GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

NEW BREAST CANCER CLASSIFICATION:

Traditional pathology and molecular subtypes
Prognostic and predictive factors

Frédérique Penault-Llorca

Preceptorship in breast cancer 2019

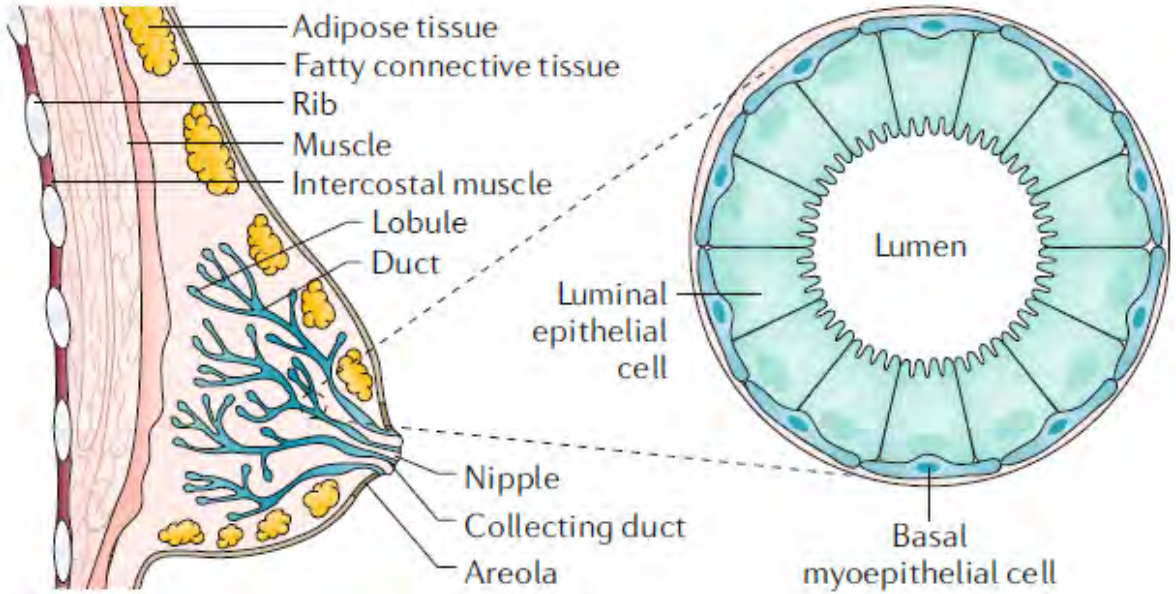
DISCLOSURE OF INTEREST

Frédérique Penault-Llorca

- Personal financial interests: Abbvie, Astrazeneca, Bayer, BMS, Genomic Health, Lilly, MERCK lifa, MSD, Myriad, Nanostring, Novartis, Pfizer, Pierre-Fabre, Roche, Tesaro
- Institutional financial interests: Astrazeneca, Bayer, BMS, Genomic Health, MSD, Myriad, Nanostring, Roche
- Congress invitations: Abbvie, Astrazeneca, BMS, MSD, Novartis, Roche

Objectives

To learn about the biology of breast cancer and its implication in the management of BC patients



Histological subtypes

Preinvasive

Ductal carcinoma in situ (DCIS)

- Spreads through ducts and distorts ductal architecture; can progress to invasive cancer; unilateral

Lobular carcinoma in situ (LCIS)

- Does not distort ductal architecture; can be bilateral
- Risk factor rather than precursor

Invasive

Ductal carcinoma no special type (NST)

- Develops from DCIS; fibrous response to produce a mass; metastasizes via lymphatics and blood

Lobular carcinoma (ILC)

- Isolated tumor cells (*CDH1* mutations) minimal fibrous response; metastasizes preferentially via viscera

Harbeck N, Penault-Llorca et al Nature Review disease Primer (2019) 5:66

“What is new”: changes in the practice of breast cancer diagnostics

- **Mass screening**: smaller tumours at diagnosis
- Pre-surgery “**strategic biopsy**”: less frozen sections for breast cancer diagnosis
- Therapeutic **de-escalation** in surgery: **sentinel lymph node assessment**
- Personalized medicine:
  - **Treatment driven by tumour biology** (“intrinsic” classification) rather than by stage
  - **Reflex testing of predictive factors** (hormonal receptors, HER2)
- Therapeutic **de-escalation** in oncology: prognostic and predictive molecular **signatures**

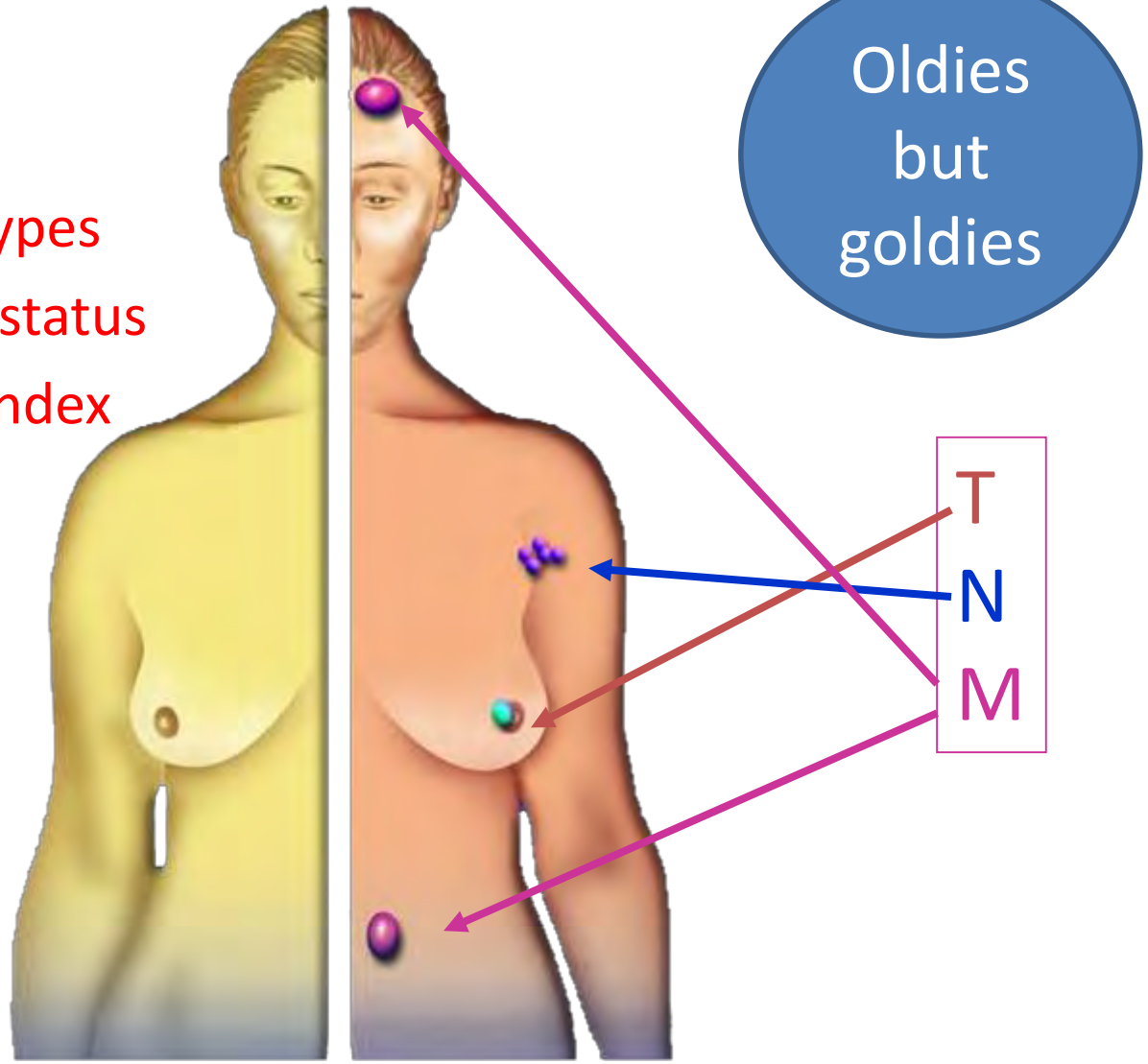
Outlines

- Breast cancer pathology: the basics revisited
- Molecular pathology
- Specific subtypes
- Molecular signatures
- Molecular stratification of metastatic breast cancer

THE CLASSICS

Classical prognosis and predictive factors

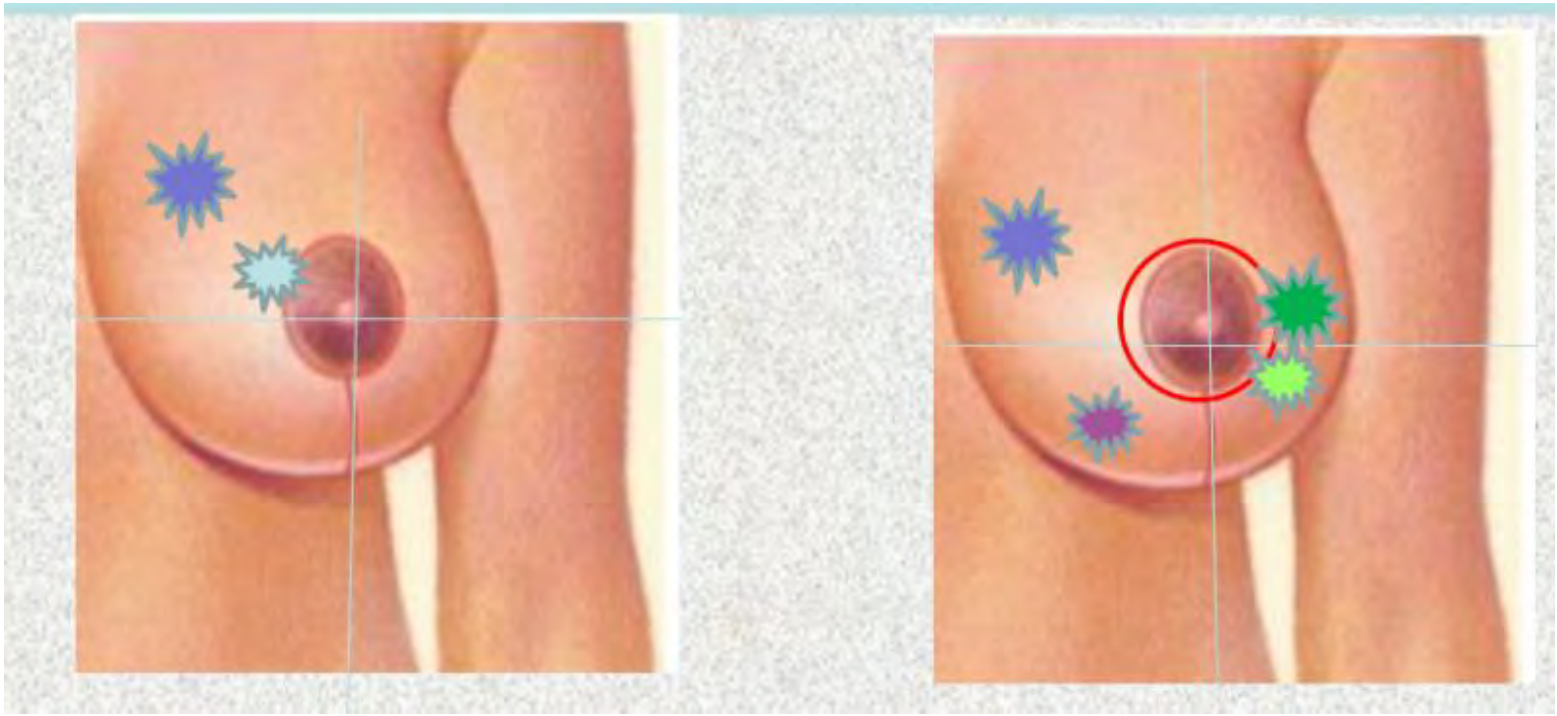
- Age
- Grade
- Histological subtypes
- ER/PR and HER2 status
- Ki67 +/- mitotic index
- Vascular invasion
- **Tumor margins**



CLASSICAL PARAMETERS
TIPS AND TRICKS

T

Multifocality vs multicentricity
Fisher Cancer 1975

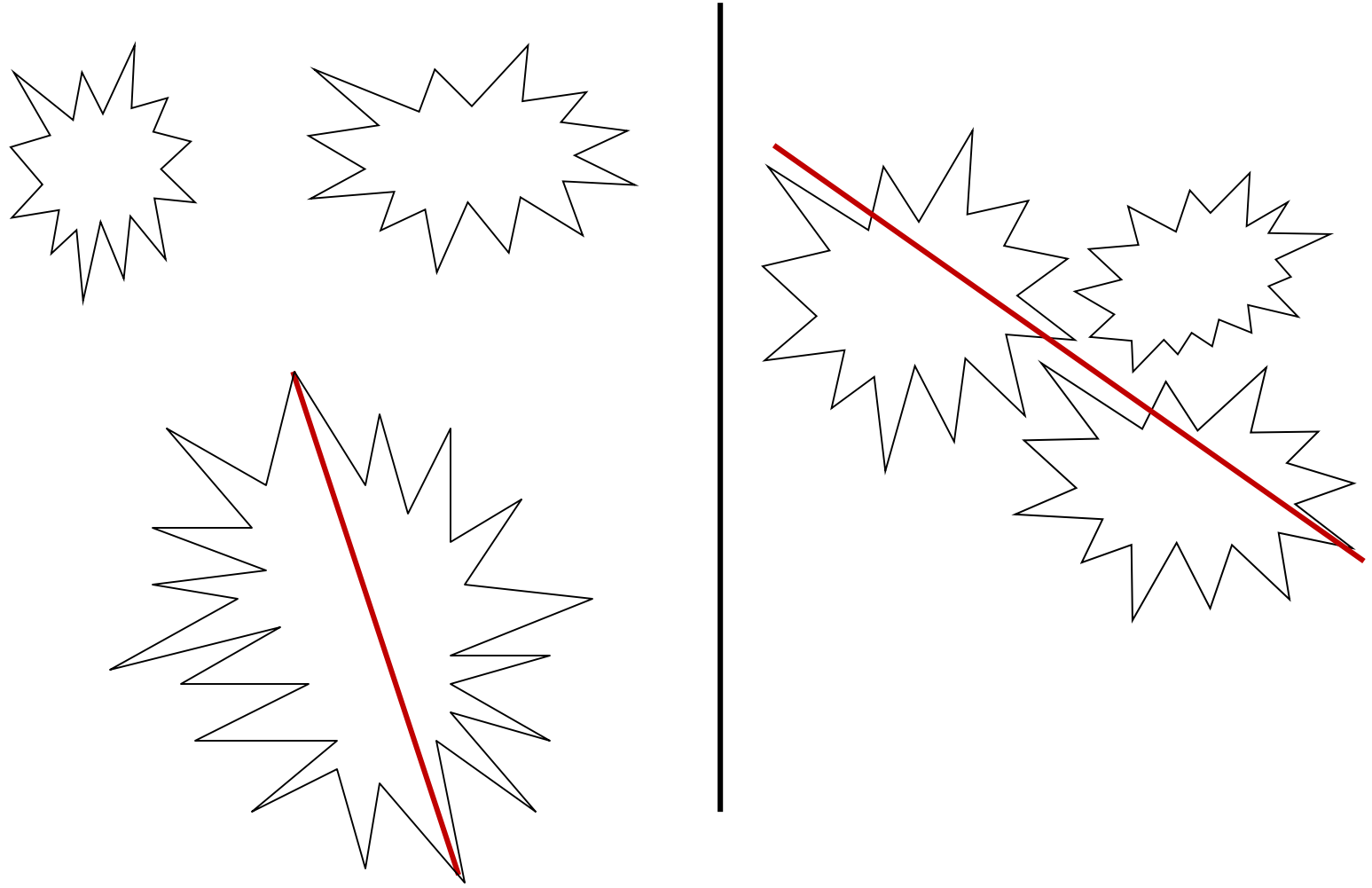


Multifocal

Multicentric

With the use of MRI: 13-70% of multiple lesions

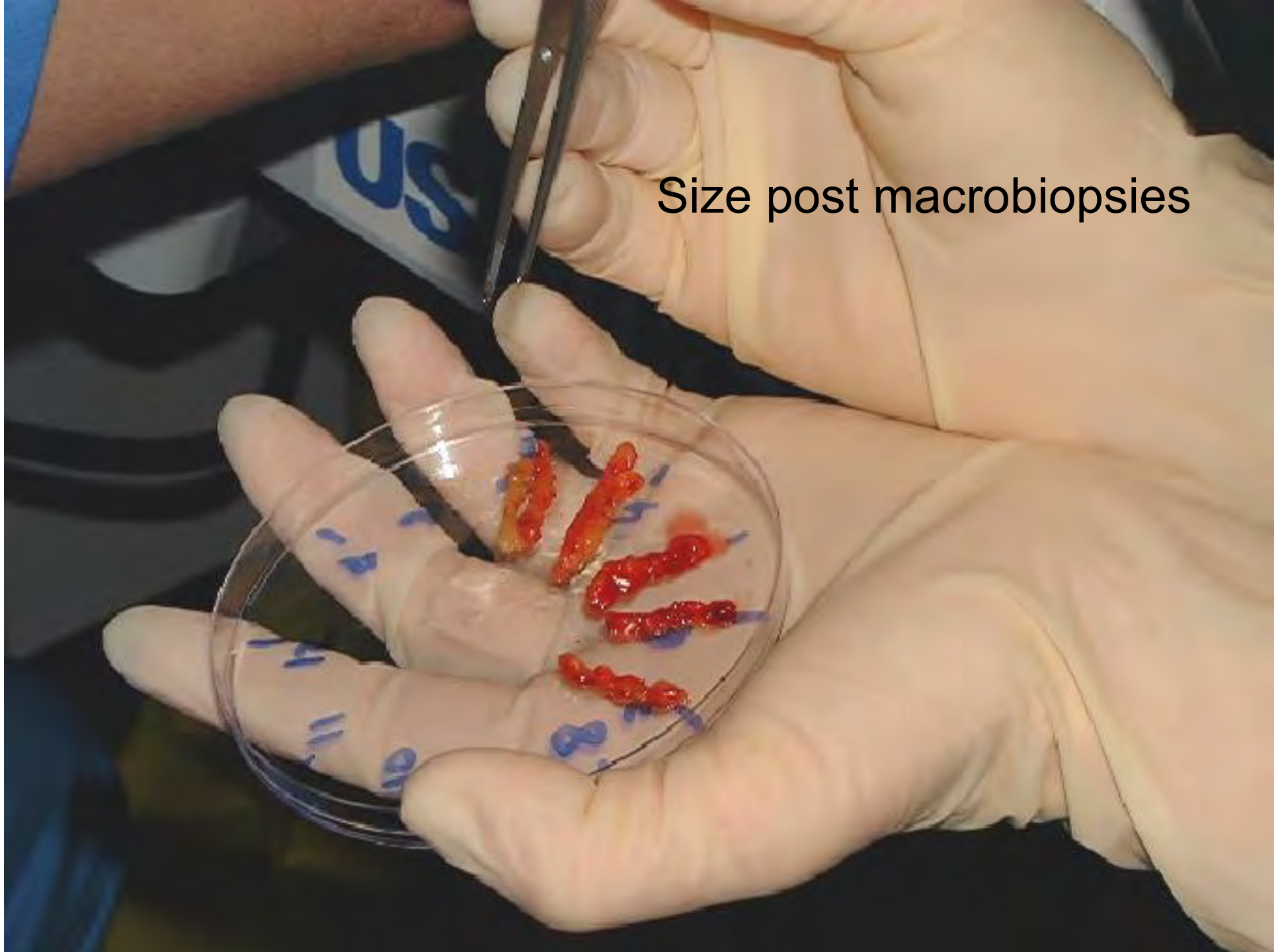
Multiple sites?

