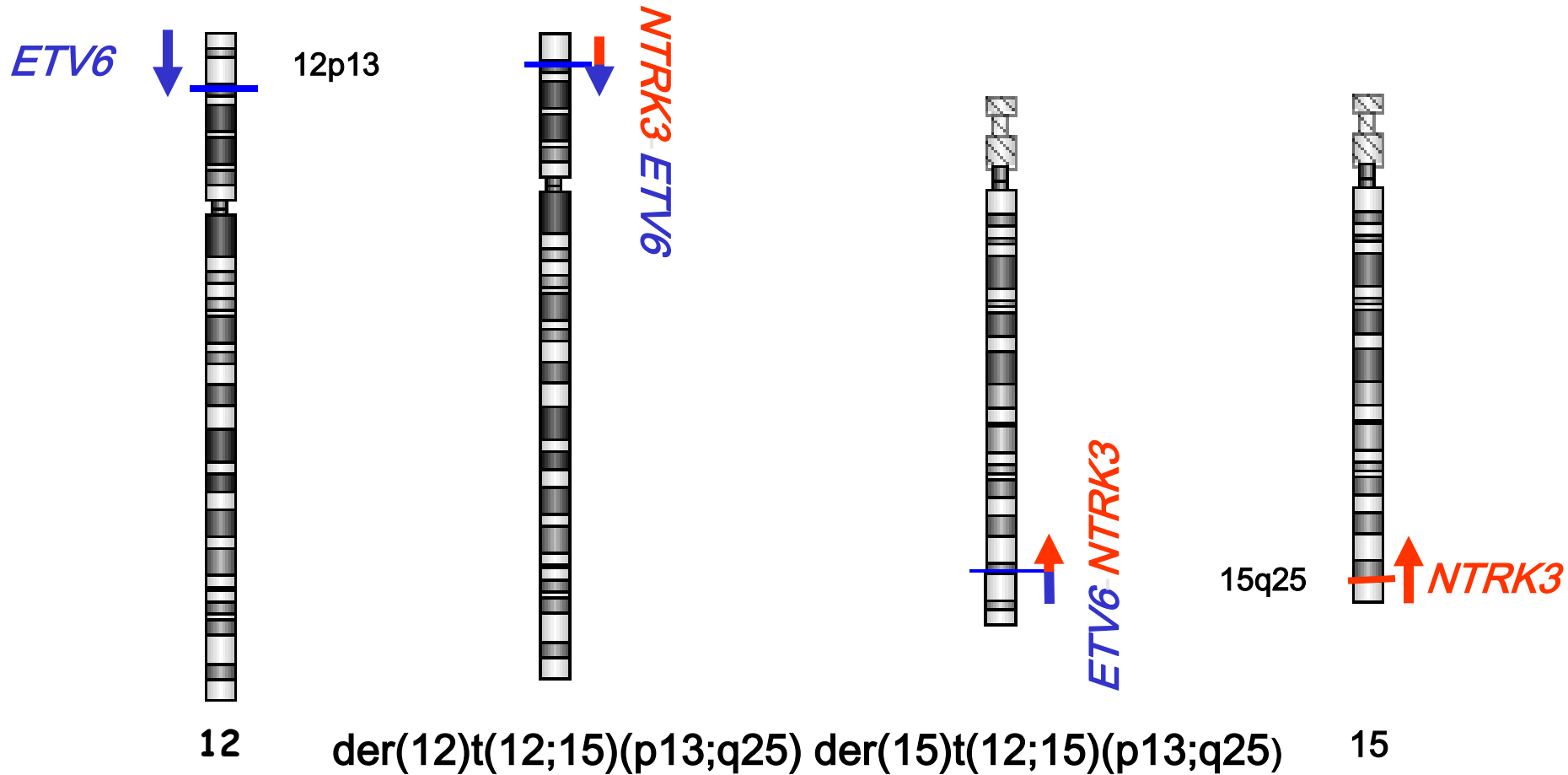






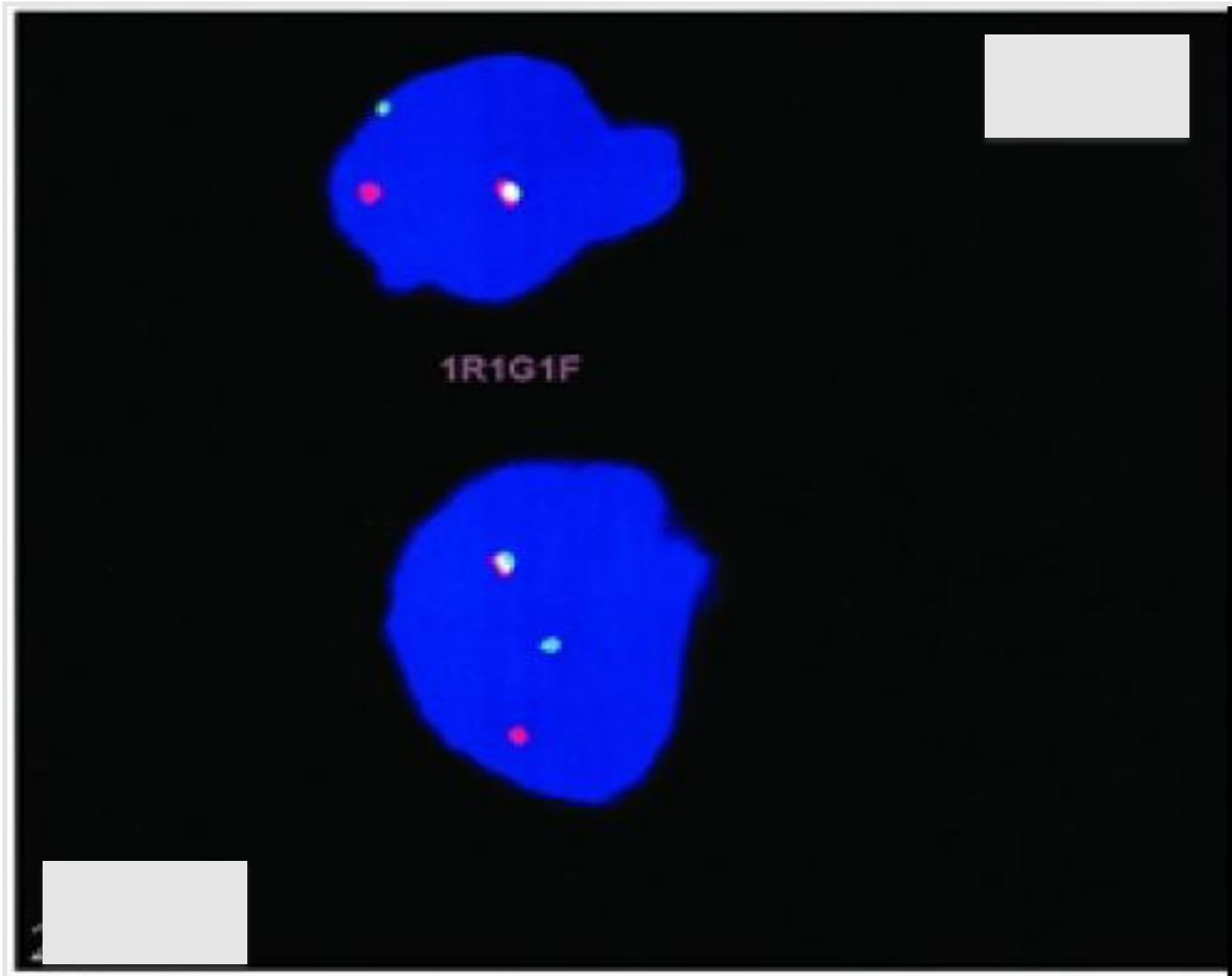


Reciprocal Translocation (12;15)



ETV6-NTRK3 is the molecular signature

Secretory Carcinoma



Potential Targeted Therapy

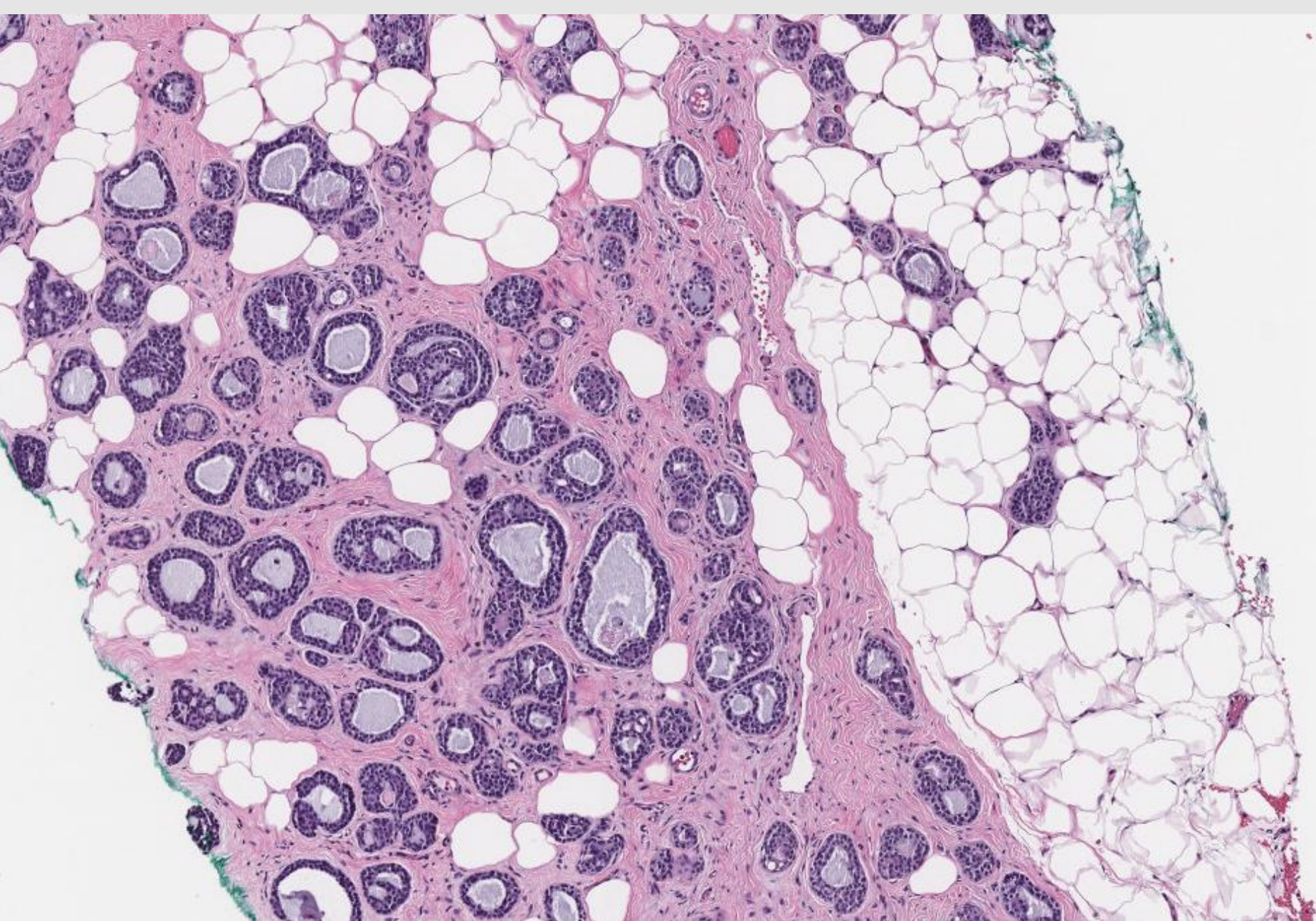
- NTKR 3 (Neurotrophic Tyrosine Kinase, Receptor, Type 3) inhibitors

Prognosis

- Usually excellent
- Regional nodal metastasis may occur at the time of diagnosis
- Distant recurrence may occur and fatal

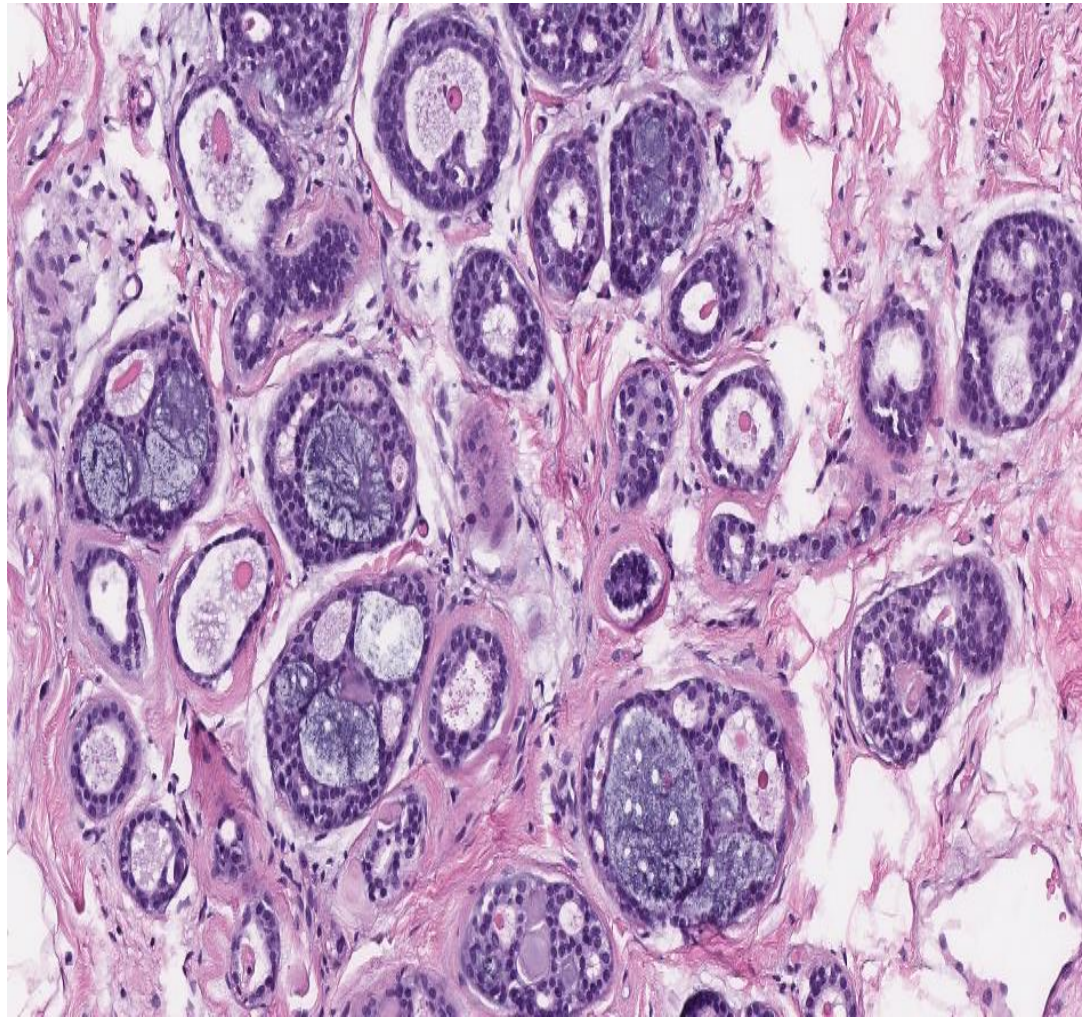
Adenoid Cystic Carcinoma

- Definition
 - Identical to salivary gland counterpart
 - May be associated with microglandular adenosis
- Epidemiology
 - Rare, 0.1% of breast carcinomas
 - Mean age 50-63 years, range 25-80 years
 - 50% are sub-periareolar



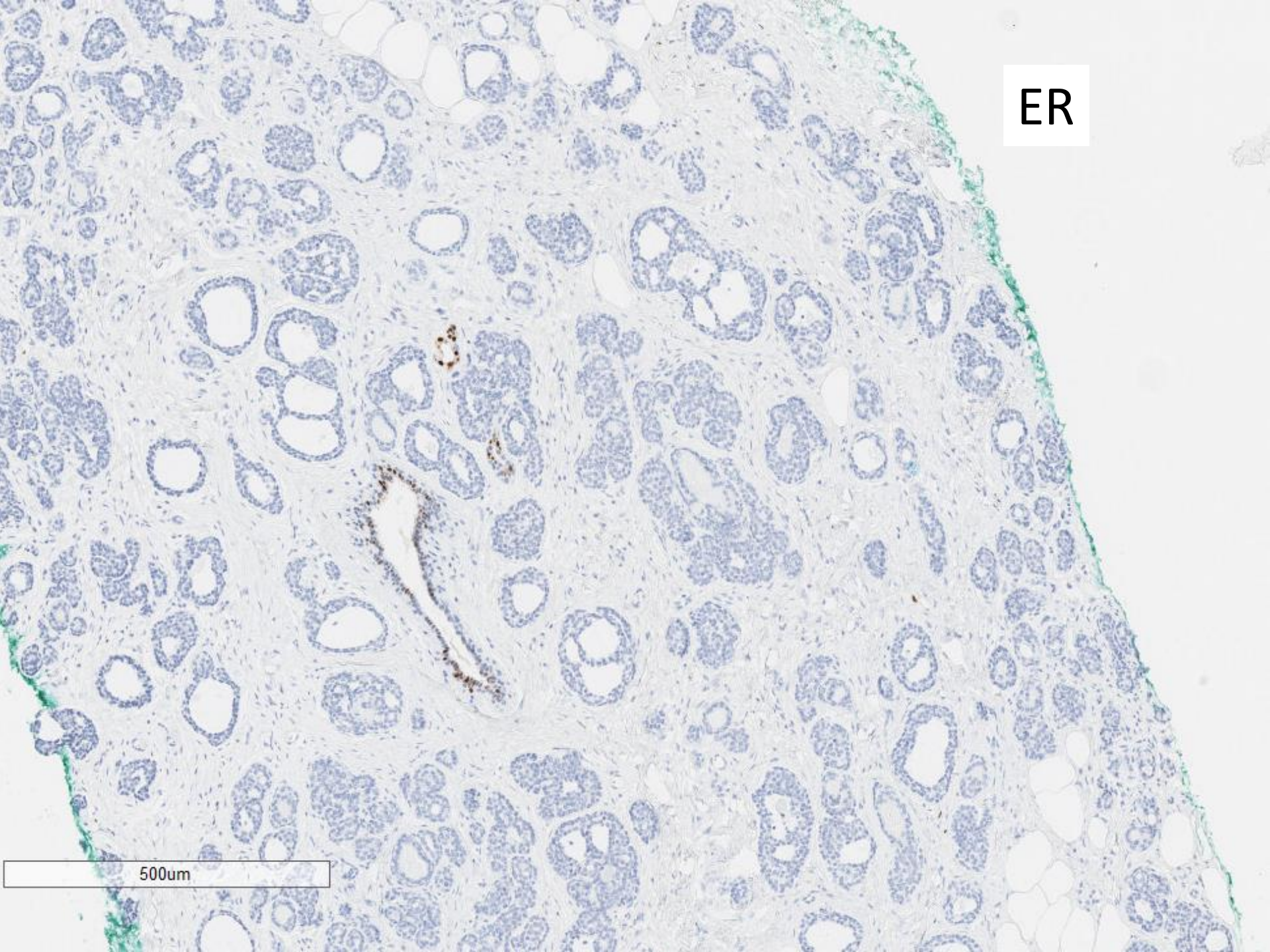
Adenoid Cystic Carcinoma

- 2 types of lumens
 - True lumen lined by acinar/glandular cells with secretions
 - Pseudolumen lined by basal cells contains basement membrane material