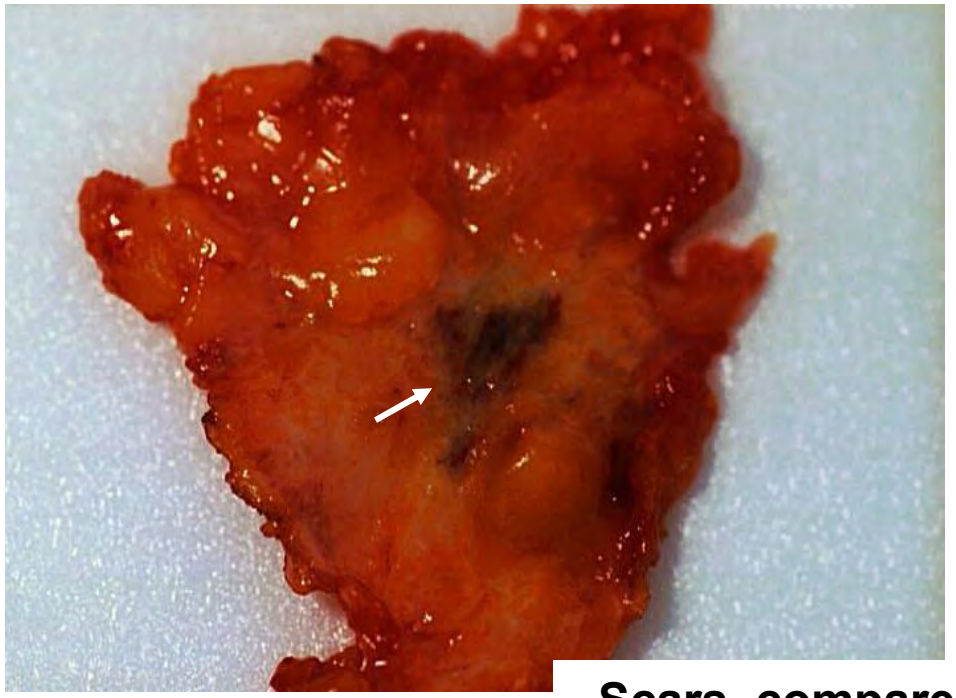


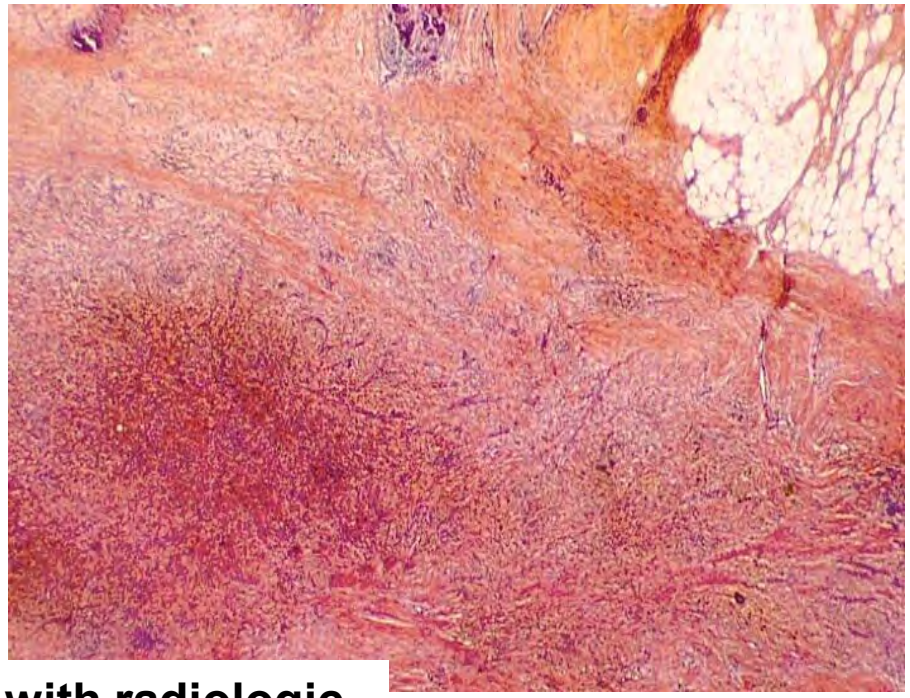
Clarification of the AJCC 7th edition

Staging multiple tumors

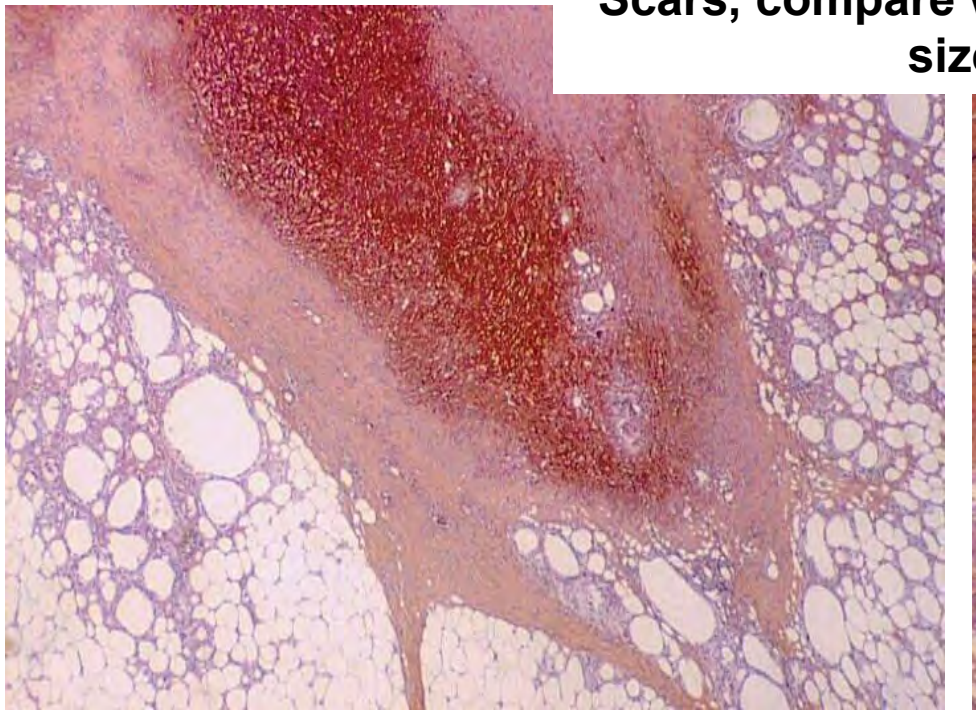
- If in same breast:
  - T category is based on **single largest tumor focus**
  - Don’t include satellite foci when measuring tumor size
  - If multiple foci of microinvasion, report the # of foci and **the size of the largest focus** (don’t combine)
  - Use (m) modifier
- If bilateral:
  - Stage each side separately

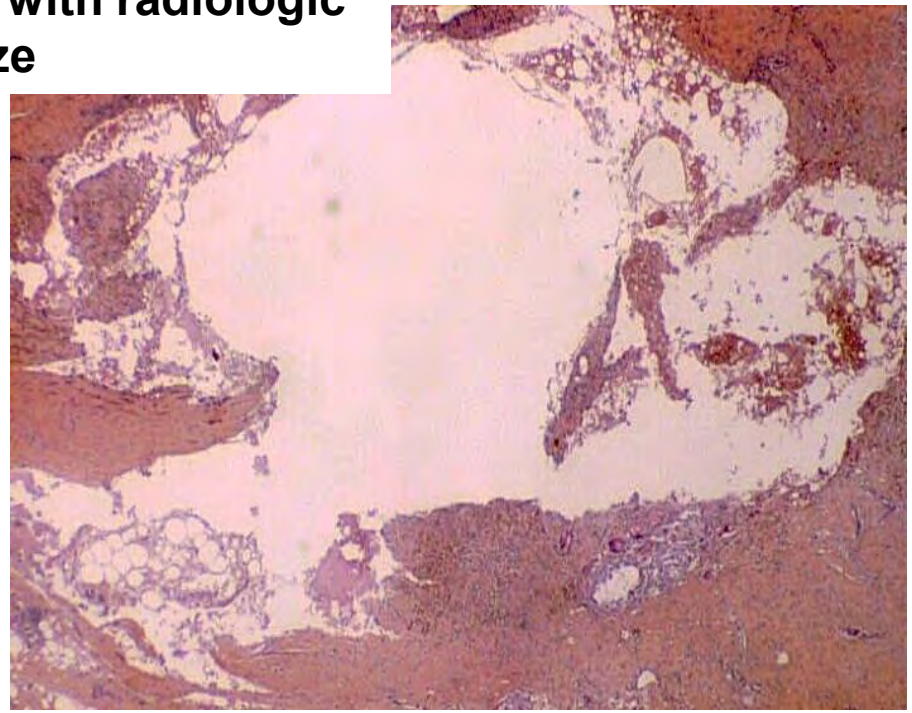

Size post macrobiopsies





Scars, compare with radiologic size





Clarification of the AJCC 7th edition in the 8th edition

- **Correlate gross, microscopic and imaging findings to assign correct pT when necessary.**

  - For small tumors diagnosed by core biopsy, measuring only the residual tumor in the excision may result in understaging.

- Example:
  - 6 mm mass by imaging; largest focus in biopsy core – 4 mm
  - 2 mm focus of residual carcinoma in excision: categorize as pT1b (not pT1a)
  - No residual cancer in excision: categorize as pT1a (not pTX)
- Same rule applies when tumor is present in multiple fragments: Use clinical and imaging findings to assign pT
- pTX should rarely be used

N

Initial concepts for the use of SLNB in Breast Cancer

- Obtention of prognostic information
- Therapeutic role (!)
- Avoid full axillary dissection for pN0 patients

Consequences:

- Better management of the nodes (full node assessment)
- Changes in the TNM

Facts about SLNB

- Completion **ALND is not providing benefit** of OS and DFS in **microscopic** metastatic SLN [pN0(i+) and pN1mi].
- Even **macrometastasis** in 1 or 2 SLN(s) in ACOSOG Z0011 did not affect OS.
- SLN biopsy alone can be a **standard practice** demonstrating its efficacy, accuracy **in staging** and equivalent survival outcome when compared to complete ALND and SLNB alone in **T1–T2** breast cancer

SLNB conclusion

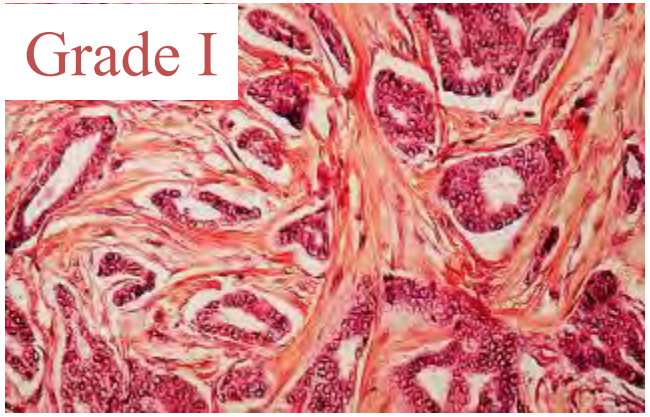
- **No longer systematic intraoperative assessment**
- In case of + SLN, ALND is no longer systematic and as to be discussed in MDTB
- **Ultra-stadification:**
  - balance between what is useful for the patient or not, and should not be deleterious (over treatment)
  - Careful in case of use of molecular signatures (not validated ith SLNB)
  - Balance between what is possible or not in the lab
  - Depends upon guidelines (adjuvant TT and RTT)

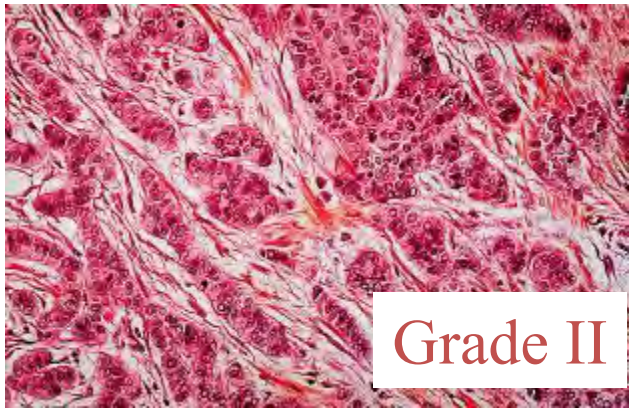
- **NACT: 2 options are possible**
- Pre NACT> post NACT

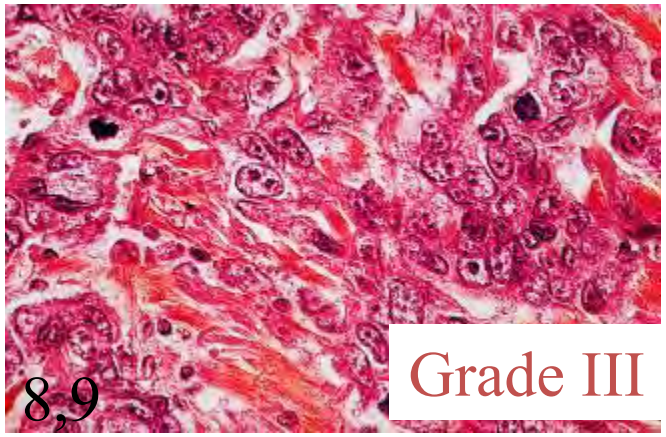
GRADE

SBR grade modified by Elston and Ellis

- Standardization of tumor grading
- France 2010: Gr I 25%, Gr II 50% , Gr III 25%
- Genomic grade : not confirmed







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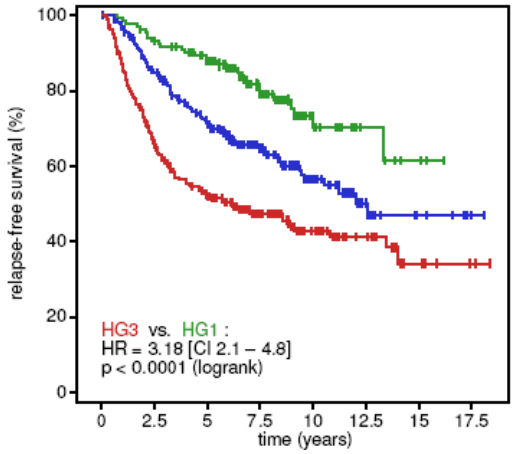
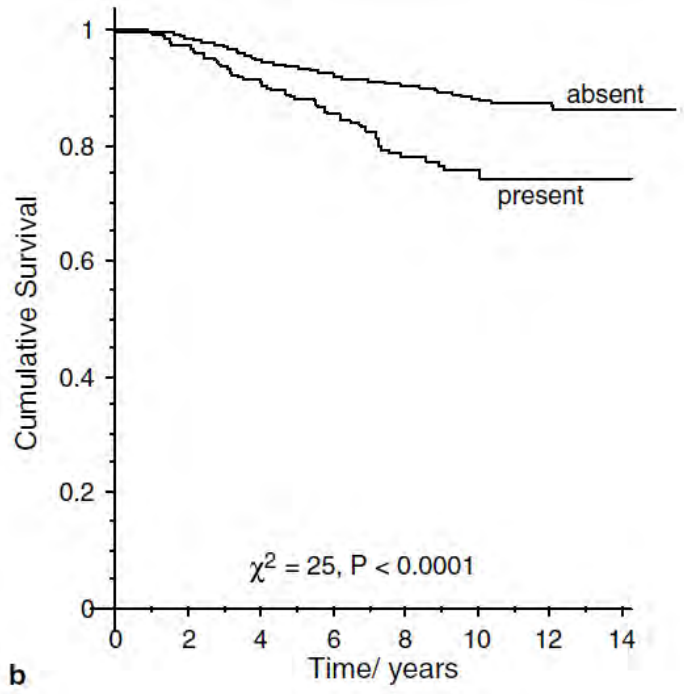