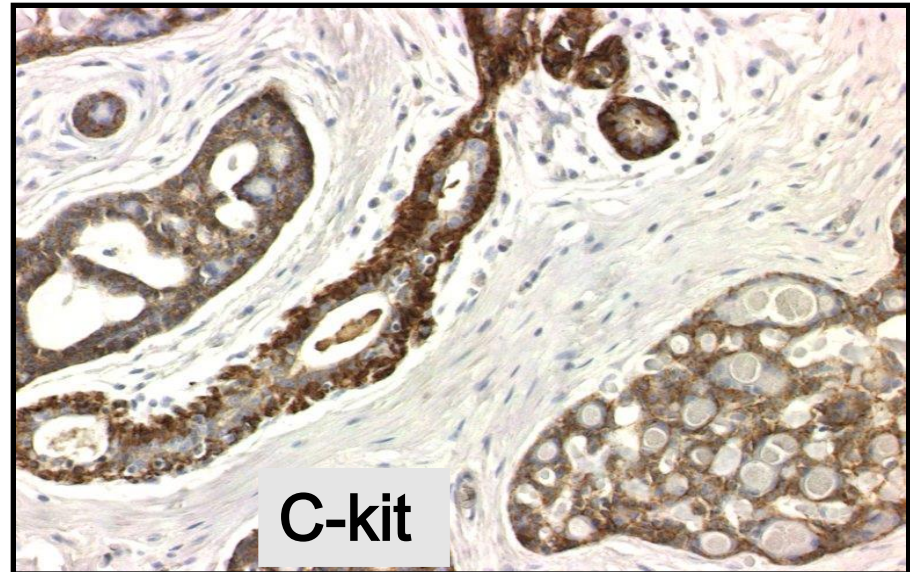
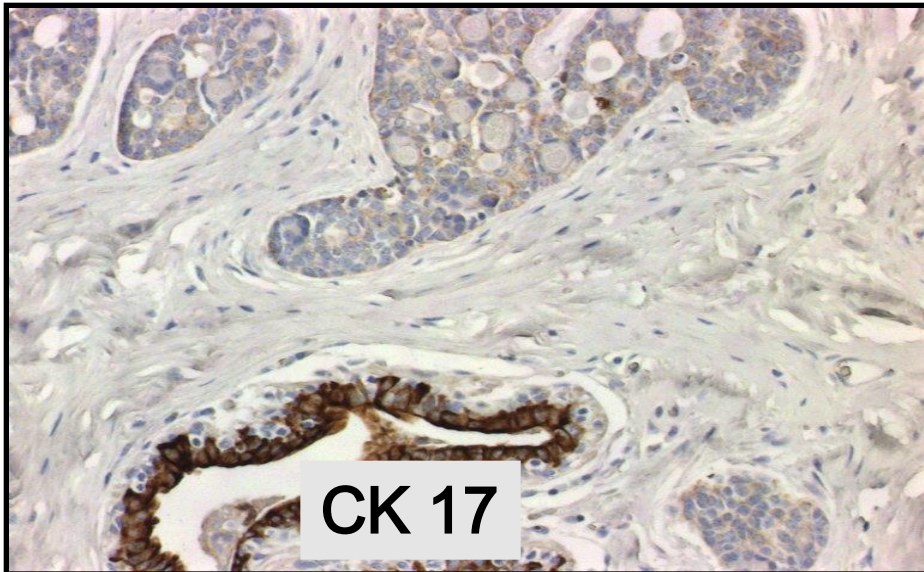
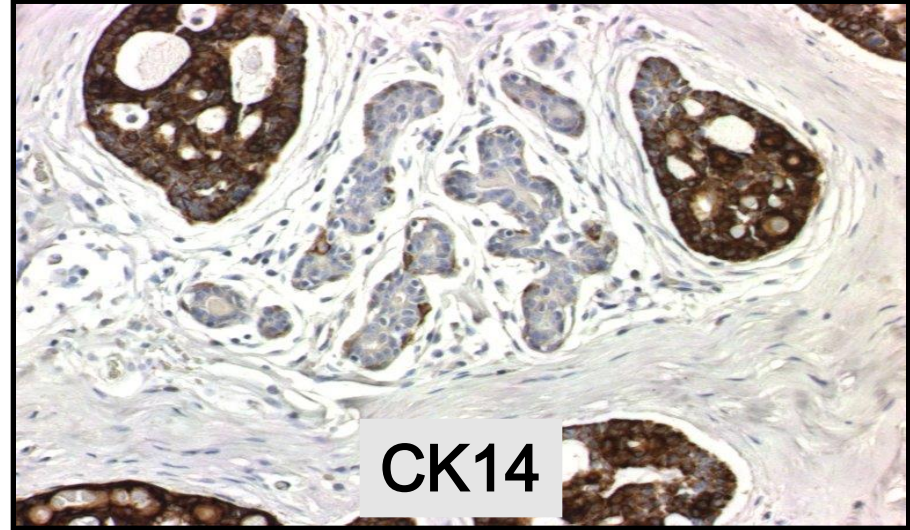
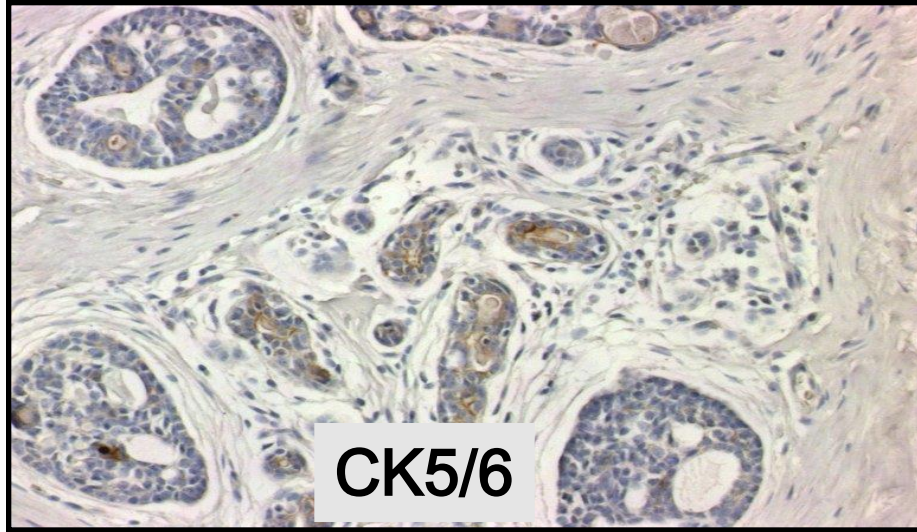


ER

500um



Adenoid Cystic Carcinoma



Adenoid Cystic Carcinoma

- Treatment and prognosis
 - Good to excellent prognosis
 - Recurrence or metastasis are less than usual ductal carcinoma
 - Axillary nodal metastases are rare
 - Treatment is excision with clear margins, possibly radiation, axillary dissection may not be necessary

Adenoid Cystic Carcinoma

Grading scheme:

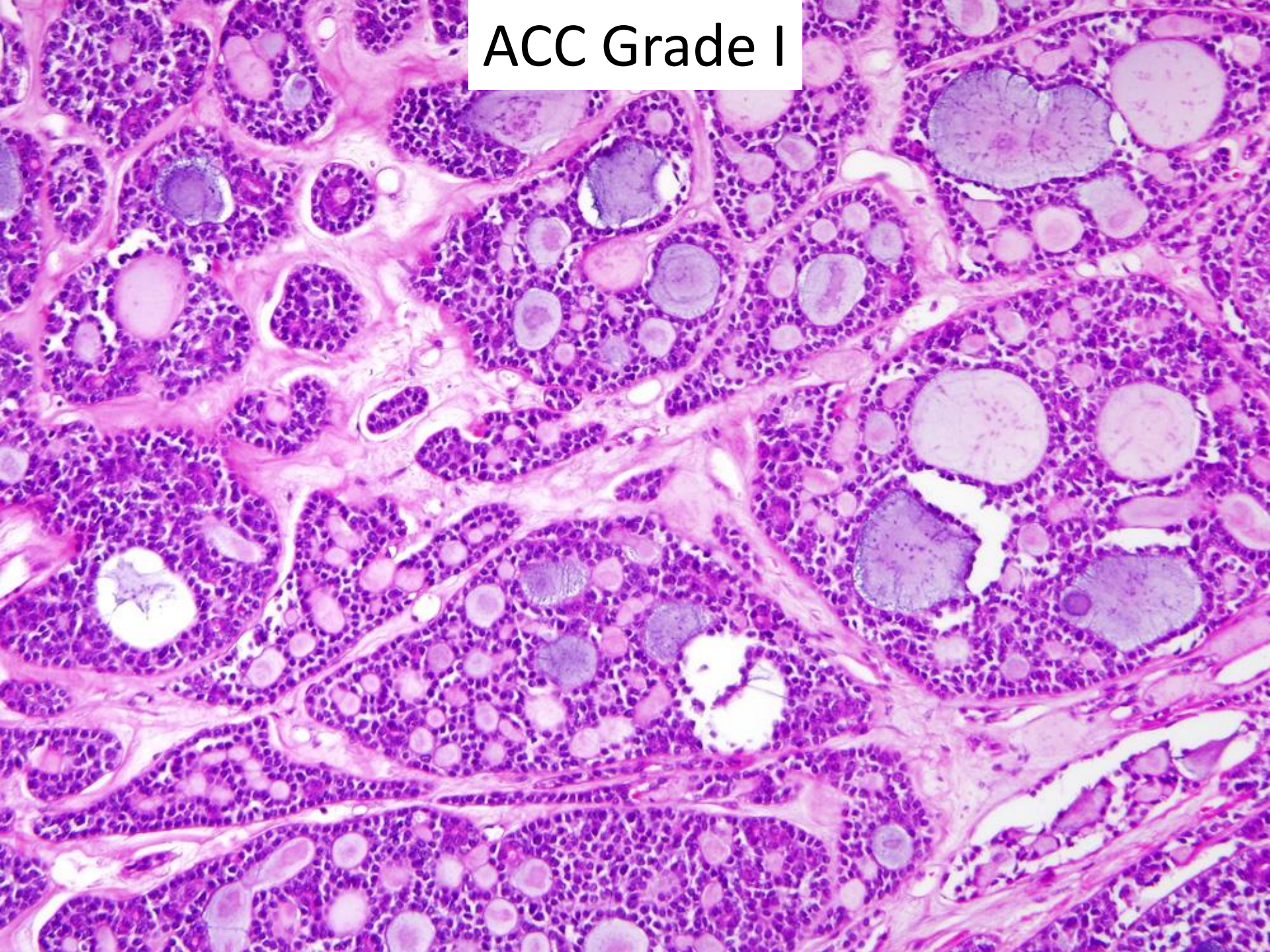
grade I: complete glandular/cystic

grade II: solid component <30%

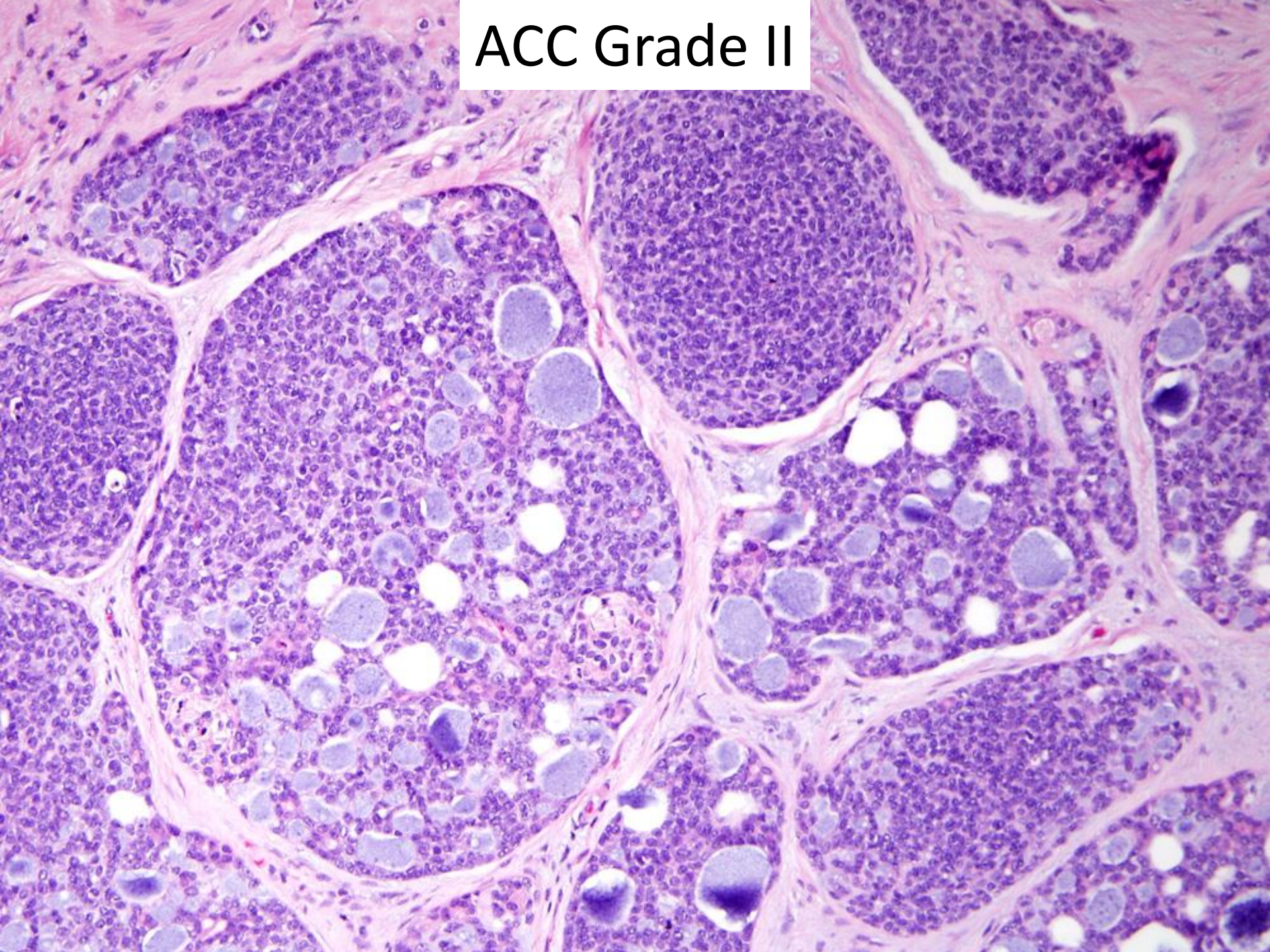
grade III: solid component >30%

Ro JY et al. Hum Pathol 1987;18(12):1276

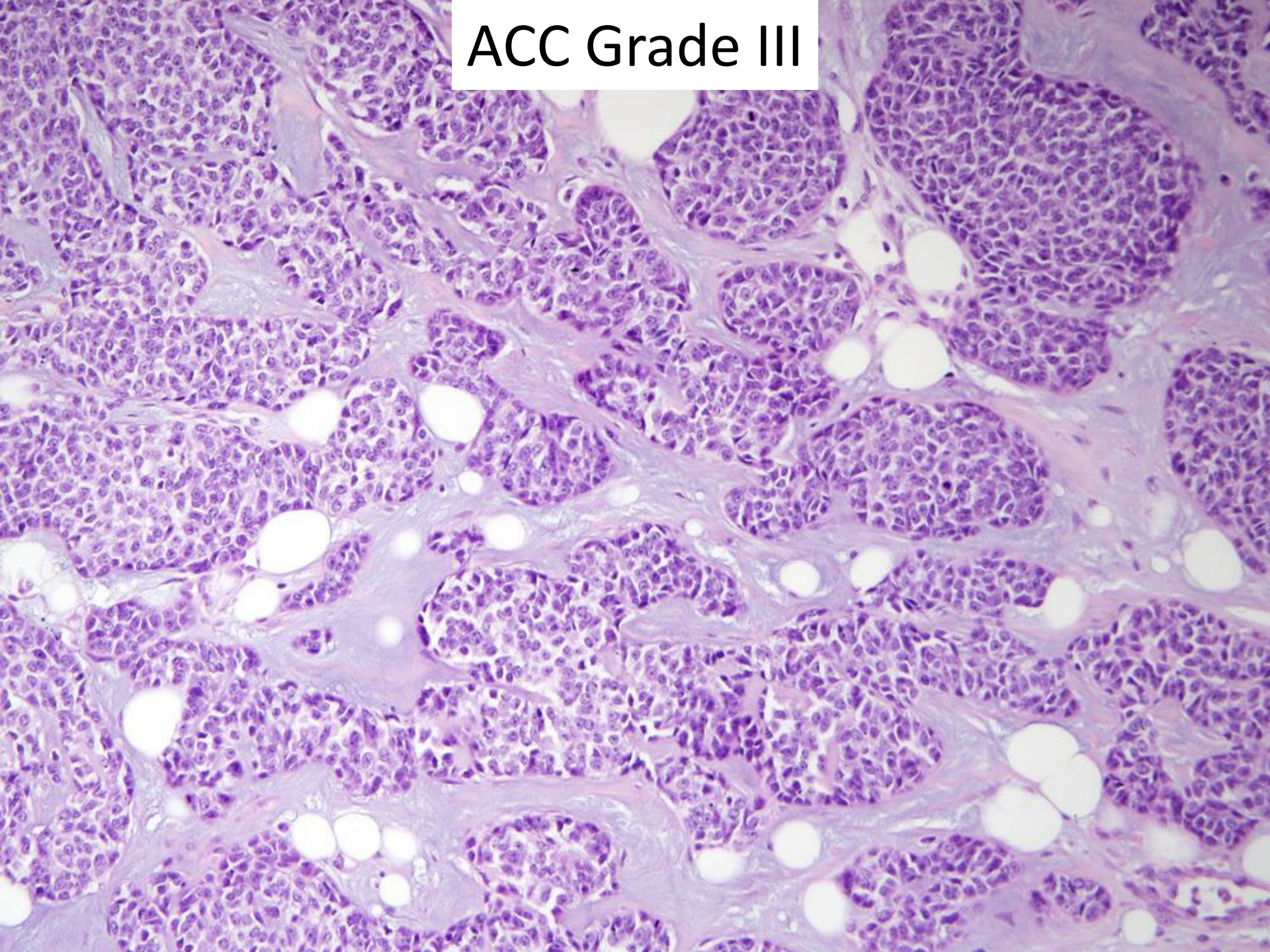
ACC Grade I



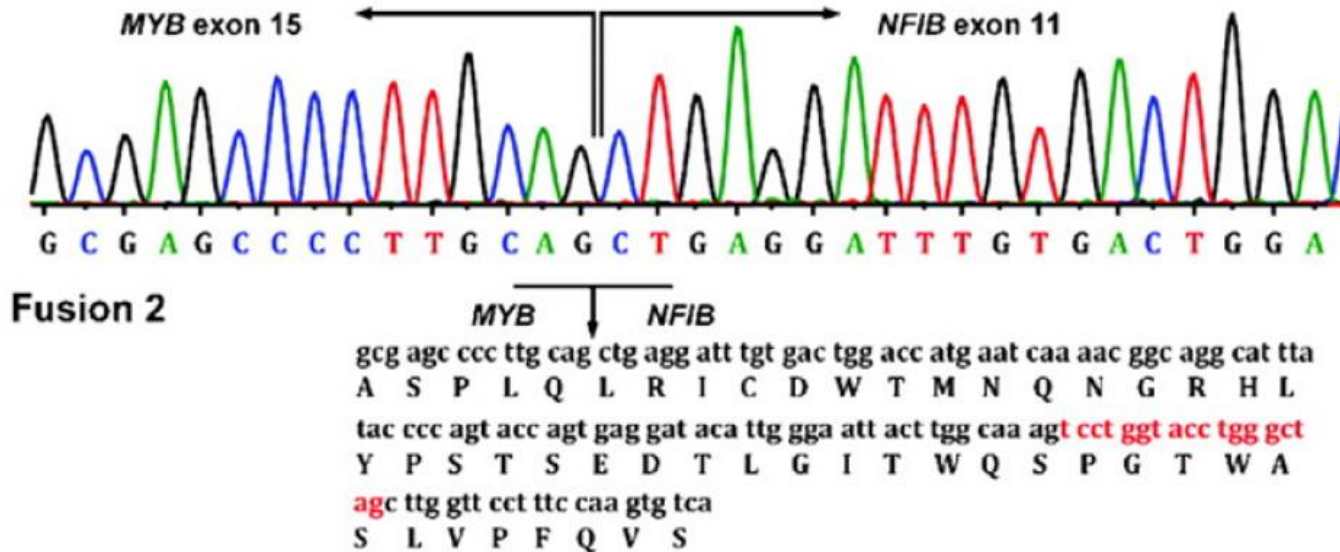
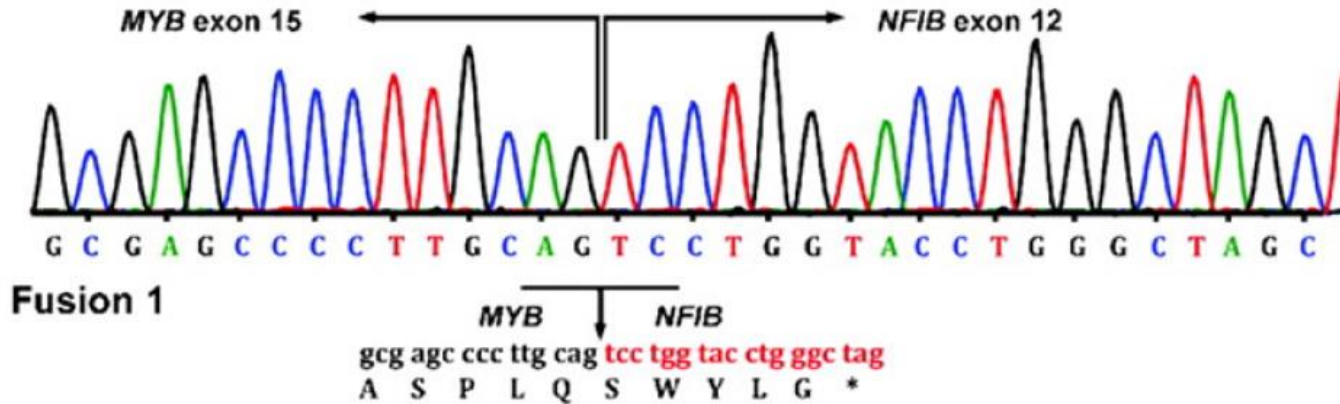
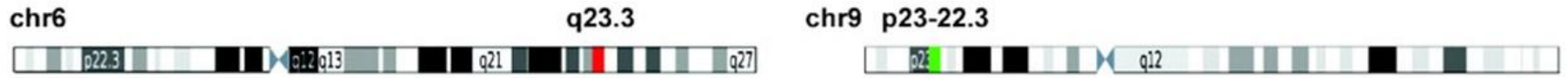
ACC Grade II

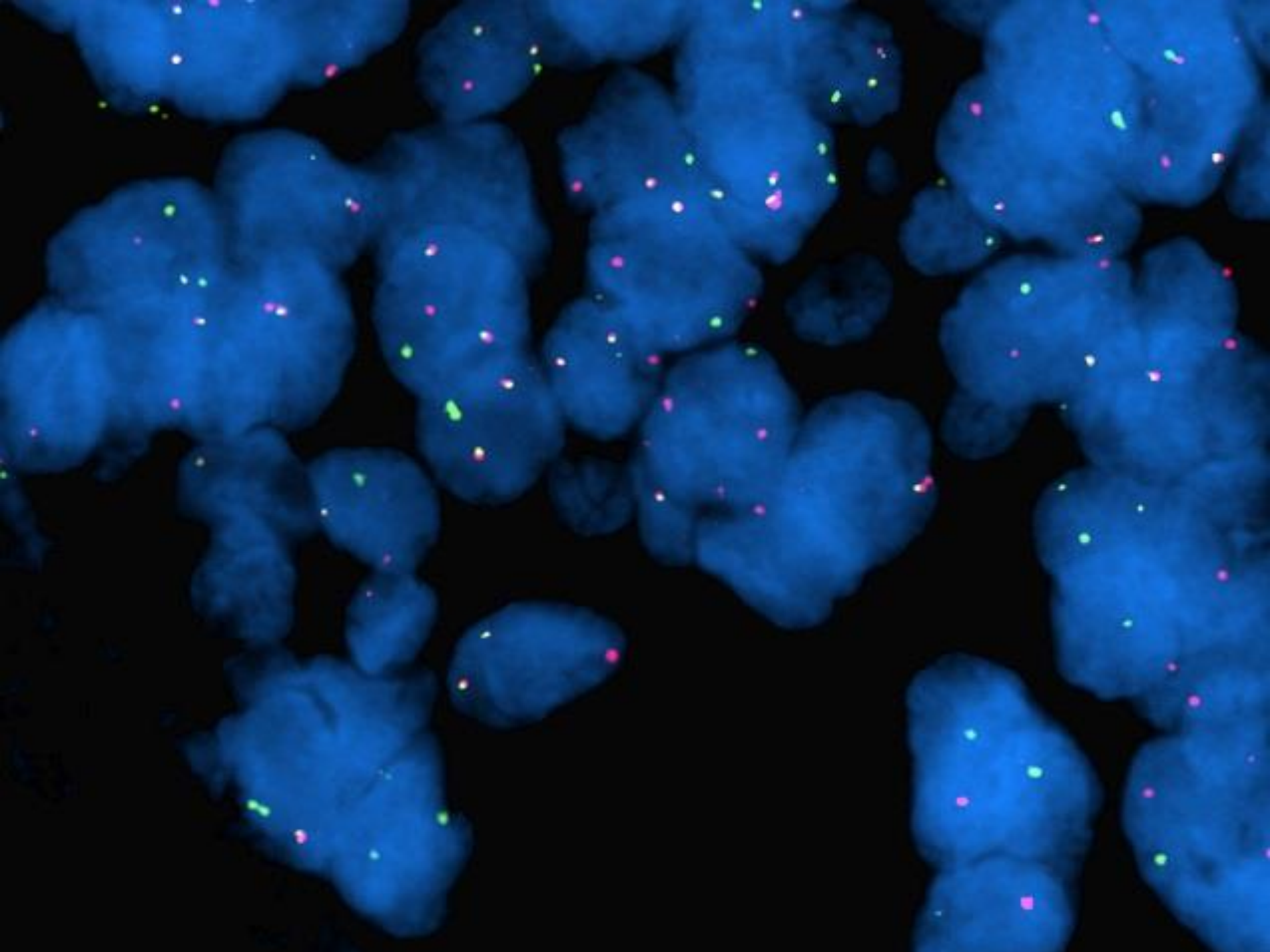


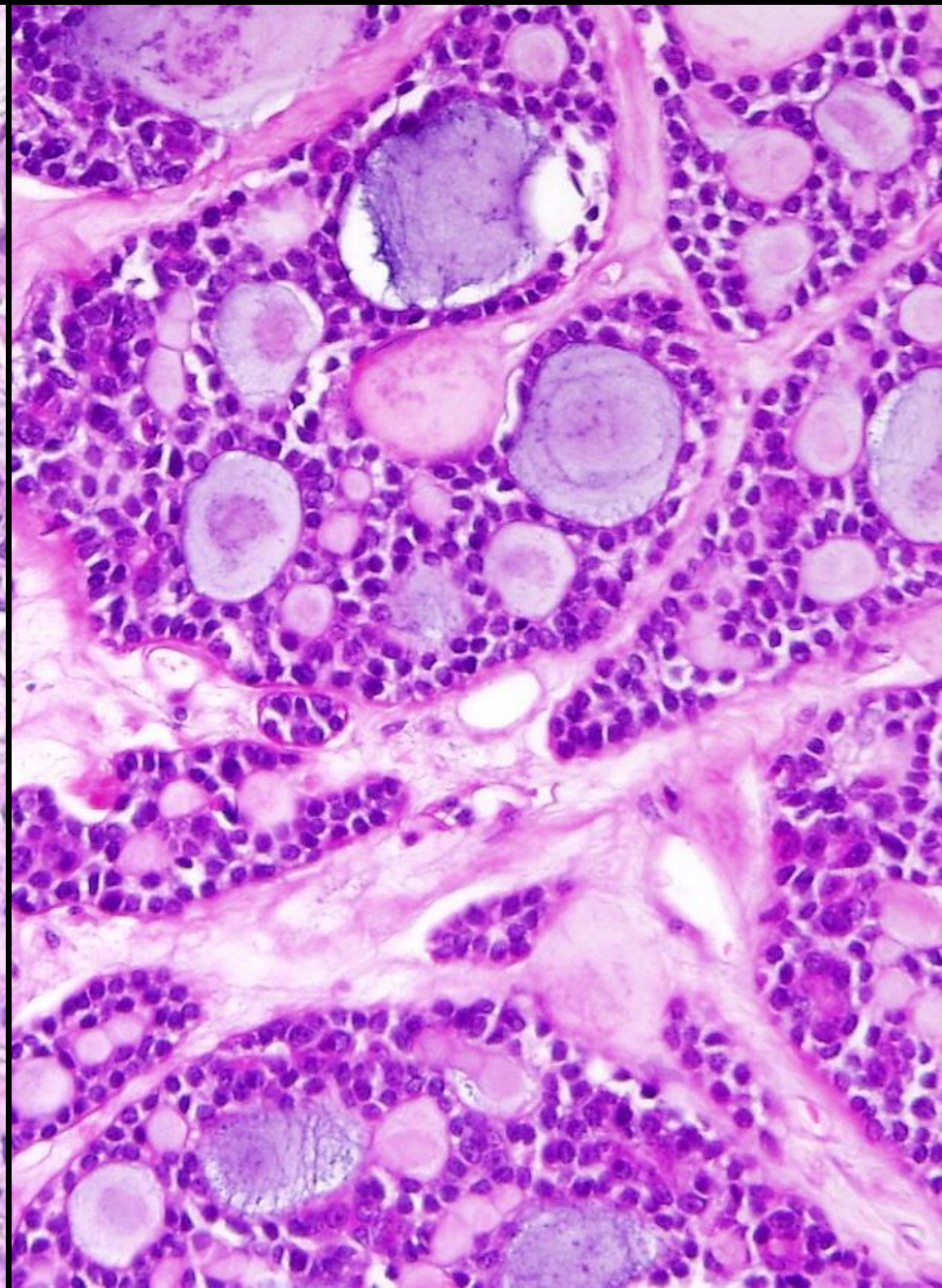
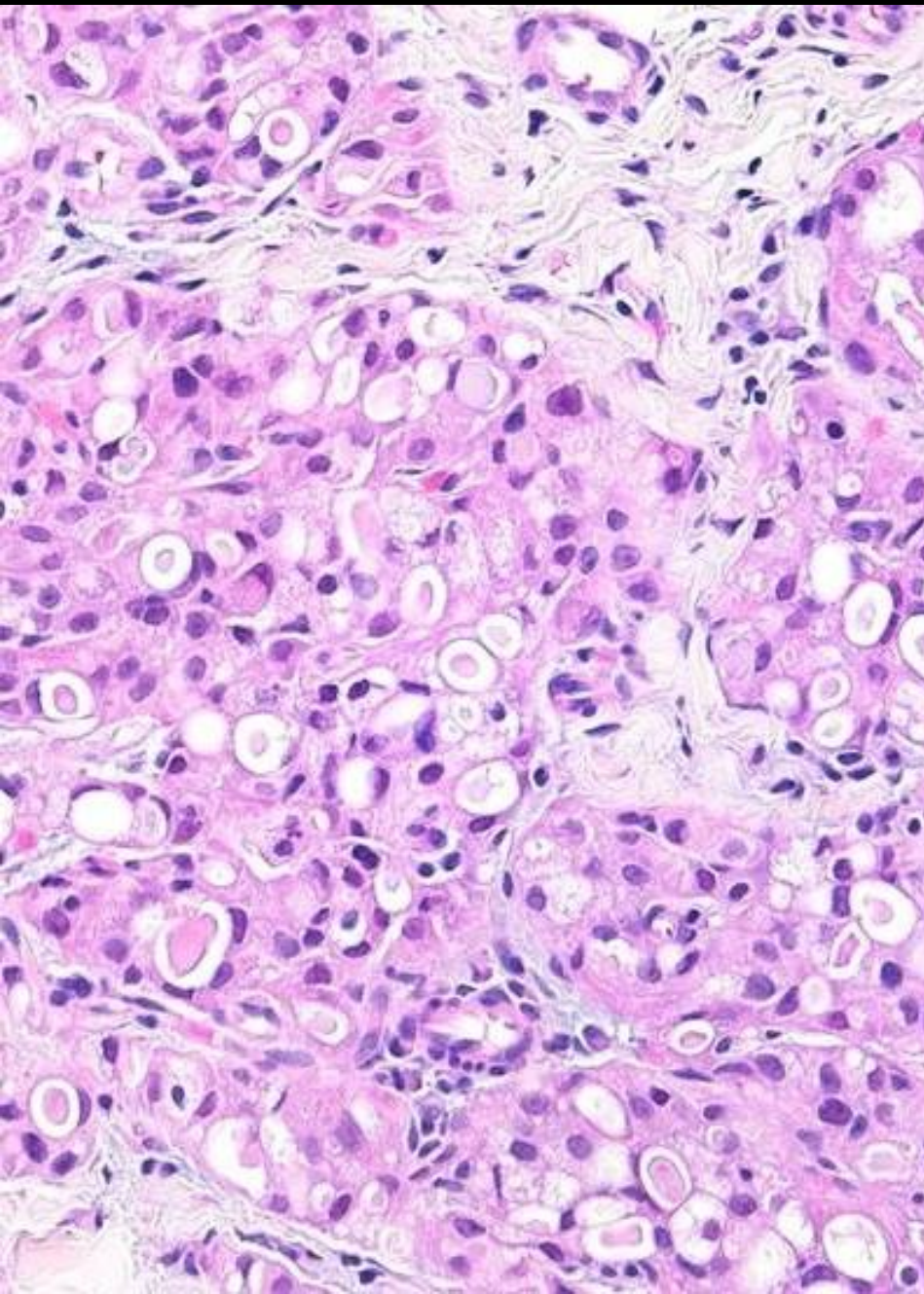