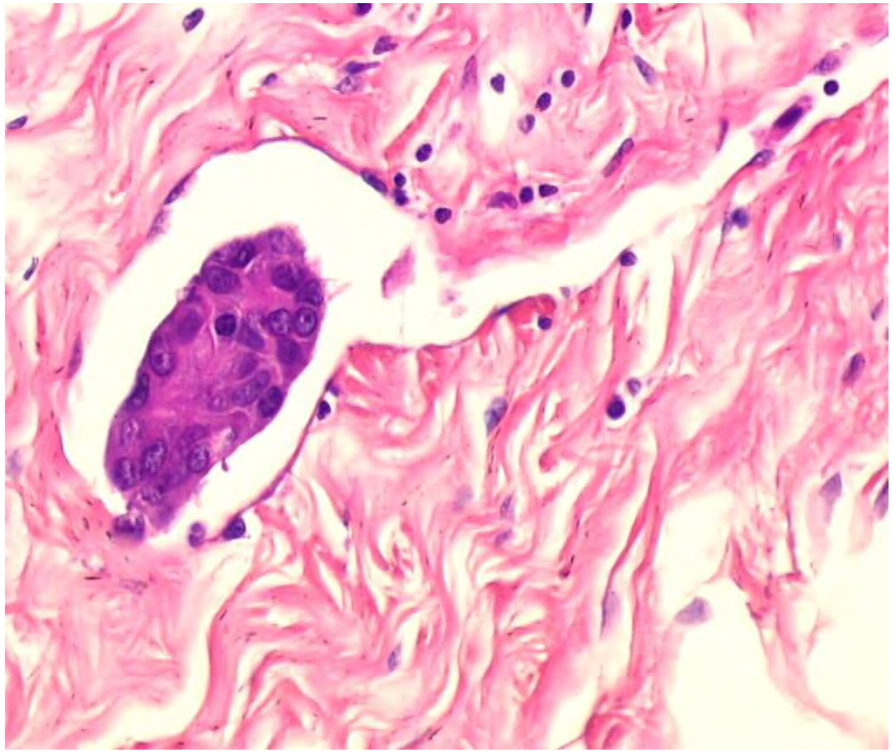
SBR grade and RFS in operable BC (57% N-) treated by adjuvant therapy

8,9

VASCULAR OR LYMPHATIC EMBOLIES

VASCULAR EMBOLI: no value on microbiopsies





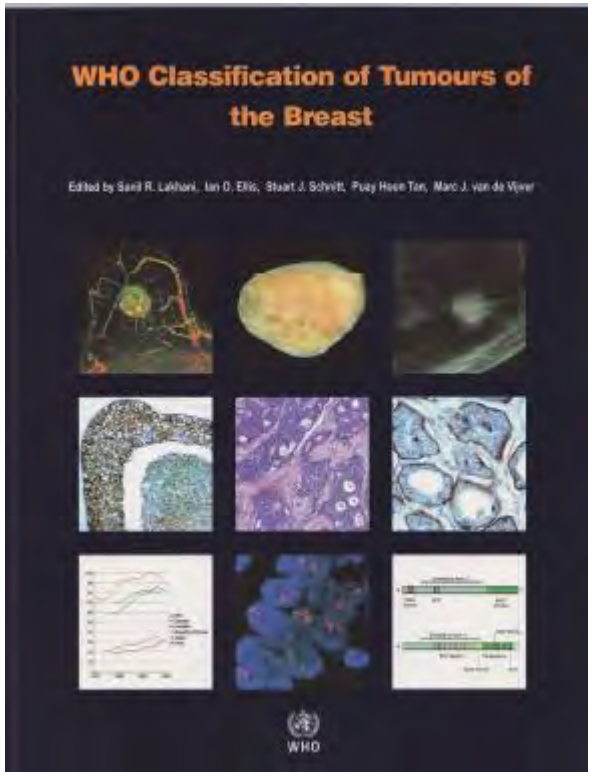
Peripheral lymphovascular invasion and BCSS in N- operable BC treated by adjuvant therapy (from Lee)

HISTOLOGIC SUBTYPES

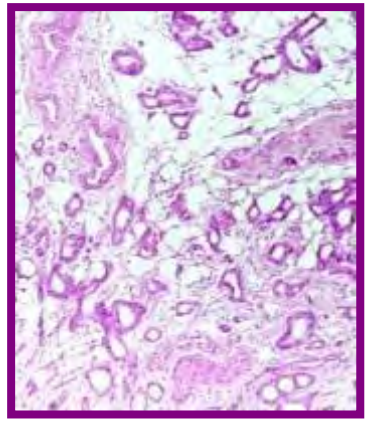
histologic subtypes Epithelial breast cancer WHO 2012

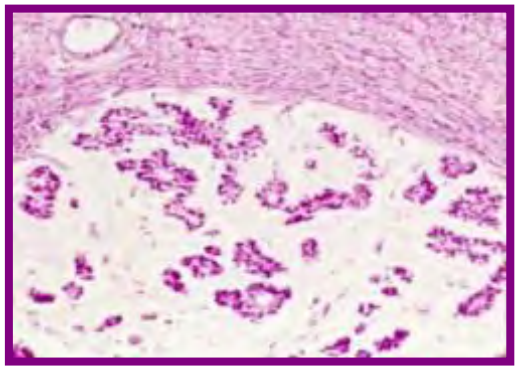
Infiltrative carcinoma

Ductal
Lobular
Tubular
Cribriform
Medullary
Mucinous
Neuroendocrine
Papillary
Micropapillary
Apocrine
Metaplastic
Secretory
Lipid Rich
Oncocytic
Adenoid Cystic
Acinar
Clear Cell
Sebaceous
Inflammatory

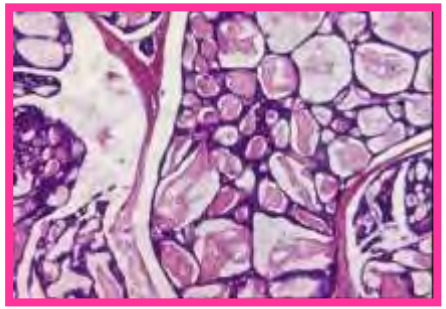


19 Histological types: **morphology matters!**

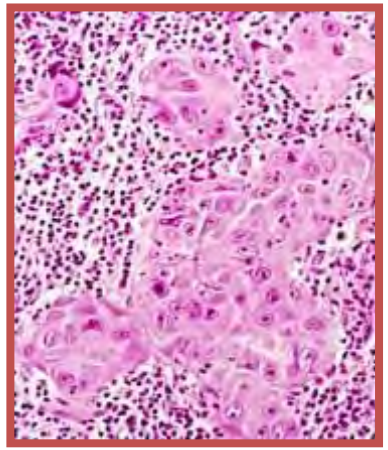




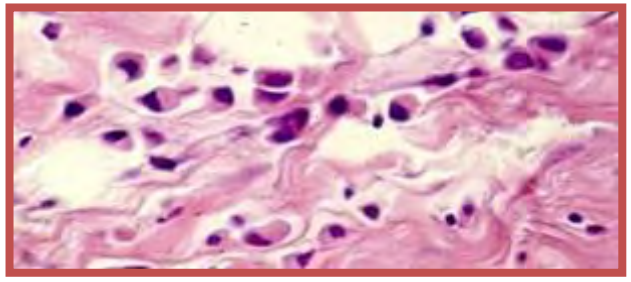
Group 1 - Excellent prognosis:
Tubular, invasive cribriform, mucinous

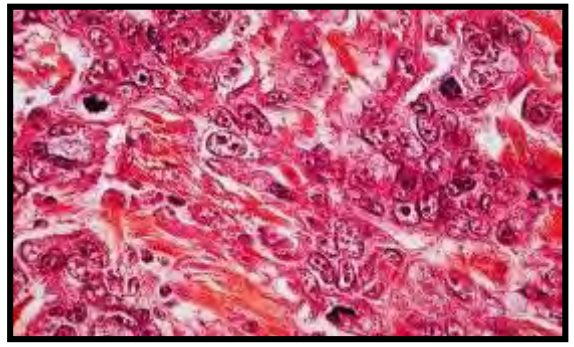


Group 2 - Good prognosis:
Tubular mixed, mixed ductal NST and special type like adenoid cystic, secretory



Group 3 - Average prognosis:
Medullary, classical lobular, lobular mixed

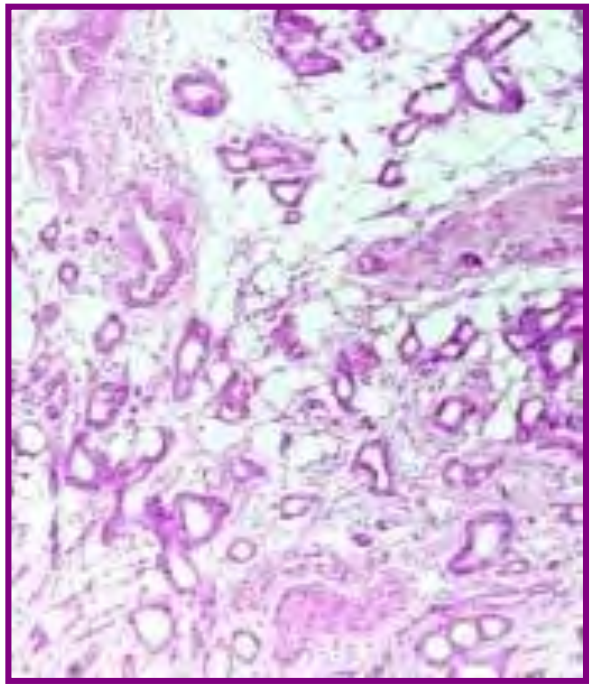


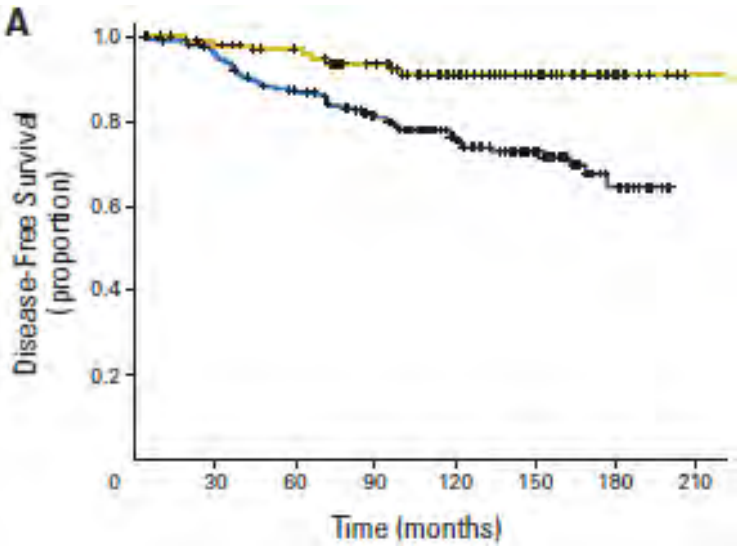


Group 4 - Poor prognosis
Ductal NST, solid lobular, mixed ductal NST and lobular, micropapillary

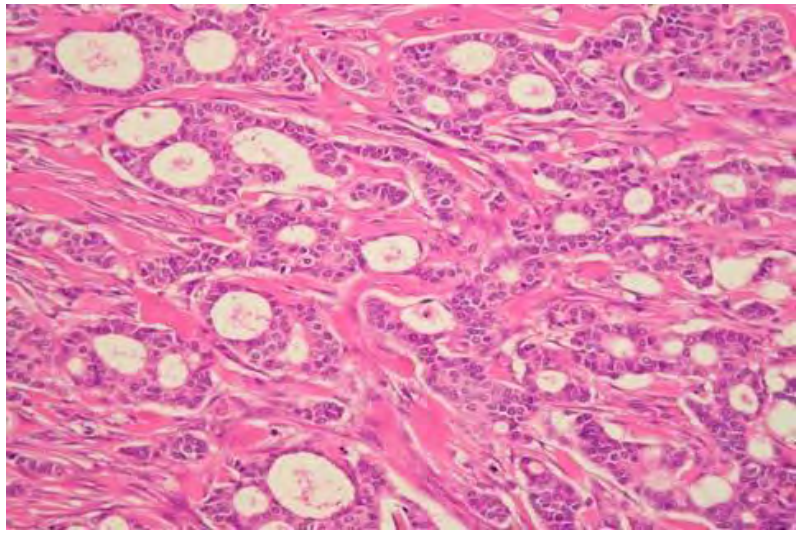
Special types

"Tubular and cribriform carcinoma may be suitable for observation without therapy or for endocrine therapy alone"





Tubular carcinoma and DFS (Rakha)



CLASSICAL TNM AND HISTOPATHOLOGICAL PARAMETERS MATTER!

Minimal items in a pathology report

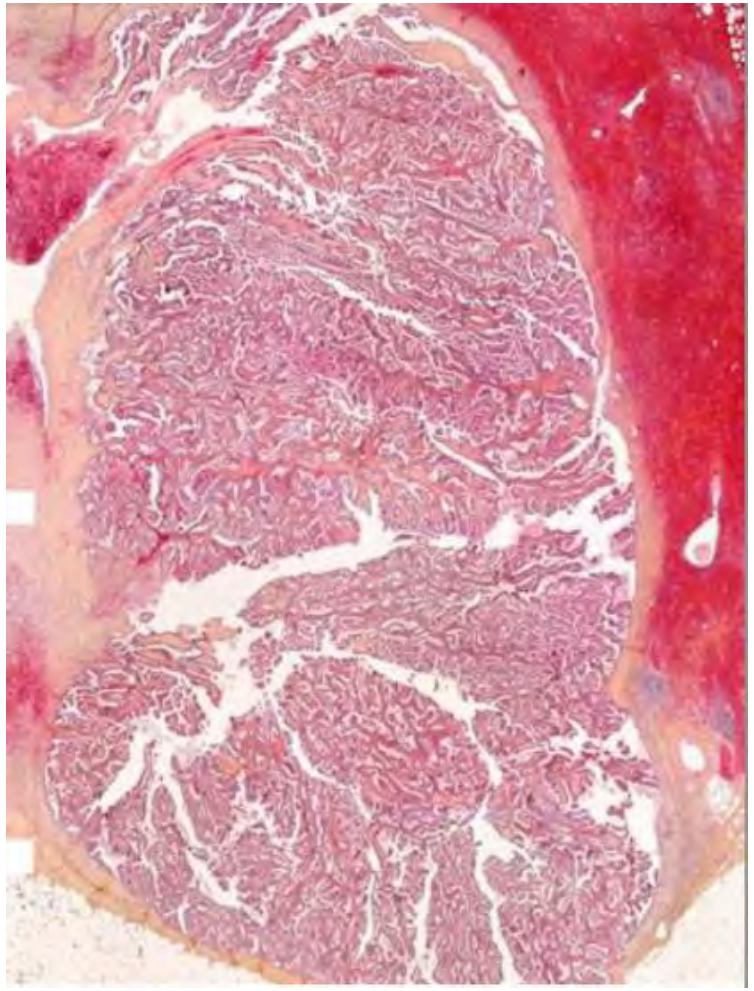
NOT ALL INVASIVE BREAST CANCERS ARE BEHAVE AS INVASIVE…. ENCAPSULATED PAPILLARY BC

Carcinomatous lesions with papillary architecture

- Papilloma with DCIS
- DCIS papillary type
- Encapsulated papillary carcinoma → consider as a DCIS, no theranostic IHC if low grade
- Papillary carcinoma massive type (solid papillary carcinoma) → consider as DCIS
- Infiltrative papillary carcinoma→pT

Encapsulated papillary carcinoma

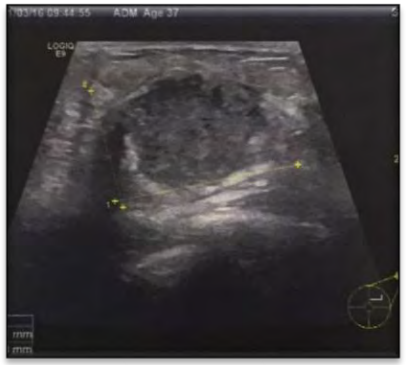
- Post menopausal patient (>60yrs)
- Palpable or infraclinical lesion
- Capsule +/- thick
- If low grade:
  - ➔pTis
  - Treat as a DCIS + SLNB
- If high grade
  - ➔pT
  - Treat as an invasive carcinoma (RE, PR, HER2)



NOT ALL BREAST NODULES ORIGINATE FROM BREAST

Metastasis to the breast

- 0.2 to 1.3% = rare
  - lymphomas
  - Melanoma
  - carcinomas (lung, GYN, kidney, digestive tract, prostate ...)
  - non-mammary neuroendocrine tumors
- 1st clinical sign of the disease in 30% of cases
- Delay between primary tumor and metastasis sometimes very long (22 years) especially for melanoma and ovary.
- Often large masses, fast growing, well limited and round, sometimes superficial
- May mimic benign lesions (ACR3)
- **Often unique**



Tumor site/type (n = 49)	No. of cases/(% of carcinomas)
Ovary (n = 14)	
High-grade serous carcinoma	10 (21)
Low-grade serous carcinoma	3 (6)
Clear cell carcinoma	1 (2)
Lung (n = 11)	
Adenocarcinoma	4 (8)
Large cell neuroendocrine	3 (6)
Poorly differentiated carcinoma	2 (4)
Small cell carcinoma	1 (2)
'Large' cell carcinoma	1 (2)
Gastrointestinal tract (n = 7)	
Colonic adenocarcinoma	3 (6)
Pancreatic adenocarcinoma	2 (4)
Carcinoid (colon)	1 (2)
Carcinoid (liver)	1 (2)
Genitourinary tract (n = 5)	
Urothelial carcinoma (bladder)	2 (4)
Renal cell carcinoma	2 (4)
Prostatic adenocarcinoma	1 (2)
Gynecologic tract (excluding ovary) (n = 5)	
Endometrioid adenocarcinoma (endometrial)	1 (2)
Combined endometrioid/small cell carcinoma (endometrium)	1 (2)
Undifferentiated carcinoma (endometrium)	1 (2)
Choriocarcinoma	1 (2)
Small cell carcinoma (cervix)	1 (2)
Thyroid (n = 2)	
Papillary thyroid carcinoma	2 (4)
Medullary thyroid carcinoma	1 (2)
Skin (n = 2)	
Merkel cell carcinoma	2 (4)
Submandibular gland (n = 1)	
Adenoid cystic carcinoma	1 (2)
Tongue (n = 1)	
Squamous cell carcinoma	1 (2)

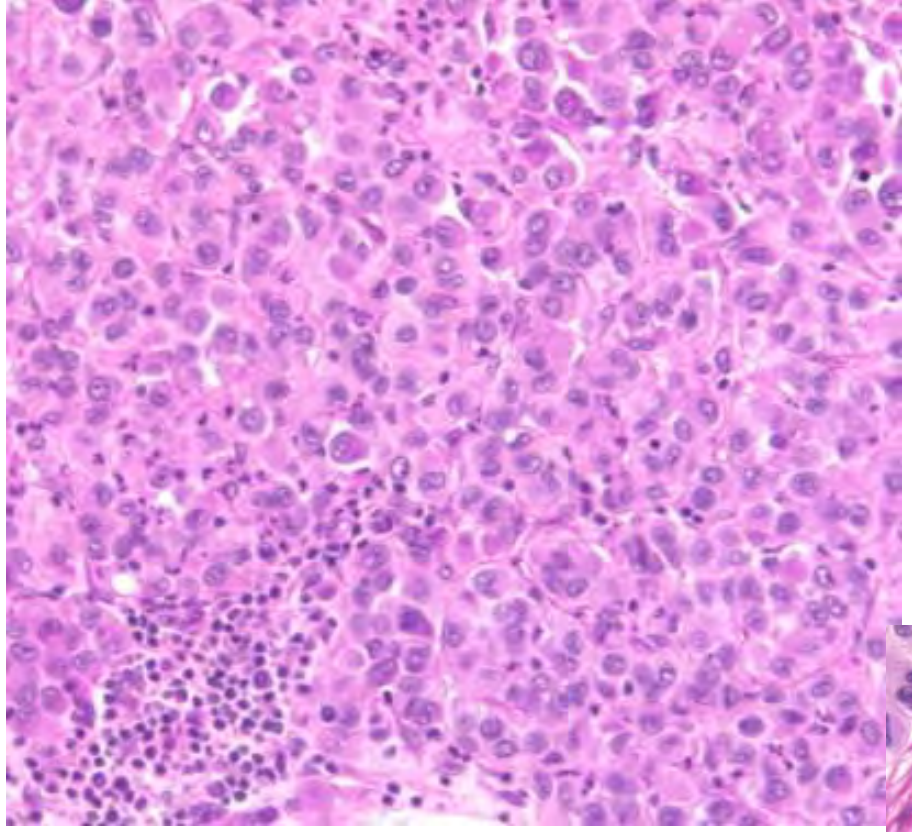
Most frequent primary tumors

- Carcinoma (58%, 49/85)
- Mélanoma (21%, 18/85)
- Sarcoma (21%, 18/85)

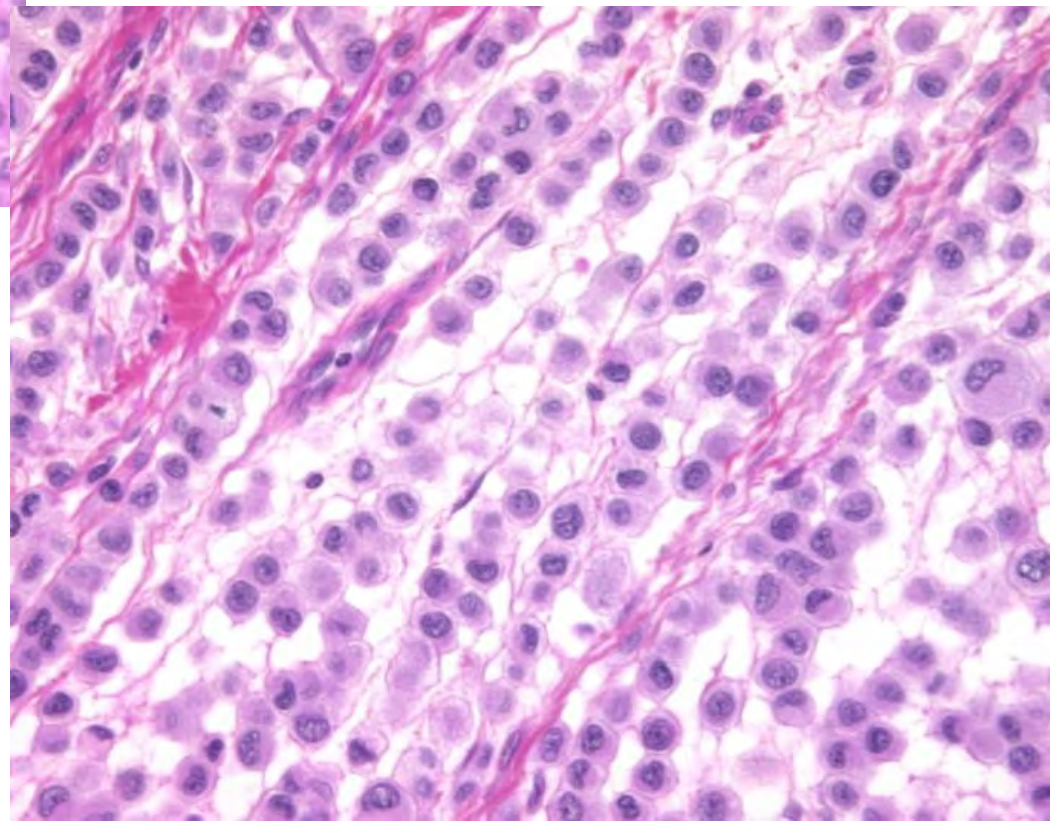
Among carcinoma :

- **GYN cancer**(39%, 19/49)
- Including ovarian K (29%, 14/49)

Non-mammary metastases to the breast and axilla : a study of 85 cases, DeLair and al, Modern Pathology, 2014



Histology

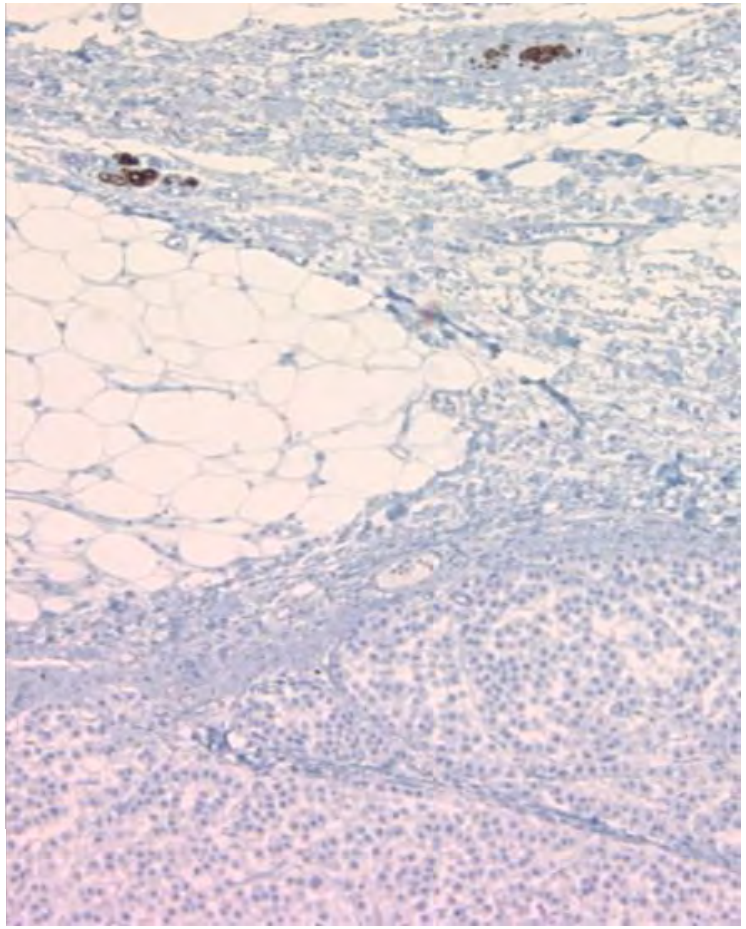


Looks like a lobular
But triple negative

Mammary or not?

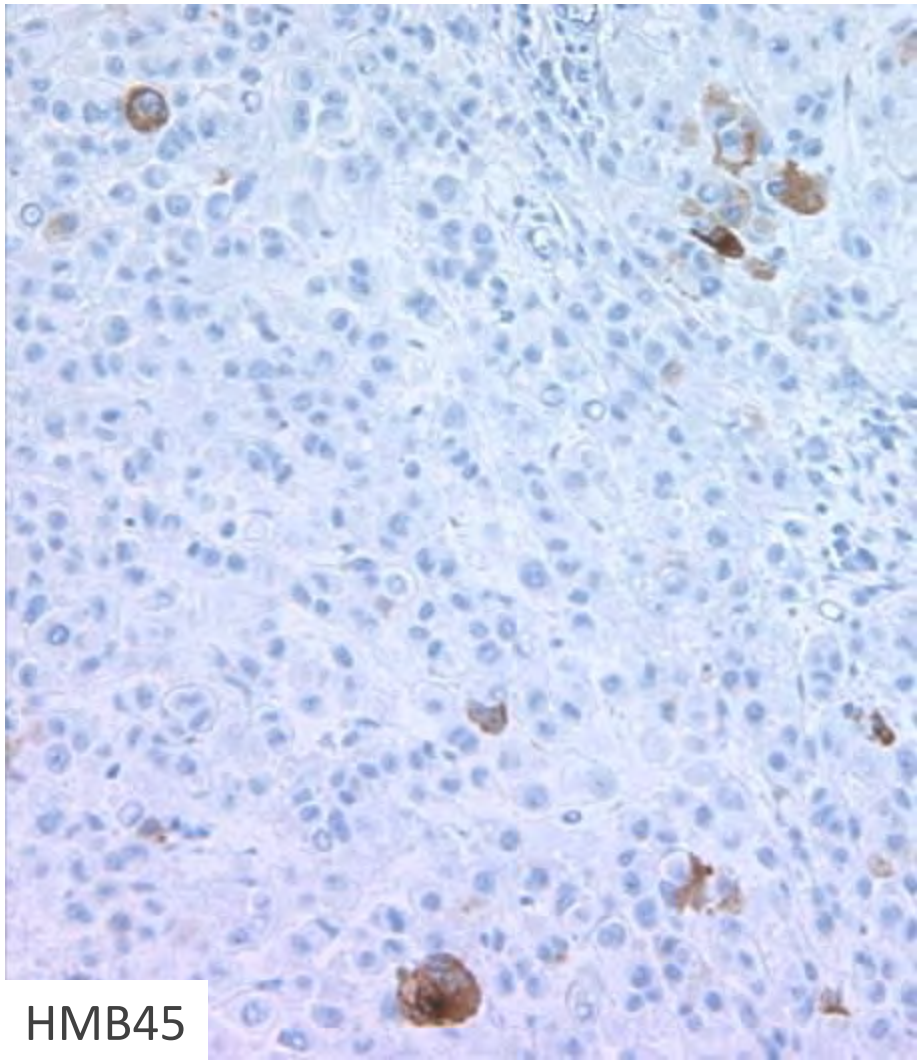
- triple negative (?!) very unusual for a lobular
- So we did GATA3 ➔ neg

➔CK7 & EMA neg



GATA3

Metastasis from a melanoma



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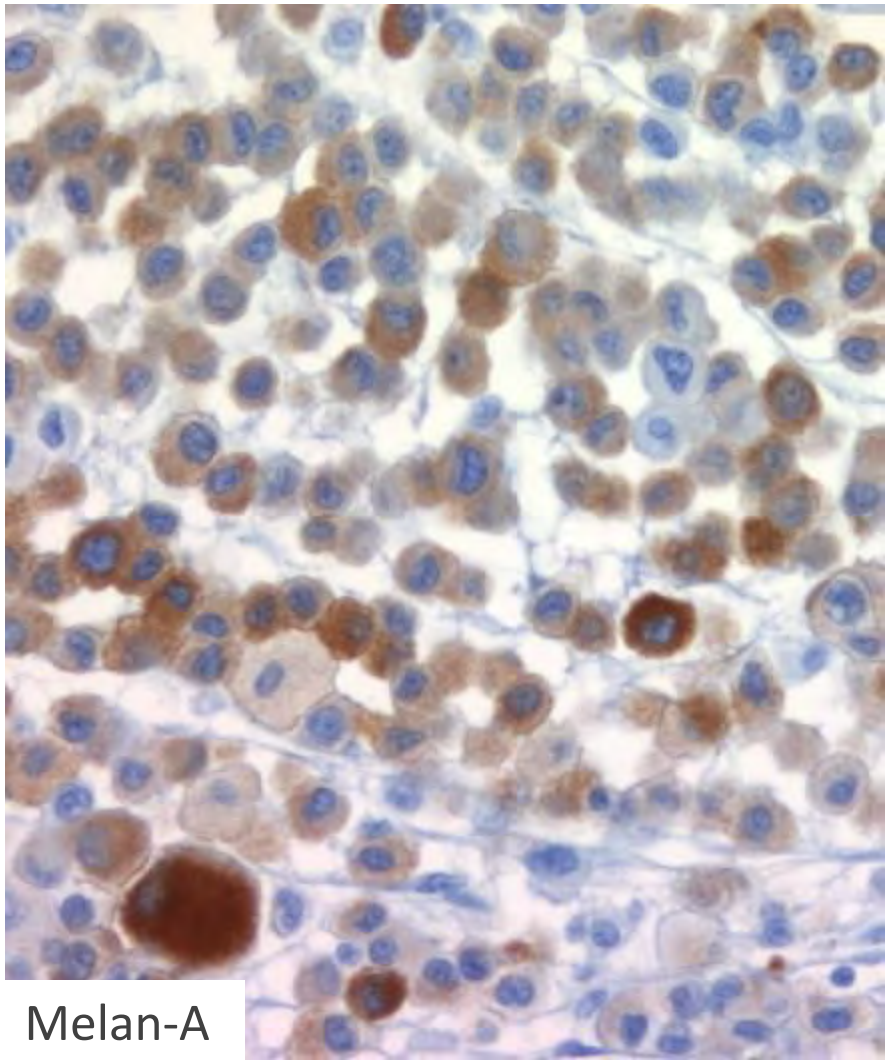


Melan-A

Always question unusual triple negative tumors

- Unusual clinical presentation
- Clinical history
- The pathologist plays an important role
  - Unusual microscopic aspect
  - Unusual phenotype
  - Absence of DCIS…..

But sometimes the metastasis is HR+!

1) Tumors usually expressing HR:
Significant expression of ER, PR +/-

-Breast carcinoma: 80%

-Carcinoma of **gynecological origin**: endometrioid carcinoma and serous carcinoma:> 80%

2) Tumors rarely expressing HR:
Often low expression

-**Bronchopulmonary adenocarcinoma** (5%)

-**Salivary gland tumor**: a minority can express HR (ER and PR): weak expression

-**Neuroendocrine carcinomas** and pseudopapillary solid carcinomas of the pancreas: PR only

Take home message: Is it a primary breast cancer?