ACC Grade III

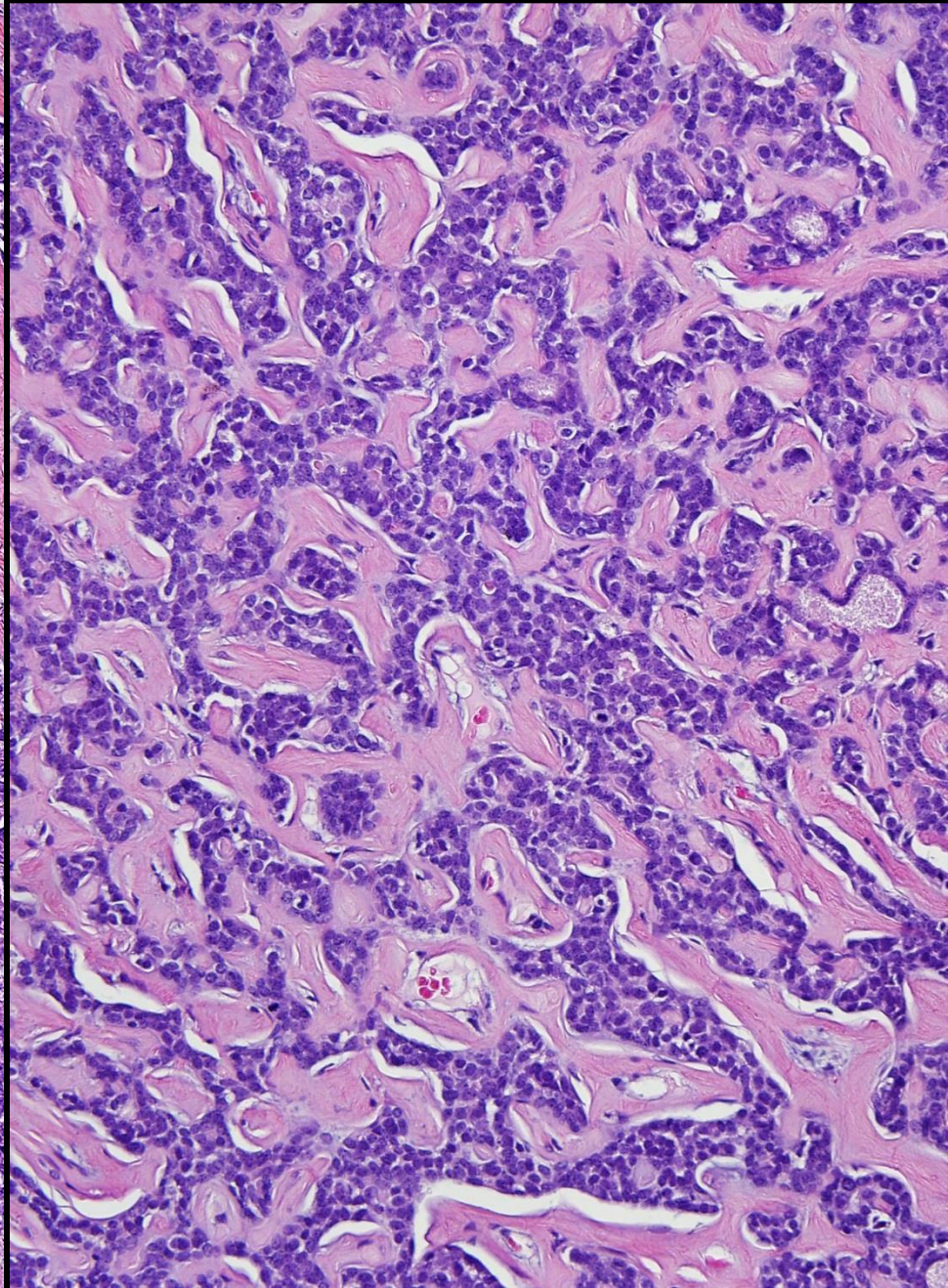
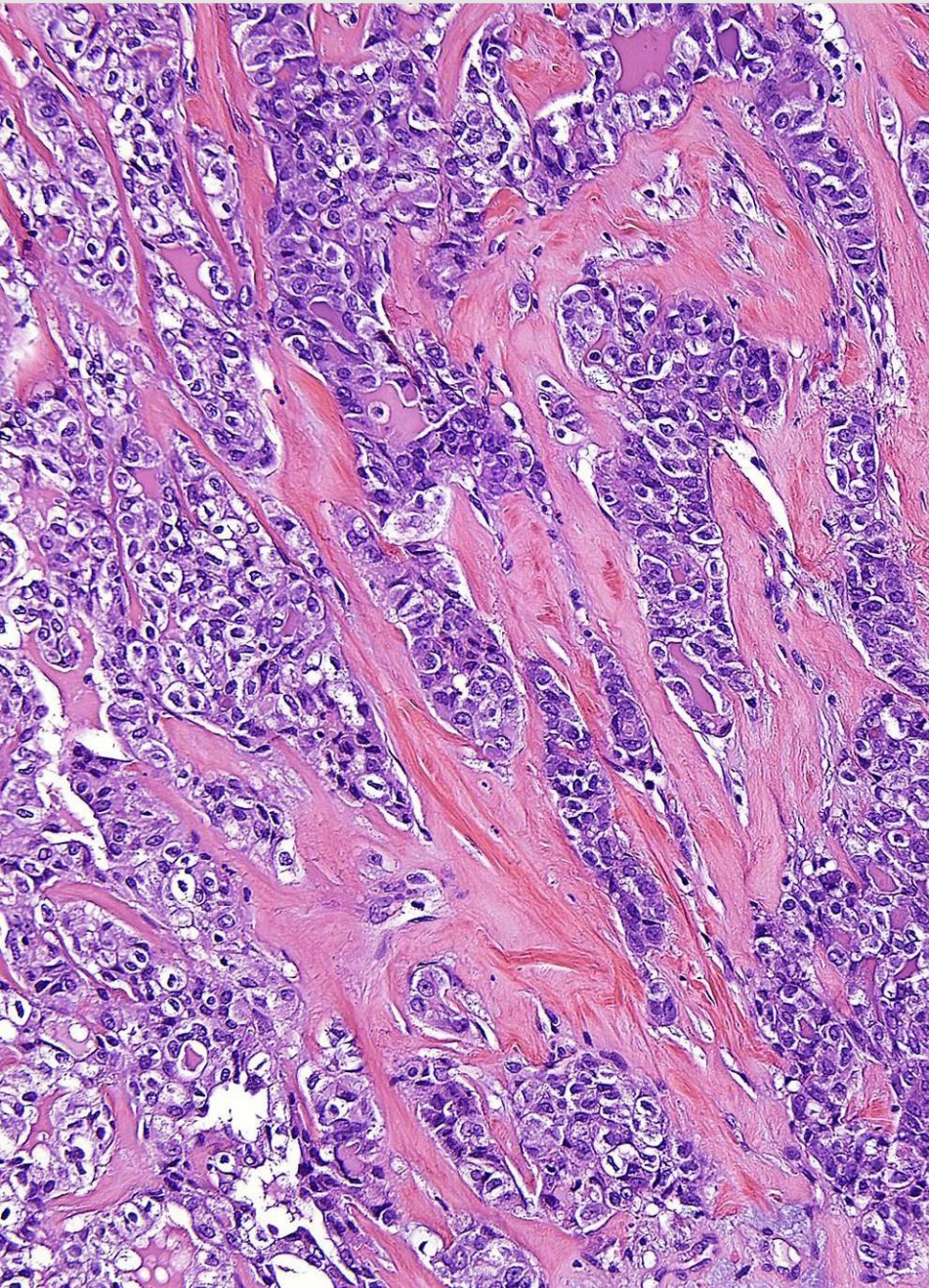