- Clinical presentation **large nodules**, growing fast, well demarcated sometimes they are supercial.
- **Can mimmick benign lesions** (ACR3)
- Frequently unique
- ➔ **beware of triple negative lesions with an unusual presentation** (mucinous for instance)
- ➔**beware of ER+ with papillary aspects and psammomas**
- ➔ **aspect of lobular carcinoma in a men**

Prediction

Biomarker	Prognostic	Predictive	Technical validation	Clinical validation
ER	++	+++	YES LOE Ib	YES
PgR	+++	++	YES LOE Ib	NO
HER2	++	+++	YES LOE Ib	YES
Ki67	++	+	NO	NO
	Test and scoring recommendations			
ER	IHC ≥1%			
pgR	IHC ≥1%			
HER2	IHC ≥10% cells with complete membrane staining ISH: number of HER2 gene copies ≥4 or the ratio HER2/chromosome 17 ≥2			
Ki67	IHC no final consensus on cut-off around 20% (Ki67< 10% = low ; Ki67>30% =high)			

Low ER+ Breast Cancer

Is This a Distinct Group?

Nika C. Gloyeske, MD, David J. Dabbs, MD, and Rohit Bhargava, MD

From the Magee-Womens Hospital of University of Pittsburgh Medical Center, Pittsburgh, PA.

Key Words: Low ER+/HER2–; Morphology; Response to neoadjuvant chemotherapy

Am J Clin Pathol May 2014;141:697-701

DOI: 10.1309/AJCP34CYSATWFDPQ

Conclusions: *The low ER+/HER2– cases have morphologic features and a response to the chemotherapy rate that are more similar to triple-negative tumors than the usual type of ER+ tumors.*

- **5%** of BC, usually Grade 3
- Solid and necrotic T
- **80% Ki67> 50%**
- 94% PR-
- 33% of pCR if NACT

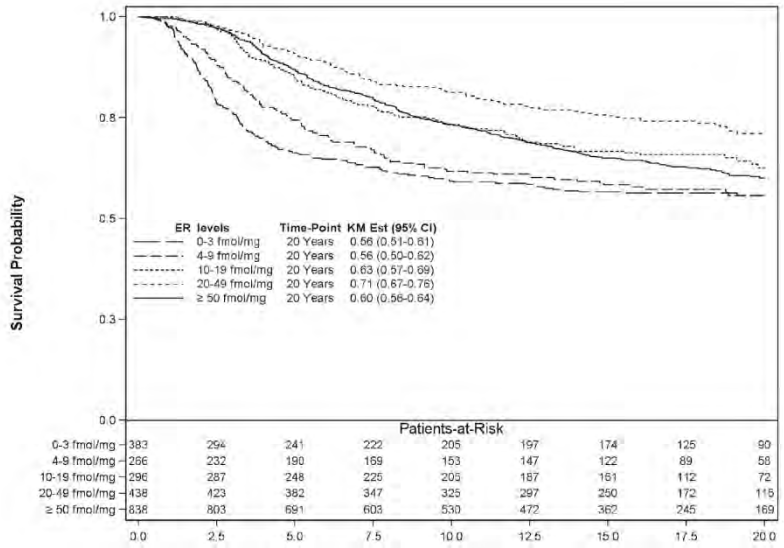
CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Curr Oncol. 2017 Apr;24(2):e106-e114

Prognostic and predictive value of low estrogen receptor expression in breast cancer

A. Bouchard-Fortier MD MSc,* L. Provencher MD MA,†‡§ C. Blanchette MSc,§ and C. Diorio PhD†‡§



- Cytosolic
- tamoxifen
- Follow up >20 yrs
  - **17%** (383) 0–3 fmol/mg cytosol protein
  - 12% (266) 4–9 fmol/mg cytosol protein.
- **56% 20 yrs OS** vs 71% for high ER

IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

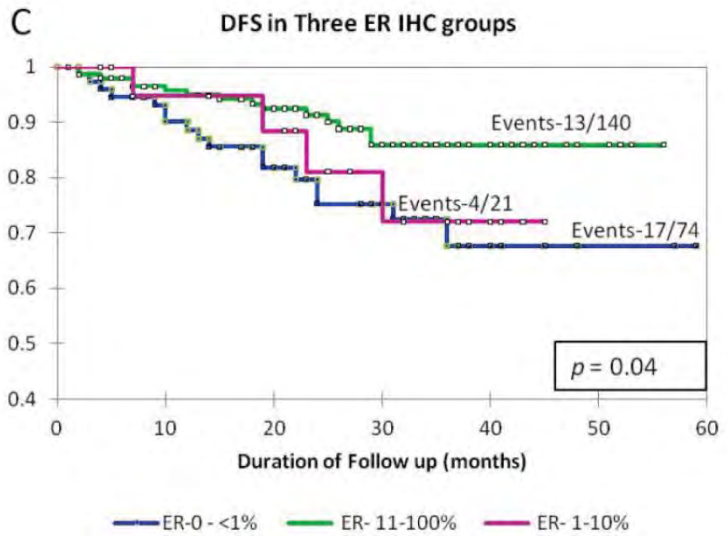
2014; 5(2): 156-165. doi: 10.7150/jca.7668

Research Paper

A Majority of Low (1-10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors

Jyothi S. Prabhu[1]✉, Aruna Korlimarla[1], Krisha Desai[1], Annie Alexander[1], Rohini Raghavan[1], CE Anupama[1], Nandini Dendukuri[3], Suraj Manjunath[2], Marjorrie Correa[4], N Raman[5], Anjali Kalamdani[5], MSN Prasad[5], K.S Gopinath[5], B.S. Srinath[6] and T.S. Sridhar[1]

- 240 cases
- 144 high ER (>10%), 75 ER negative and 21 low-ER (1-10%) tumors by IHC
- qRT-PCR test with 6 ER related genes
- **½ low-ER positive tumors ➔ER negative group based on the probability score**
- 95% of ER negative and 92% of the high ER positive tumors classified correctly (p<0.0001).
- **Survival of the low-ER group was intermediate** between that of the high ER positive and ER negative groups (p<0.05).



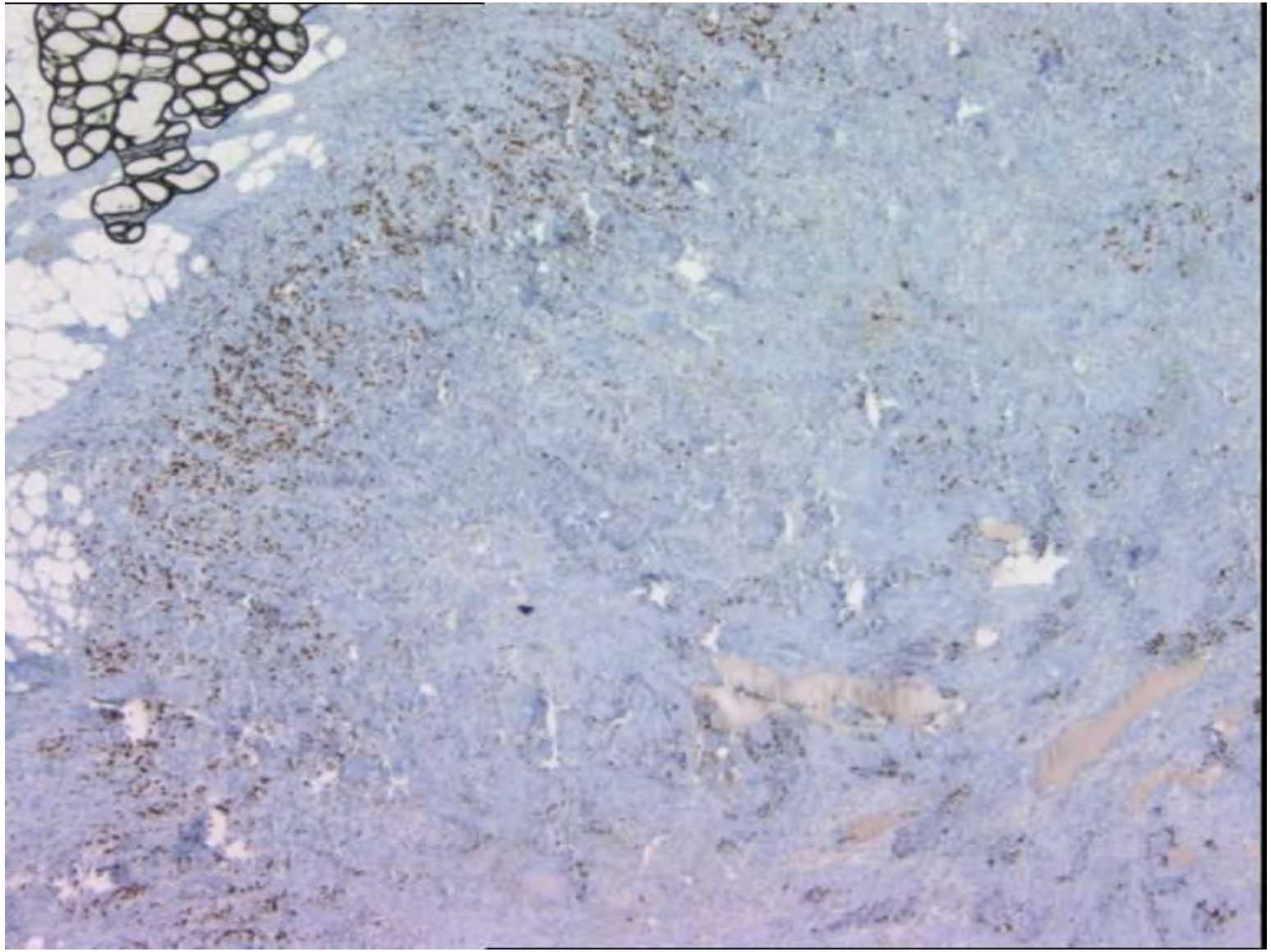
In case of weak ER (1-9%) in practise

- On biopsy: redo on surgical specimen
- On surgical specimen:take into account also the other parameters
- Role of Gene Expression Signatures (GES) ?

Ki67 why?

- Definition of luminal A and B
- Decision of CT for ER+, Grade II tumors

Ki67 = Not standardized



Reproducibility

J Natl Cancer Inst;2013;105:1897–1906

An International Ki67 Reproducibility Study

Mei-Yin C. Polley, Samuel C. Y. Leung, Lisa M. McShane, Dongxia Gao, Judith C. Hugh, Mauro G. Mastropasqua, Giuseppe Viale, Lila A. Zabaglo, Frédérique Penault-Llorca, John M.S. Bartlett, Allen M. Gown, W. Fraser Symmans, Tammy Piper, Erika Mehl, Rebecca A. Enos, Daniel F. Hayes, Mitch Dowsett, Torsten O. Nielsen, on behalf of the International Ki67 in Breast Cancer Working Group of the Breast International Group and North American Breast Cancer Group

Manuscript received April 2, 2013; revised September 3, 2013; accepted September 16, 2013.

Correspondence to: Torsten Nielsen, MD, PhD, FRCPC, University of British Columbia Pathology and Laboratory Medicine, Anatomical Pathology, JP 1401, Vancouver Hospital & Health Sciences Centre, 855 W 12th Ave, Vancouver, BC V5Z 1M9, Canada (e-mail: torsten@mail.ubc.ca).

Cancer Science | Cancer Sci | November 2013 | vol. 104 | no. 11 | 1539–1543 | The official journal of the Japanese Cancer Association | JCA

Interobserver concordance of Ki67 labeling index in breast cancer: Japan Breast Cancer Research Group Ki67 Ring Study

Yoshiki Mikami,[1,10] Takayuki Ueno,[2,10] Kenichi Yoshimura,[3] Hitoshi Tsuda,[4] Masafumi Kurosumi,[5] Shinobu Masuda,[6] Rie Horii,[7] Masakazu Toi[2] and Hironobu Sasano[8,9]

Departments of [1]Diagnostic Pathology, [2]Breast Surgery, Kyoto University Hospital, Kyoto; [3]Translational Research Center, Kyoto University Hospital, Kyoto; [4]Diagnostic Pathology Section, Clinical Laboratory Division, National Cancer Center Hospital, Tokyo; [5]Department of Pathology, Saitama Cancer Center, Saitama; [6]Department of Pathology, Nihon University School of Medicine, Tokyo; [7]Department of Pathology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo; [8]Department of Pathology, Tohoku University School of Medicine, Sendai, Japan

PLOS ONE | DOI:10.1371/journal.pone.0125131 May 1, 2015

An Interobserver Reproducibility Analysis of Ki67 Visual Assessment in Breast Cancer

Ruohong Shui[1,2], Baohua Yu[1,2], Rui Bi[1,2], Fei Yang[1,2], Wentao Yang[1,2]*

1 Department of Pathology, Fudan University Shanghai Cancer Center, Fudan University, Shanghai 200032, China, **2** Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

* yangwt2000@163.com

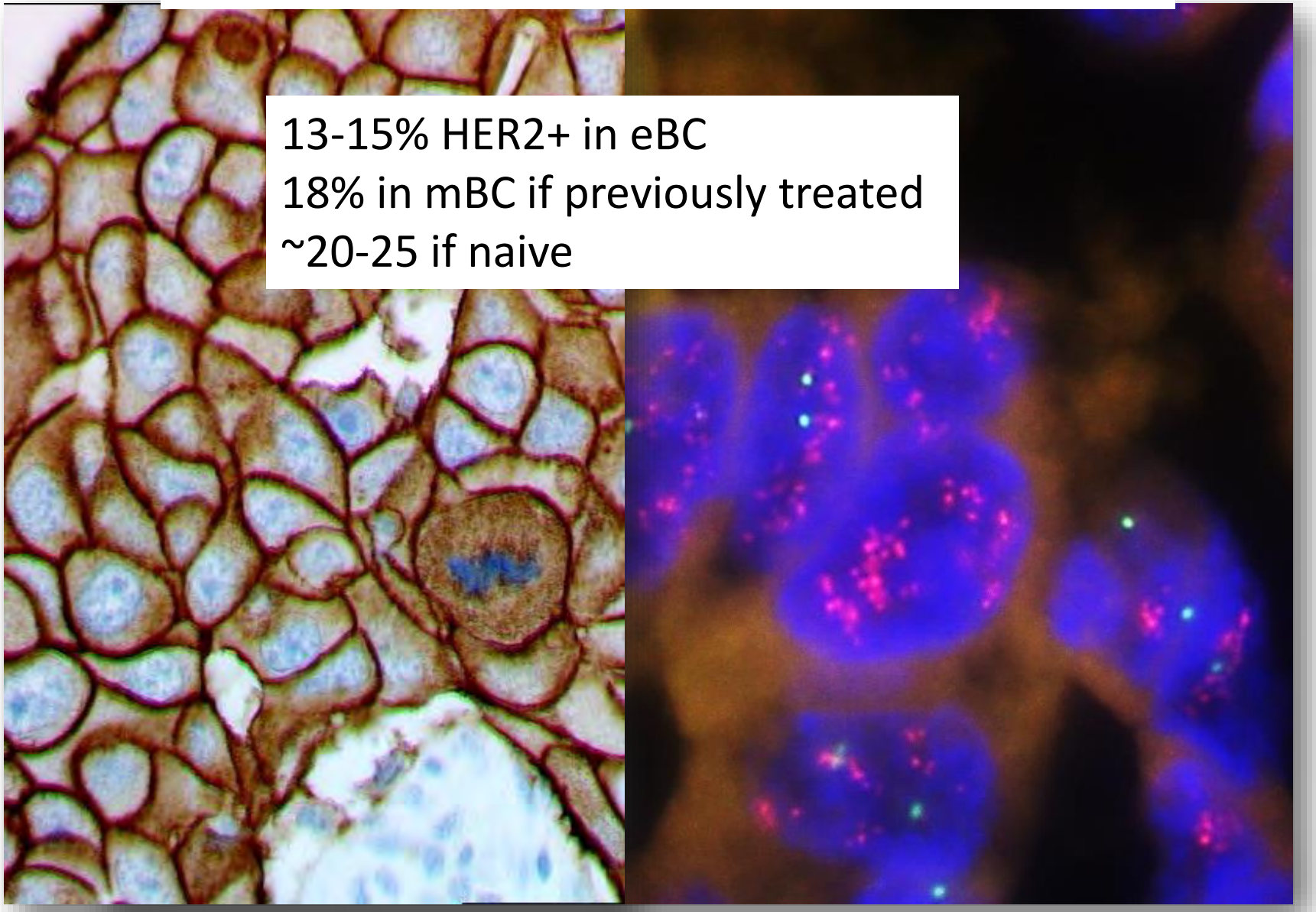
MODERN PATHOLOGY (2015) 28, 778–786

An international study to increase concordance in Ki67 scoring

Mei-Yin C Polley[1], Samuel CY Leung[2], Dongxia Gao[2], Mauro G Mastropasqua[3], Lila A Zabaglo[4], John MS Bartlett[5], Lisa M McShane[1], Rebecca A Enos[6], Sunil S Badve[7], Anita L Bane[8], Signe Borgquist[9], Susan Fineberg[10], Ming-Gang Lin[11], Allen M Gown[12], Dorthe Grabau[9], Carolina Gutierrez[13], Judith C Hugh[14], Takuya Moriya[15], Yasuyo Ohi[16], C Kent Osborne[13], Frédérique M Penault-Llorca[17], Tammy Piper[18], Peggy L Porter[11], Takashi Sakatani[19], Roberto Salgado[20], Jane Starczynski[21], Anne-Vibeke Lænkholm[22], Giuseppe Viale[23], Mitch Dowsett[24], Daniel F Hayes[25], Torsten O Nielsen[2] on behalf of the International Ki67 in Breast Cancer Working Group of the Breast International Group and North American Breast Cancer Group (BIG-NABCG)

FOCUS ON HER2 GUIDELINES

Huge benefit from anti HER2 therapies for patients with mBC and eBC




JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE
2013
Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE
30th may 2018 !
Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/ College of American Pathologists Clinical Practice Guideline Focused Update
Antonio C. Wolff, M. Elizabeth Hale Hammond, Kimberly H. Allison, Brittany E. Harvey, Pamela B. Mangu, John M.S. Bartlett, Michael Bilous, Ian O. Ellis, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, Lisa M. McShane, and Mitchell Dowsett
JOURNAL OF CLINICAL ONCOLOGY
CORRESPONDENCE
Reply to E.A. Rakha et al

Heterogeneity: Where to count?