Recurrent t(6;9) in ACC

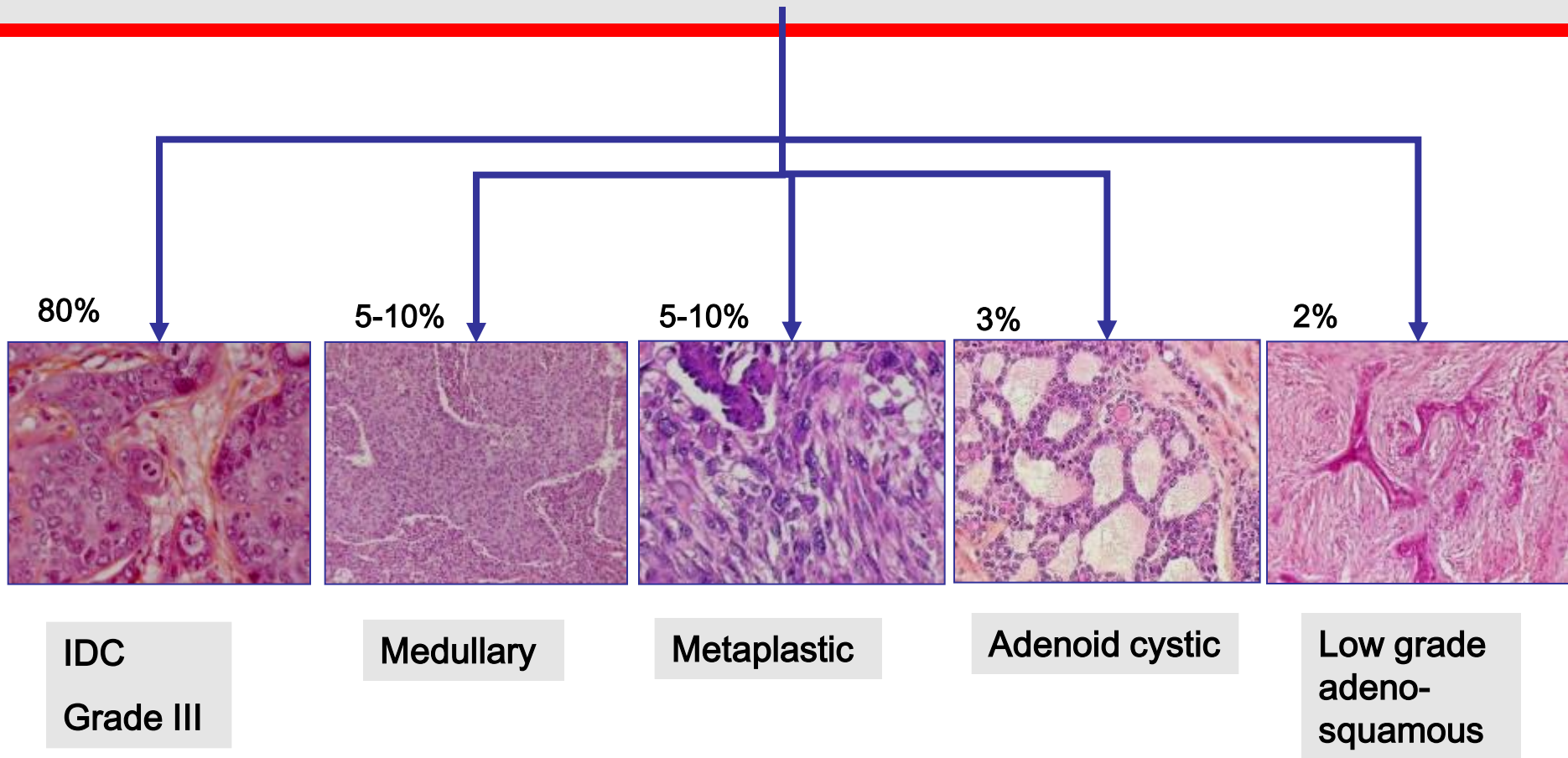








T N B C



**Different Morphology - Different Biology - Different Prognosis
Different Therapy Options**

Targeting Subtypes

- Distinctly different subtypes
- Challenges grouping diverse biology into a limited number of categories
- Stroma likely matters