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE 2018

Act III?

1. Simplification of IHC 2+ definition (moderate/weeak)
2. Re-testing on surgical specimen if a biopsy is HER2 - :

   "may" in instead of "should"
3. Revision and/or definition of difficult ISH categories (monosomies, co-amplification, "equivocal")➔ avoid as much as possible "equivocal/eligible" cases

Based on IHC results

Messages for HER2 ASCO/CAP new guidelines

- **Simplification of HER2 2+** 2
- No longer systematic re-testing
  - **Difficult ISH categories**: between 4-6 copies +/- ratio HER2/CEP17<2
    - Interpretation with IHC++++
    - Independant (second reader for ISH) for 2+
    - Disparition of equivocal ISH category
      - Category 2 (monosomy): rather negative
      - Caegory 3 3 (co-ampl): rather positive
      - Category 4(ex-equivocal): rather negative
  - Avoid single probe ISH

THE PATHOLOGY REPORT

Box 4 | **The pathology report for breast cancer**

- Histological type according to the current WHO classification[107]
- Histological grade according to the Elston- and Ellis-modified Scarff–Bloom–Richardson system[108]
- Peritumoral vascular or lymphatic emboli[a]
- Hormone receptor status (oestrogen receptor (ER) and progesterone receptor)
- Human epidermal growth factor receptor 2 (HER2) status
- Excision margins (mm)[a]
- Tumour size, single or multiple tumours
- Ductal carcinoma in situ component type, grade and percentage
- Lymph node status
- Pathological stage according to the Union for International Cancer Control TNM system[122]
- Ki67 score according to the international group guidelines[b]

[a]Information obtained at surgical resection. [b]Particularly relevant for ER-positive, HER2-negative breast cancers.

When to question a pathology report

- PgR+, ER-
- Lobular, tubular carcinoma HER2+
- Grade 1, ER+++, PgR+++, HER2+
- Grade 3, ER-, ki67 <5%
- Grade 3 ER+++, PgR+++
- Medullary carcinoma is extremely rare and has been removed from WHO classification

➔May redo HER2 (and ER) on surgical specimen if grade 3, ER- or ER+

➔ If ER and/or PgR is negative on a biopsy redo on surgical specimen

Does Estrogen Receptor–Negative/ Progesterone Receptor–Positive Breast Carcinoma Exist?

De Maeyer L et al. J Clin Oncol, DOI: 10.1200/JCO.2007.14.8411

Hefti *et al. Breast Cancer Research* 2013, **15**:R68
http://breast-cancer-research.com/content/15/4/R68

RESEARCH ARTICLE Open Access

Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype

Marco M Hefti[1], Rong Hu[2], Nicholas W Knoblauch[1], Laura C Collins[1], Benjamin Haibe-Kains[3], Rulla M Tamimi[2] and Andrew H Beck[1*]

ER-/PR+

- Approximately 70% of breast cancers are ER+,
  - ER+/PR+ 57% EBC
  - 25% ER+/PR− with a more aggressive biological behavior than ER+/PR+ tumors [8]
- ER−/PR+ controversial +++ breast cancers incidence of 1% to 4%
  - **Technical artifact** arising from inadequate tissue fixation or failure of the immunohistochemical assay ?
  - Others argued that even using optimally fixed tissues and any level of nuclear immunoreactivity of tumor cells as a positive result, the ER−/PR+ was still retained as a **unique entity**
- ER−/PR+ classification was too rare to be of clinical use ?

Human Pathology (2015) 46, 1776–1784

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

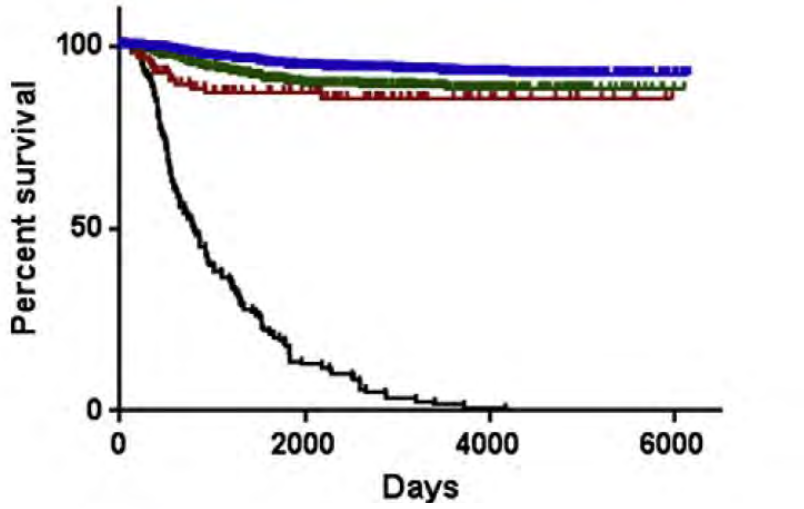
Original contribution

Characterization of estrogen receptor–negative/ progesterone receptor–positive breast cancer☆,☆☆

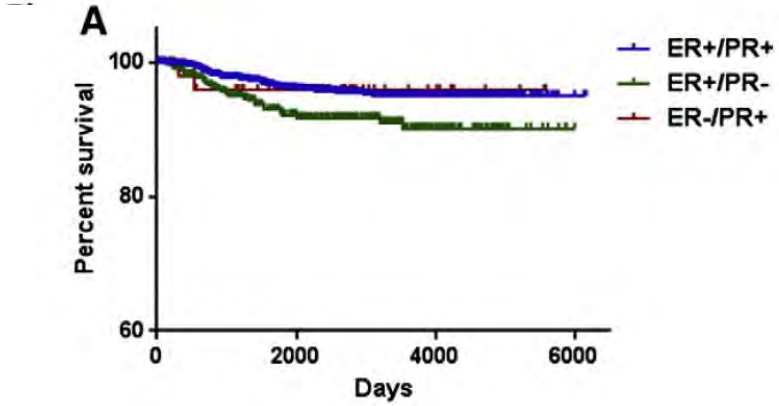
Tiansheng Shen MD, PhD, Margaret Brandwein-Gensler MD, Omar Hameed MD, Gene P. Siegal MD, PhD, Shi Wei MD, PhD*

- 5374 consecutive breast cancers
- **2.3% ER–/PR+ tumors**
- High grade and significantly seen in younger patients and African American women (vs ER+/PR+ and ER+/PR–)
- **Similar to ER–/PR– phenotype** (P <0 .0001).

Survival



A significantly prolonged relapse-free survival (RFS) was associated with the ER+/PR+ subtype when compared with the ER+/PR− (P =.0002) or ER−/PR+ (P = .0004) tumors, whereas all 3 groups showed a superior outcome to that of the ER−/PR− phenotype.



RFS in patients HR+ treated with endocrine therapy.

- ER+/PR+ associated with a significantly prolonged RFS when compared with the **ER+/PR–** group p=0,001
- No significant difference was found **between ER+/PR+ and ER-/PR+**
- Same trends for disease specific deaths p=0,005

Hefti et al. Breast Cancer Research 2013, 15:R68
http://breast-cancer-research.com/content/15/4/R68

Breast Cancer RESEARCH

RESEARCH ARTICLE Open

Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype

Marco M Hefti[1], Rong Hu[2], Nicholas W Knoblauch[1], Laura C Collins[1], Benjamin Haibe-Kains[3], Rulla M Tami and Andrew H Beck[1*]

classified cases were relatively evenly split between ER+ and ER- subgroups on repeat testing.

Taken together, our data do not support that ER-/PR+ represents a biologically distinct or clinically useful breast cancer subtype. These data suggest that PR testing is not warranted in ER- breast cancer, as ER-/PR+ breast cancer is very rare and non-reproducible, thus the vast majority of cases classified as ER-/PR+ will represent false classifications. Our data suggest that ER+/PR-

- 4,111 cases from 20 published studies with gene expression microarray (GEM) and clinicopathological data (ER + / PR +, ER + / PR-, ER- / PR-, ER- / PR +) and basis of 2011 Nurses' study patients
- Health Study (NHS) with ER / PR data, clinical data and molecular analysis
- The ER- / PR + subtype is rare (1 to 4%) and not reproducible in the molecular classes
- Most patients classified as ER- / PR + in the clinical databases (97 and 94% respectively) were reclassified by a second method.
- The expression of PR in RNAm in the GEM base was associated with prognosis for ER + (P <0.001) but not for ER- (p = 0.21)

ER-/PR+ what to do in practise?

- Re-test the case, check internal controls
- In case of absence of + internal controls Re-test on a other block
- If still ER-/PR+
  - If available require a GES
  - The prognosis of those lesions appears less favorable than ER+:PR+ but the positivity of PR receptor remains a strong prognostic factor in case of hormonal treatment

TILS

Advances In Anatomic Pathology. 24(5):235–251, SEP 2017
DOI: 10.1097/PAP.0000000000000162, PMID: 28777142
Issn Print: 1072-4109
Publication Date: 2017/09/01

Print

Assessing Tumor-infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method From the International Immunooncology Biomarkers Working Group Part 1 Assessing the Host Immune Response, TILs in Invasive Breast Carcinoma and Ductal Carcinoma In Situ, Metastatic Tumor Deposits and Areas for Further Research

Seminars in Cancer Biology 52 (2018) 16-25
Contents lists available at ScienceDirect
Seminars in Cancer Biology
journal homepage: www.elsevier.com/locate/semcancer

Review

Update on tumor-infiltrating lymphocytes (TILs) in breast cancer, including recommendations to assess TILs in residual disease after neoadjuvant therapy and in carcinoma in situ: A report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer☆

Maria Vittoria Dieci[a,b,*], Nina Radosevic-Robin[c,d], Susan Fineberg[e,f], Gert van den Eynden[g,h], Nils Ternes[i,j], Frederique Penault-Llorca[c,d,k], Giancarlo Pruneri[l,m], Timothy M. D'Alfonso[n],

original report

Tumor-Infiltrating Lymphocytes and Prognosis: A Pooled Individual Patient Analysis of Early-Stage Triple-Negative Breast Cancers

Sherene Loi, MD[1]; Damien Drubay, PhD[2,3]; Sylvia Adams, MD[4]; Giancarlo Pruneri, MD[5]; Prudence A. Francis, MD[1]; Magali Lacroix-Triki, MD[2]; Heikki Joensuu, MD[7]; Maria Vittoria Dieci, MD[8,9]; Sunil Badve, MD[10]; Sandra Demaria, MD[11]; Robert Gray, PhD[12]; Elisabetta Munzone, MD[13]; Jerome Lemonnier, PhD[6]; Christos Sotiriou, MD[14]; Martine J. Piccart, MD[14]; Pirkko-Liisa Kellokumpu-Lehtinen, MD[15]; Andrea Vingiani, MD[16]; Kathryn Gray, PhD[12]; Fabrice Andre, MD[2,3]; Carsten Denkert, MD[17]; Roberto Salgado, MD[1,18]; and Stefan Michiels, PhD[2,3]

J Clin Oncol 37:559-569. © 2019

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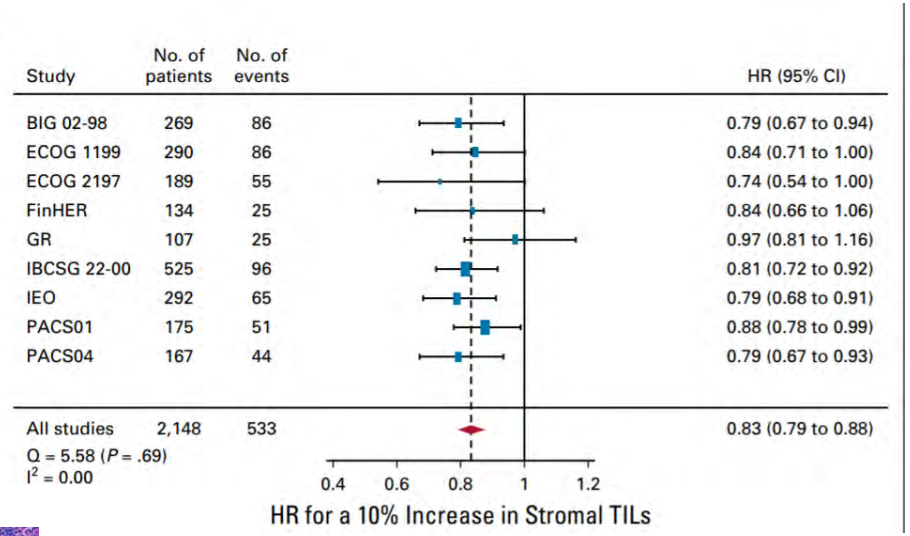
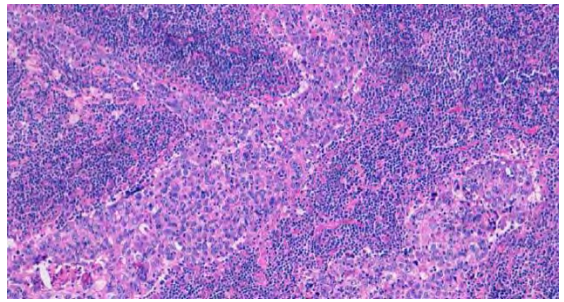
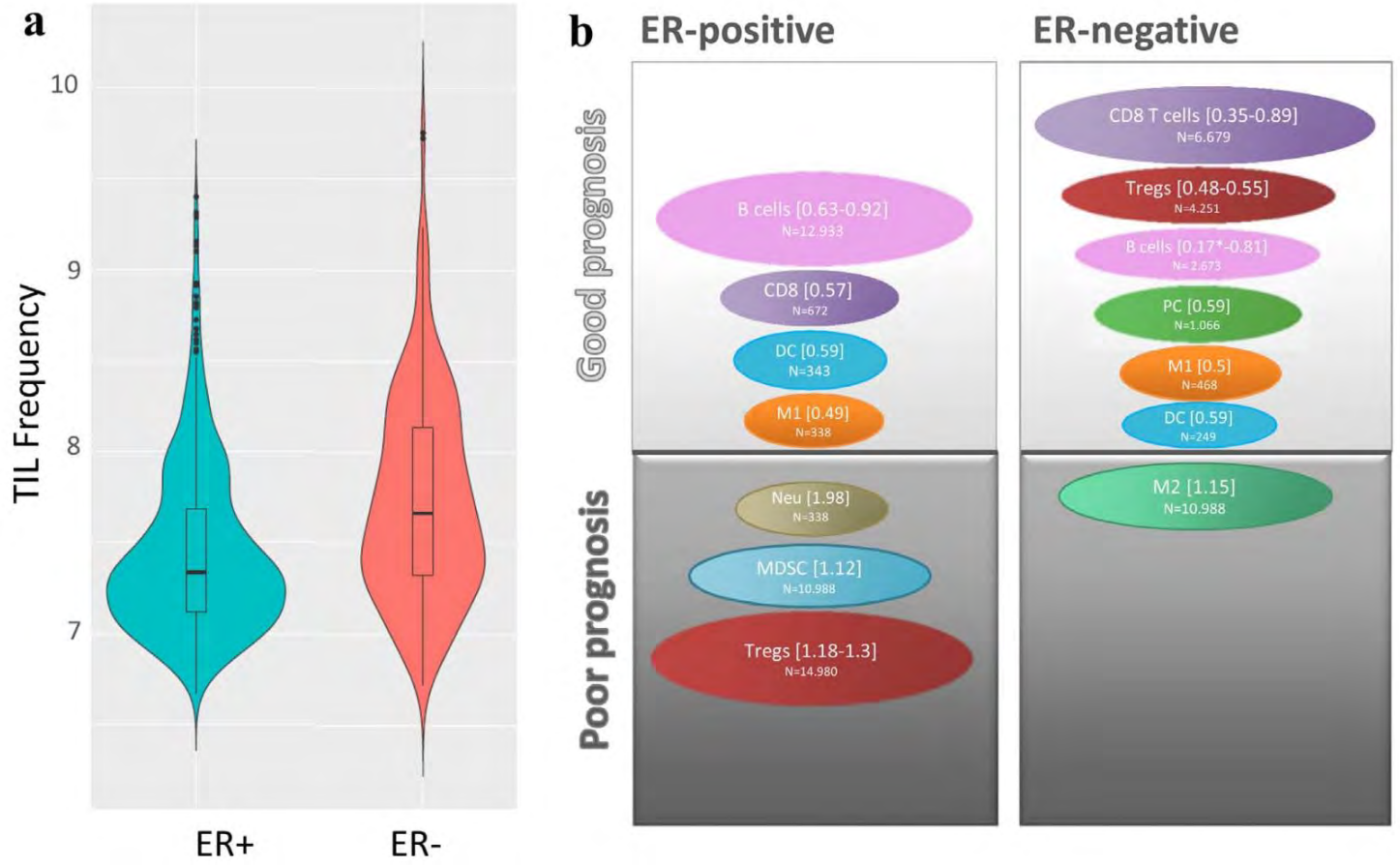