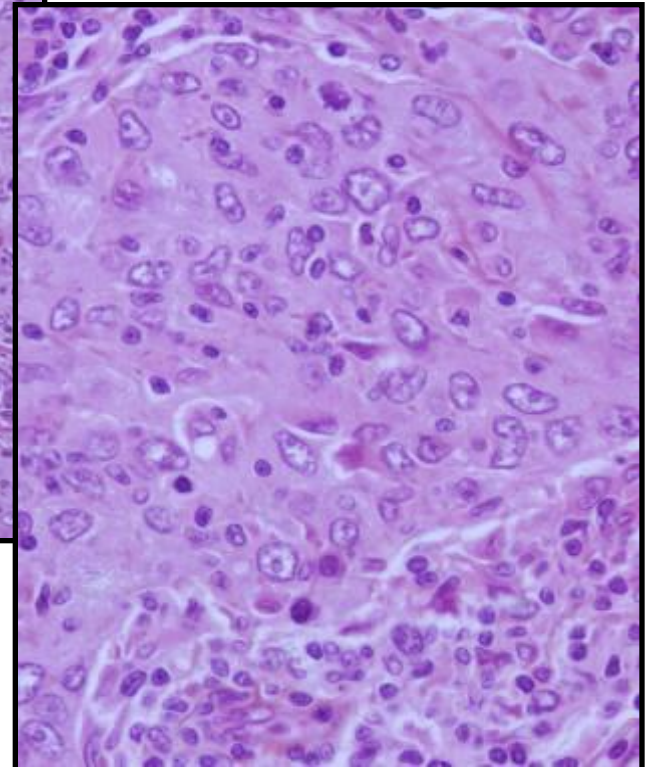
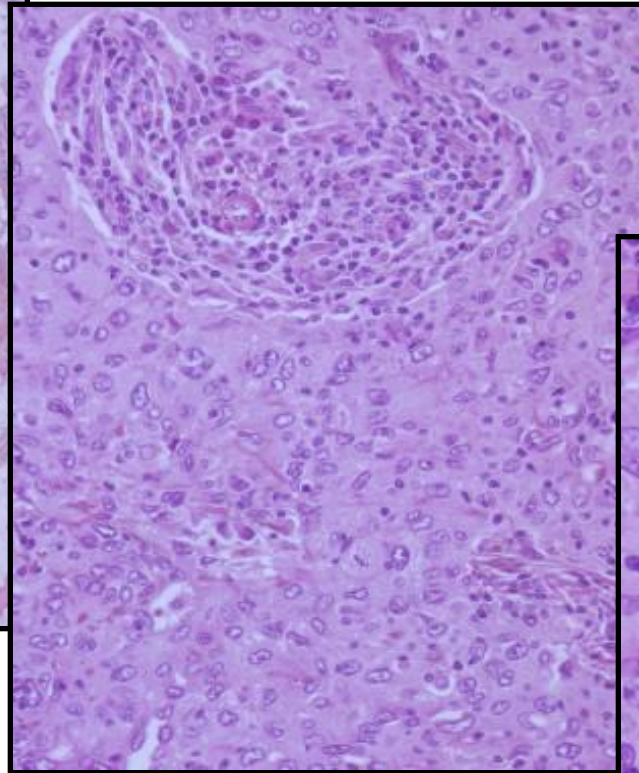
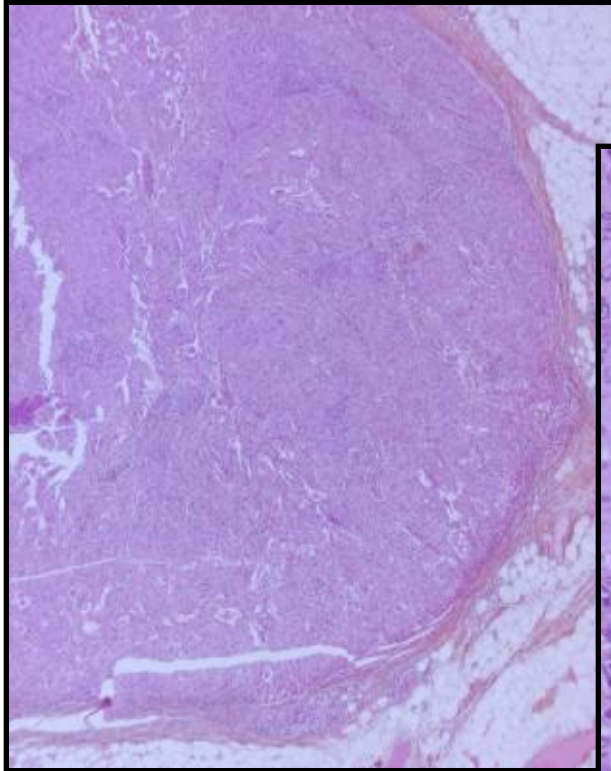
RESEARCH ARTICLE

Open Access

Cancer stem cell markers are enriched in normal tissue adjacent to triple negative breast cancer and inversely correlated with DNA repair deficiency

Rachel L Atkinson¹, Wei T Yang², Daniel G Rosen⁶, Melissa D Landis⁷, Helen Wong⁷, Michael T Lewis⁵, Chad J Creighton⁵, Krystal R Sexton⁵, Sue G Hilsenbeck⁵, Aysegul A Sahin⁴, Abenaa M Brewster¹, Wendy A Woodward^{3†} and Jenny C Chang^{7*†}

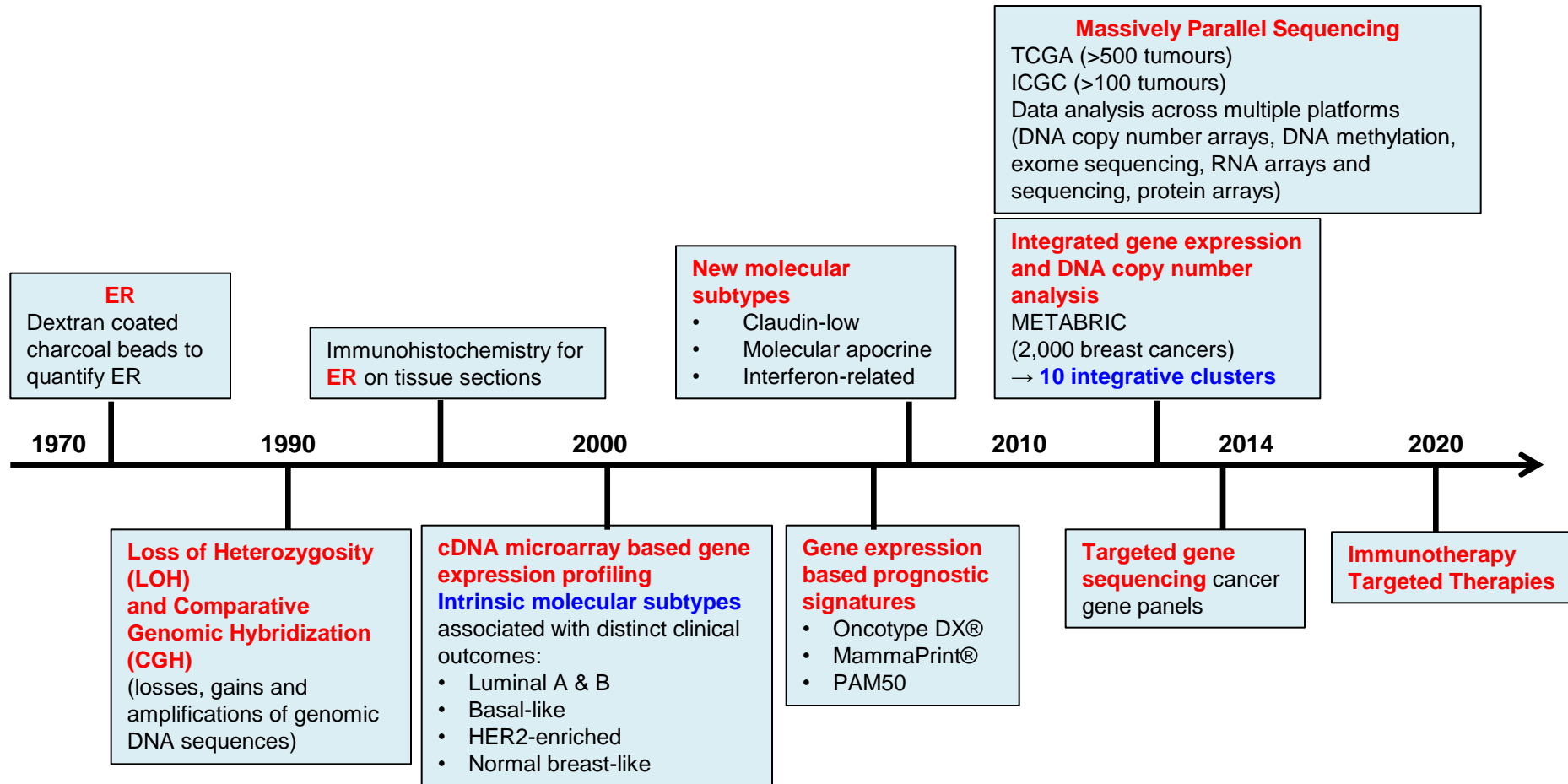
Cellular Stroma of T N B C



Summary

- Triple-negative BC is not a single disease entity
 - Differences in chemosensitivity
 - Differing potential therapeutic options for resistant disease
- Much of the biology of TNBC is now being defined
- No single target for TNBC
- Several promising “targeted” options are being tested

Breast Cancer Classification

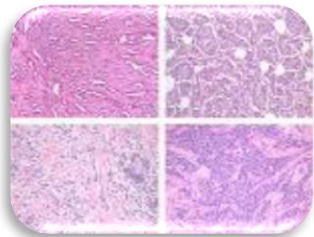
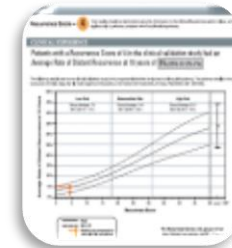
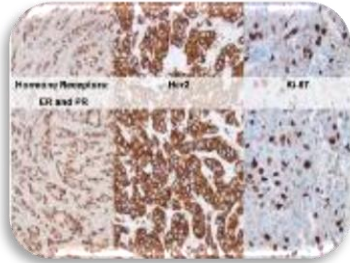


Breast Cancer

Ideal Classification Method

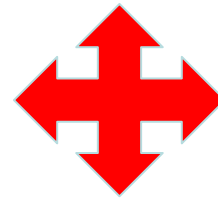
- Distinguish different prognostic categories among patients with similar clinical features and tumor characteristics
- Predict response to various therapy types in an individual patient

Pathologists as “Diagnostic Oncologists”

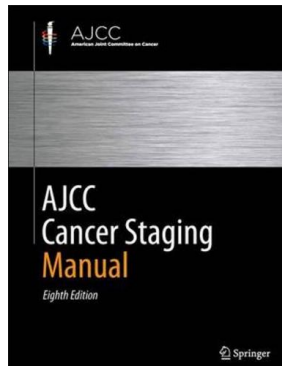


Translation and integration of biologic information

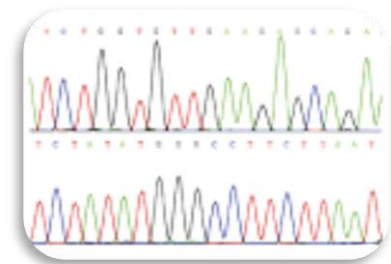
Treatment Team



Patient Factors



Individualized Treatment Decisions



USCAP 1990