9 essais randomisés TILs et survie globale dans les CSTN

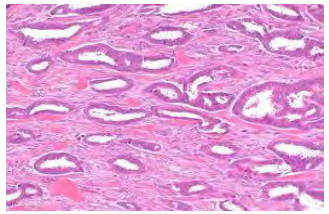


Different TILs infiltrates in different categories of breast cancer

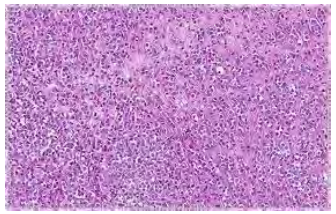


http://dx.doi.org/10.1016/j.semcancer.2017.11.003

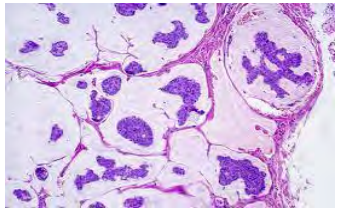
Immunogenicity of breast cancers



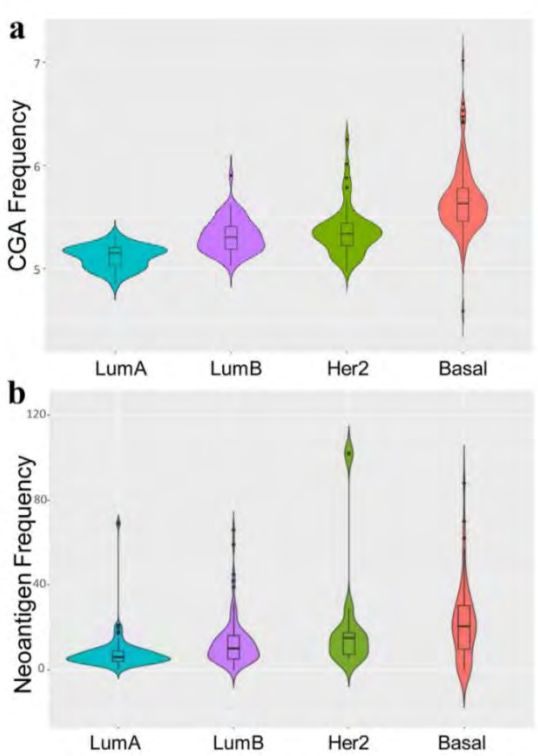
Tubular BC



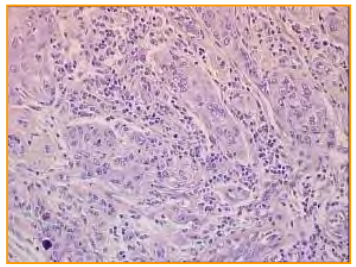
Lobular BC

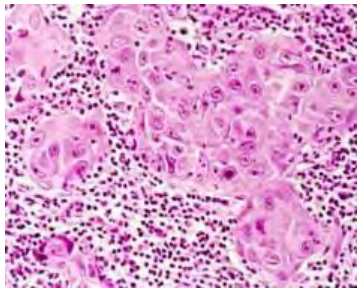


Mucinous BC



P<0,0001





Carcinoma with medullary features

http://dx.doi.org/10.1016/j.semcancer.2017.11.003

reviews

Annals of Oncology 26: 259–271, 2015
doi:10.1093/annonc/mdu450
Published online 11 September 2014

The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014

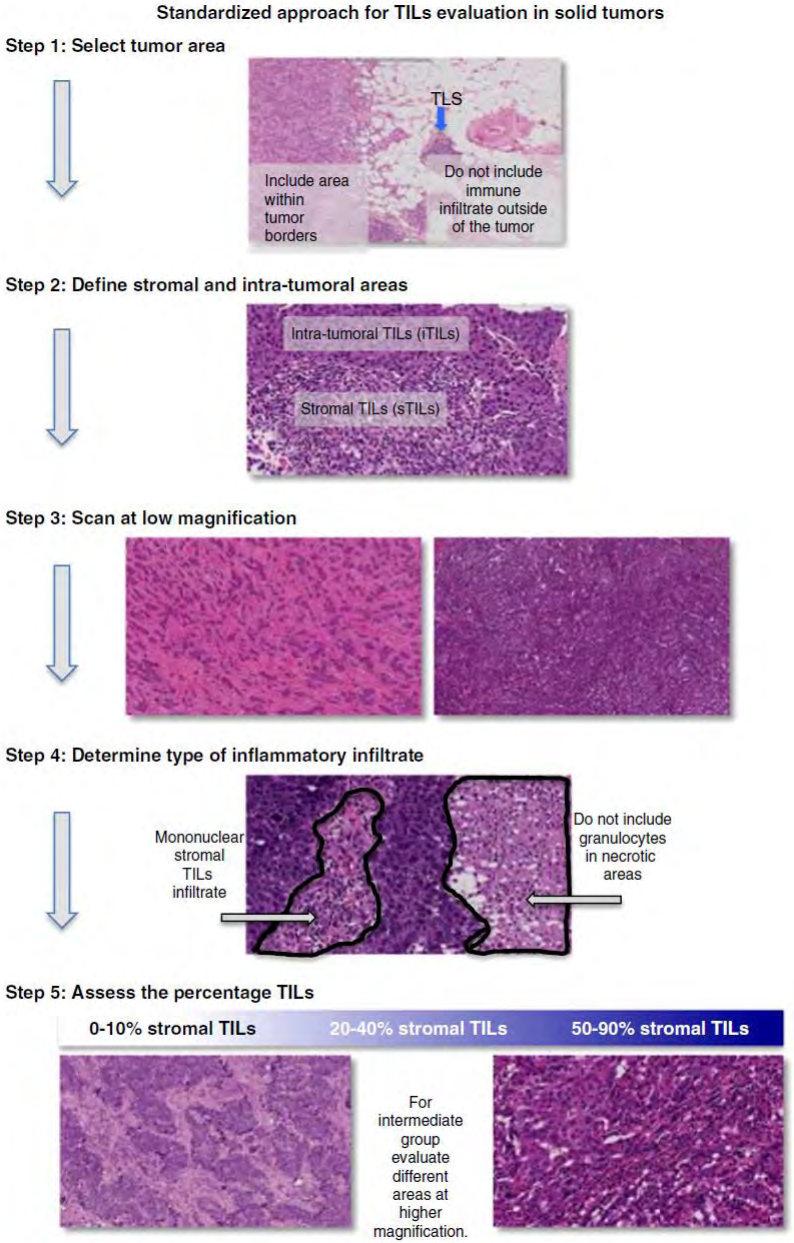
R. Salgado[1,2,†], C. Denkert[3,†], S. Demaria[4,†], N. Sirtaine[5], F. Klauschen[3], G. Pruneri[6], S. Wienert[3], G. Van den Eynden[7], F. L. Baehner[8,9], F. Penault-Llorca[10], E. A. Perez[11], E. A. Thompson[12], W. F. Symmans[13], A. L. Richardson[14,15], J. Brock[15,16], C. Criscitiello[17], H. Bailey[8], M. Ignatiadis[18], G. Floris[19], J. Sparano[20], Z. Kos[21], T. Nielsen[22], D. L. Rimm[23], K. H. Allison[24], J. S. Reis-Filho[25], S. Loibl[26], C. Sotiriou[18], G. Viale[27], S. Badve[28], S. Adams[4,†], K. Willard-Gallo[29,†] & S. Loi[30*,†]

TILs assessment requires standardized approaches

Lymphocyte predominant breast cancer can be used as a descriptive term for tumors that contain "more lymphocytes than tumor cells." However, the thresholds vary between **50%** and **60%** stromal lymphocytes.

REVIEW ARTICLE

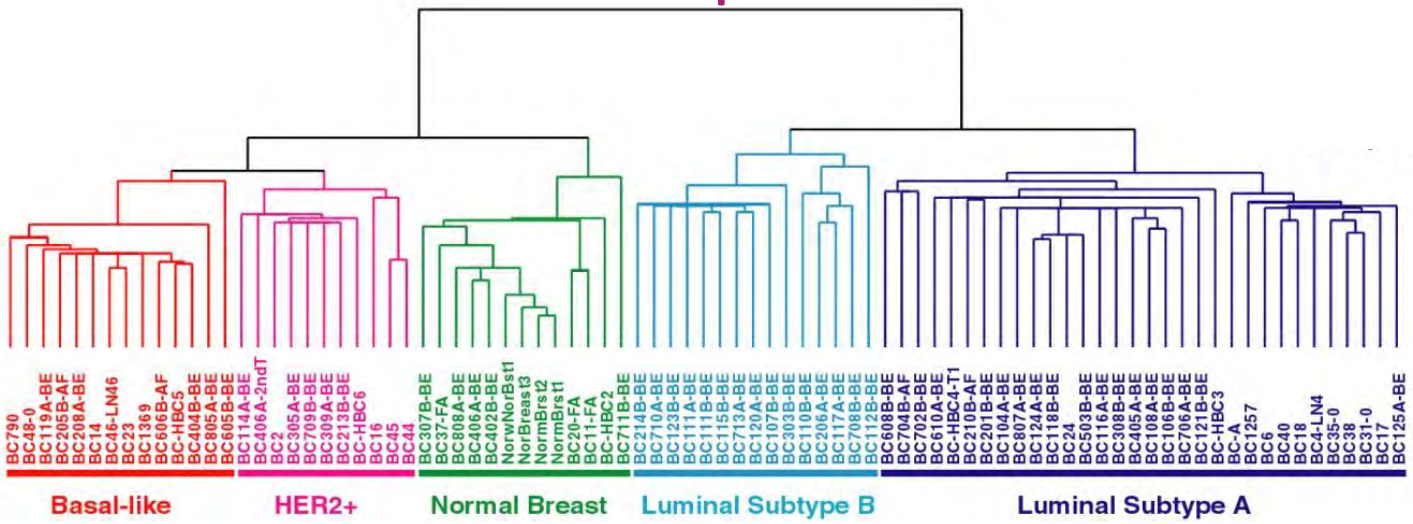
Assessing Tumor-infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method From the International Immunooncology Biomarkers Working Group: Part 1: Assessing the Host Immune Response, TILs in Invasive Breast Carcinoma and Ductal Carcinoma In Situ, Metastatic Tumor Deposits and Areas for Further Research

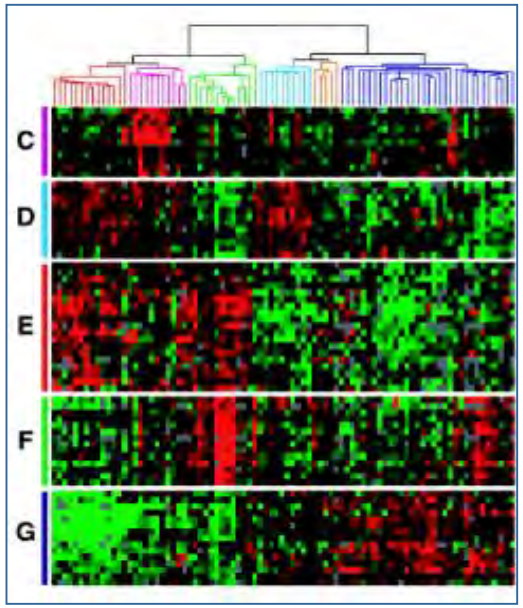


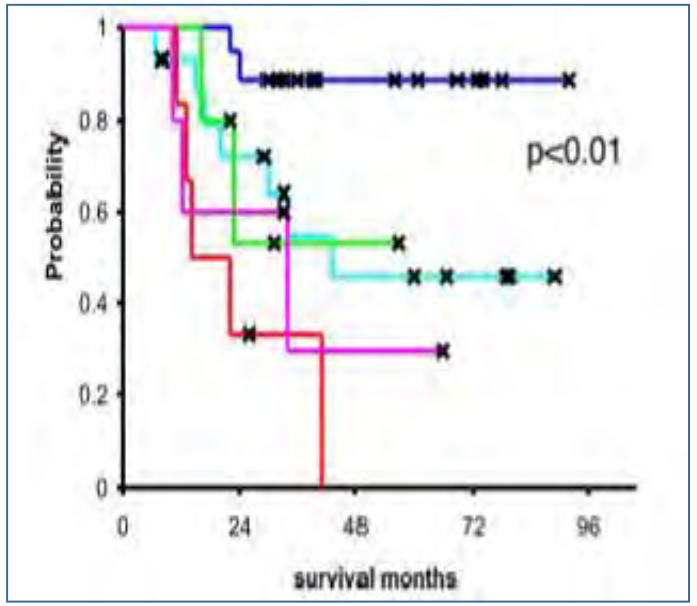
Hendry S, et al Adv Anat Pathol. 2017 Aug 2. doi: 10.1097/PAP.0000000000000161. PMID: 28777143

MOLECULAR AND HISTOLOGIC CLASSIFICATION

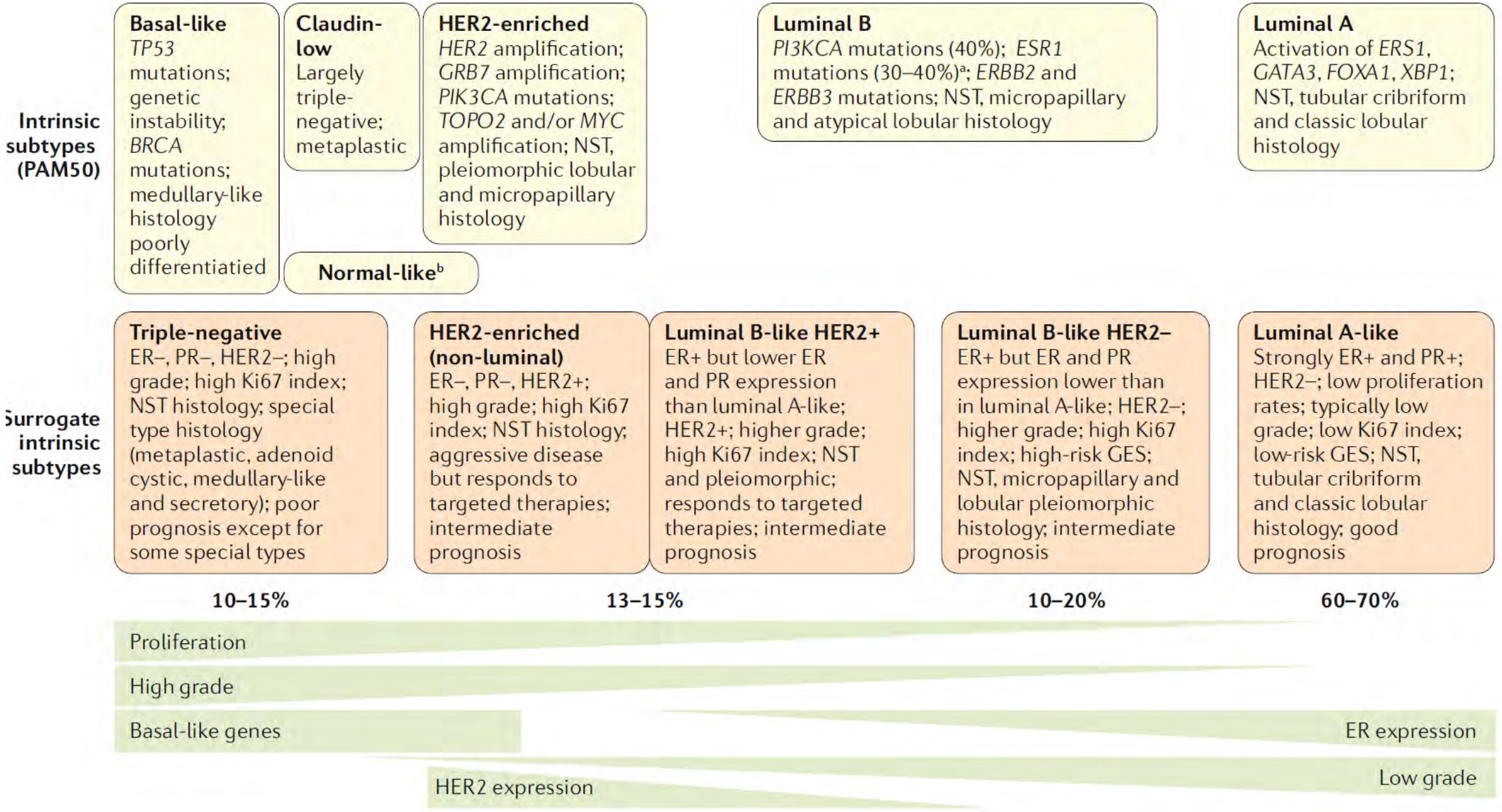
Towards a simplified taxonomy of breast cancer? « definition of intrinsic subtypes has proven efficient in defining prognosis for breast cancer patients »





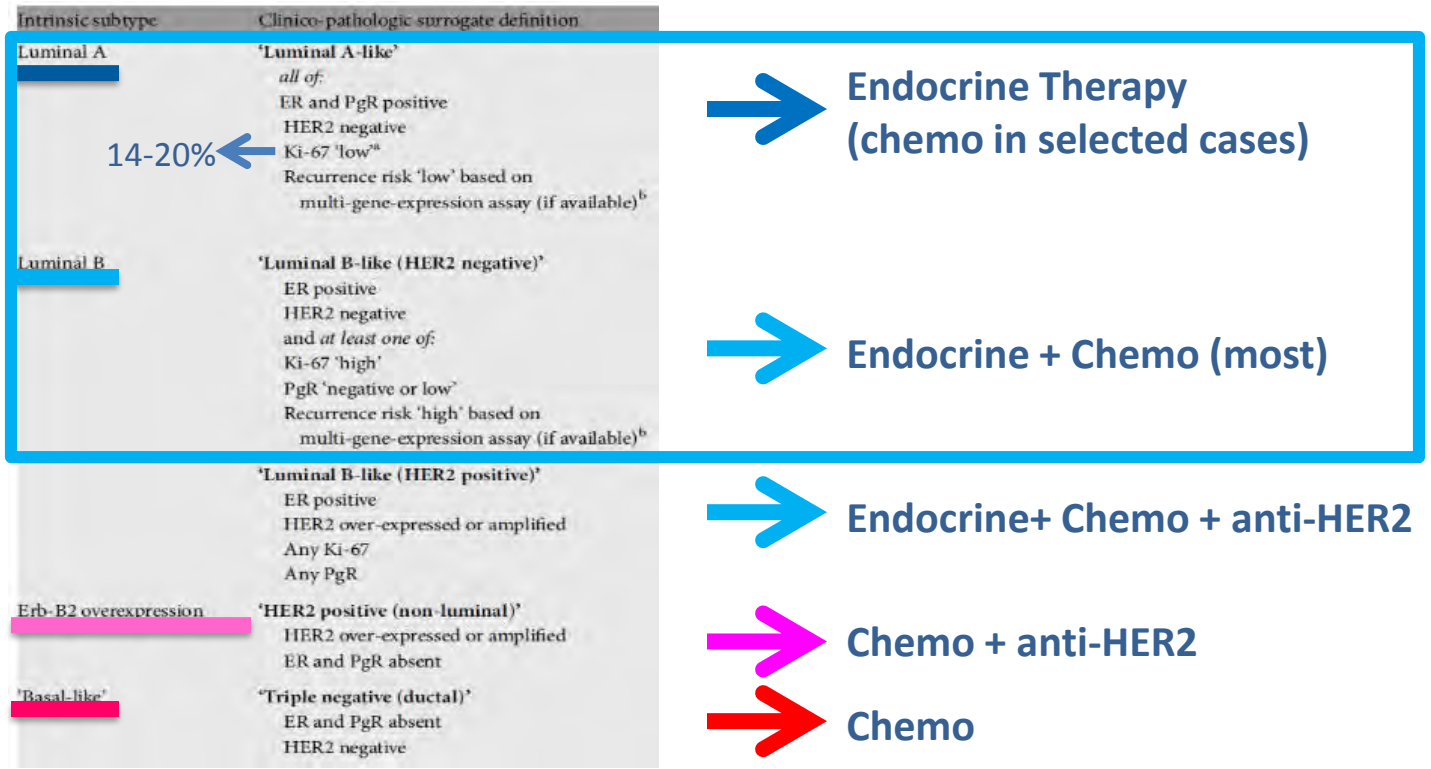


C Perou & T Sorlie



Harbeck N, Penault-Llorca et al Nature Review disease Primer (2019) 5:66

2013 St Gallen International Expert Consensus

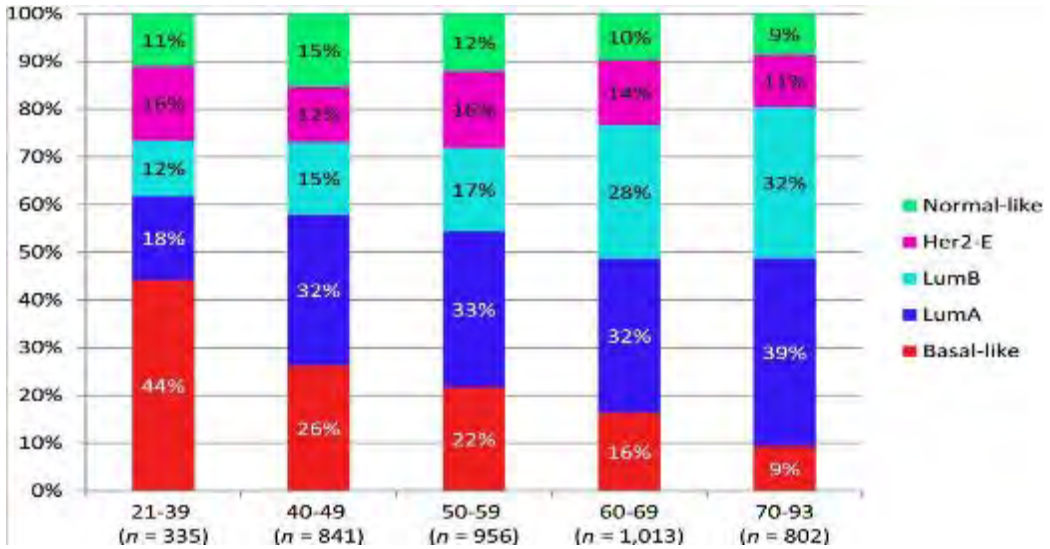


Intrinsic subtype	Clinico-pathologic surrogate definition
Luminal A	**'Luminal A-like'** *all of:* ER and PgR positive HER2 negative Ki-67 'low'[a] Recurrence risk 'low' based on multi-gene-expression assay (if available)[b]
Luminal B	**'Luminal B-like (HER2 negative)'** ER positive HER2 negative and *at least one of:* Ki-67 'high' PgR 'negative or low' Recurrence risk 'high' based on multi-gene-expression assay (if available)[b]
	'Luminal B-like (HER2 positive)' ER positive HER2 over-expressed or amplified Any Ki-67 Any PgR
Erb-B2 overexpression	**'HER2 positive (non-luminal)'** HER2 over-expressed or amplified ER and PgR absent
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative

Quote: "Panel endorsed gene expression signatures that permit avoidance of chemotherapy in many patients with ER-positive breast cancer".

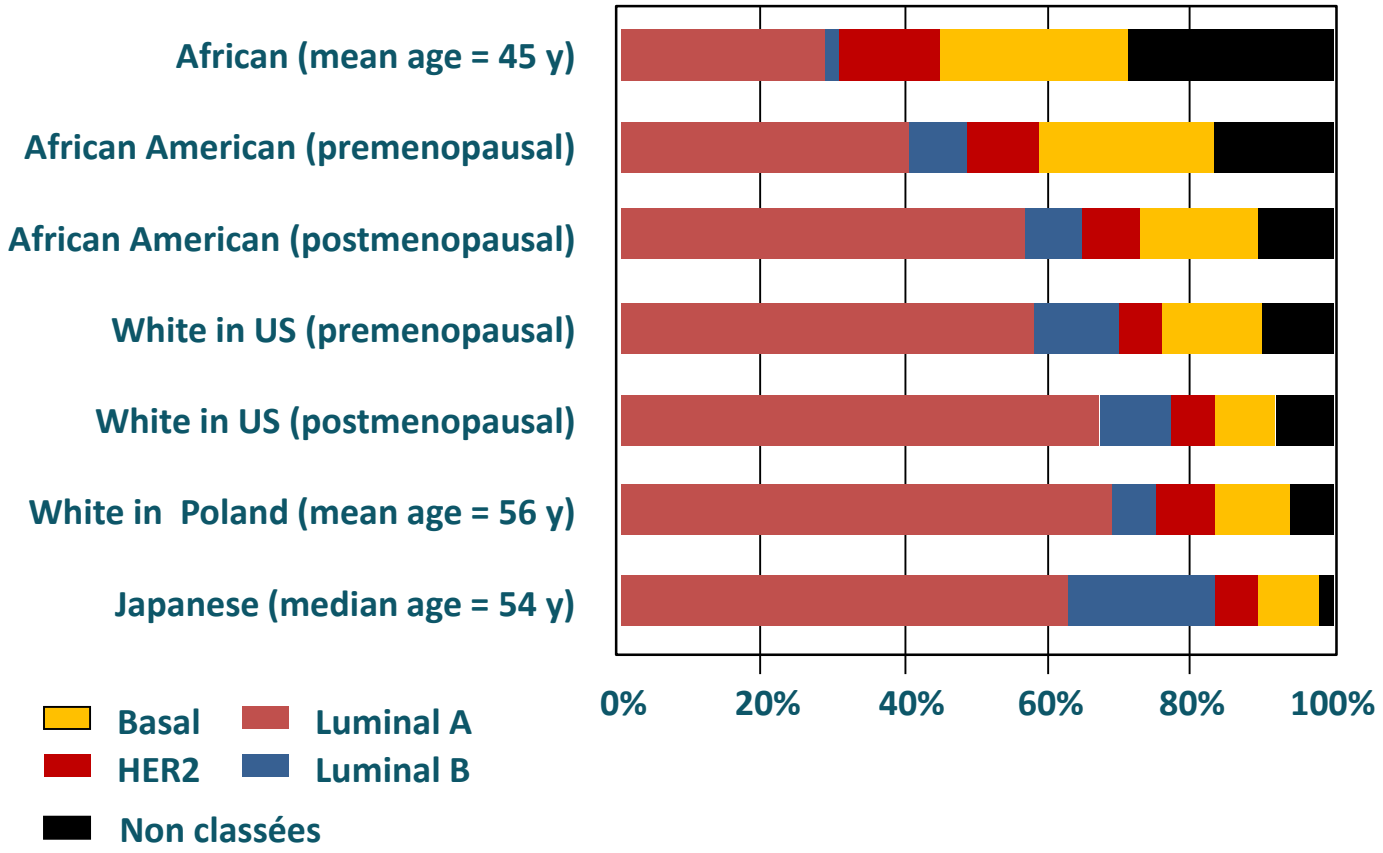
Curigliano Ann Oncol 2017
Goldhirsch et al. Ann Oncol 2013
Cheang et al. JNCI 2009

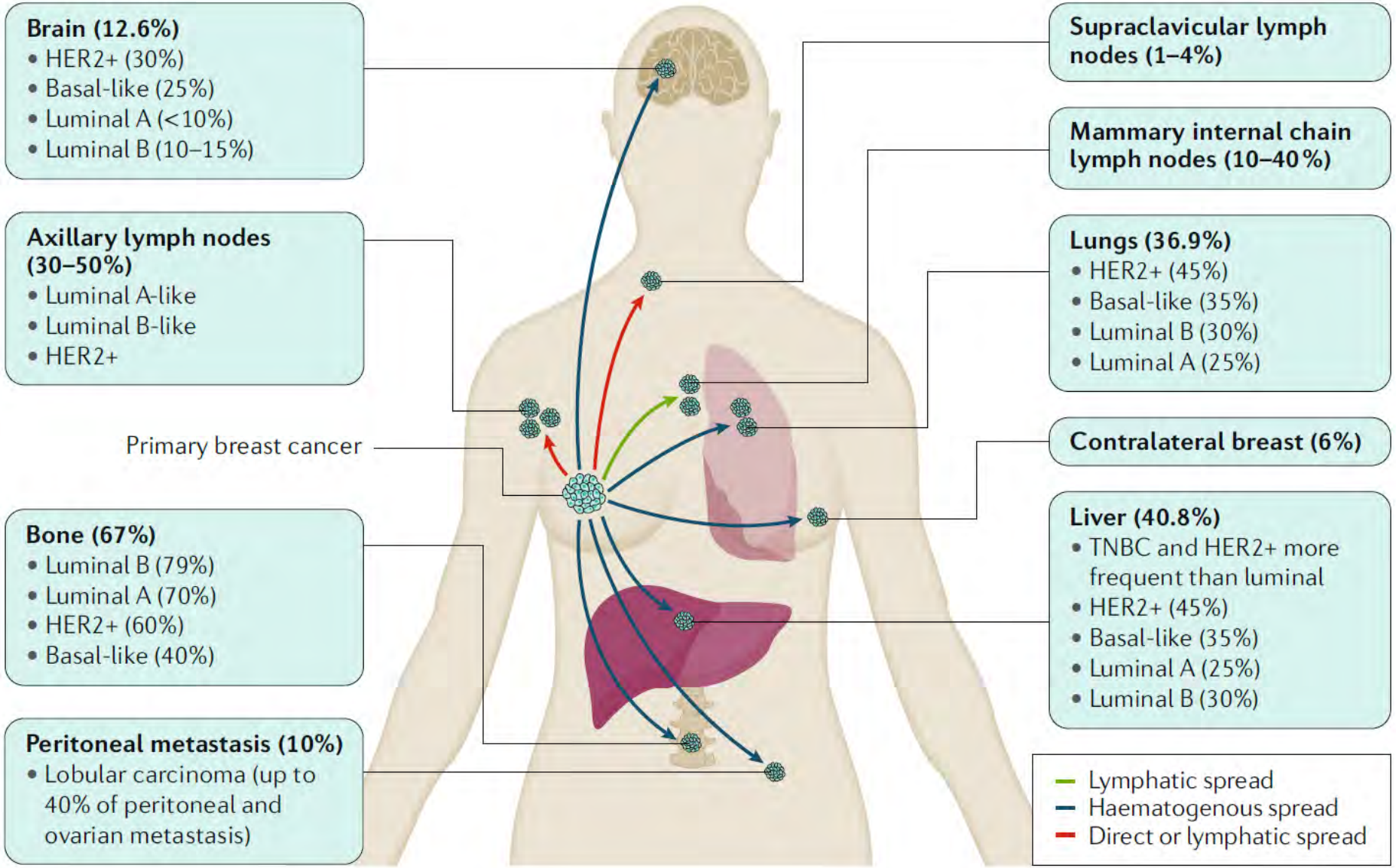
Biology of breast cancer varies with aging



de Kruijf Mol Oncol 2014, Jenskins Oncologist 2014

Molecular biology of BC is influenced by ethnies and country of residence





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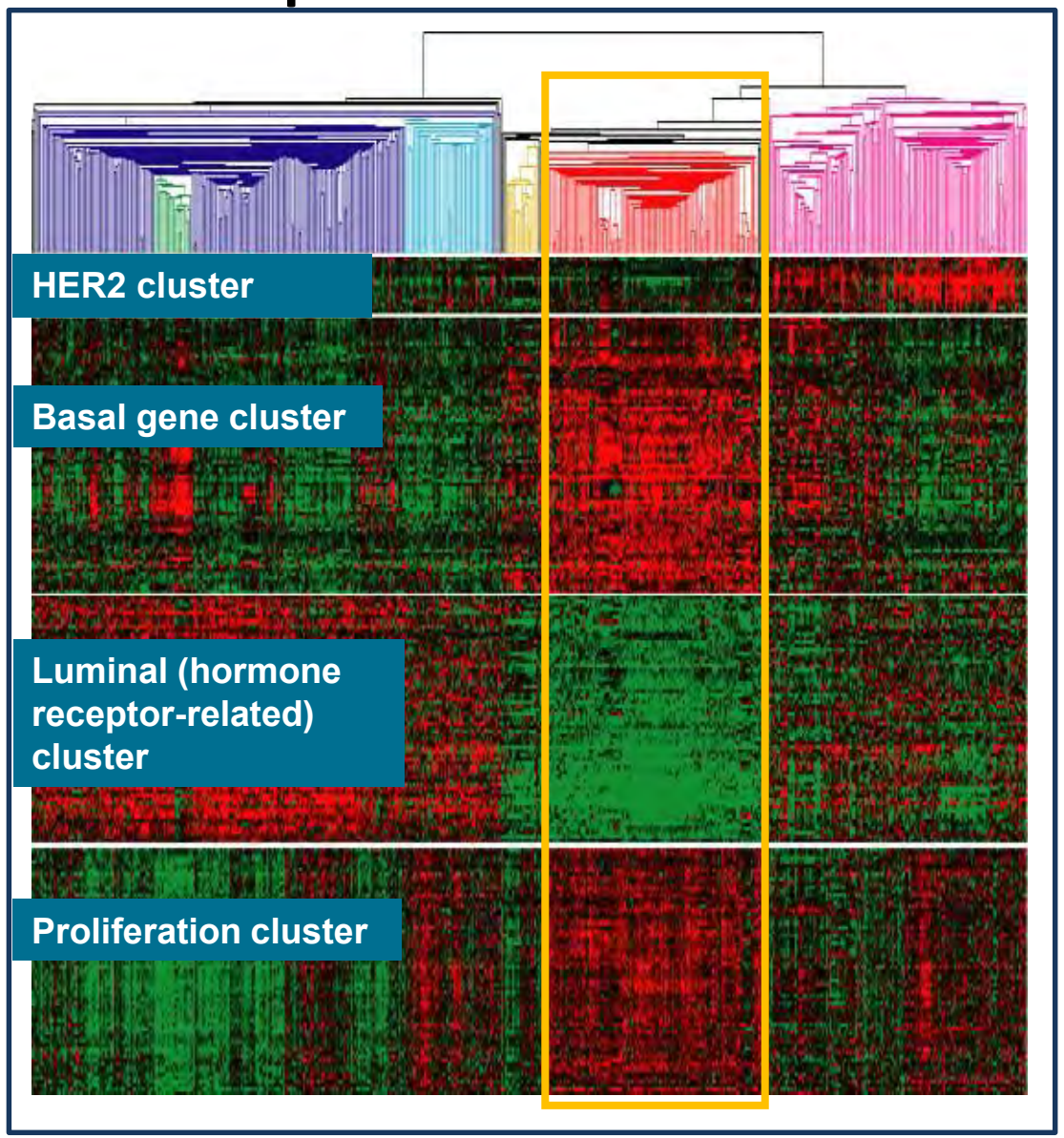
The picture of basal-like breast cancer

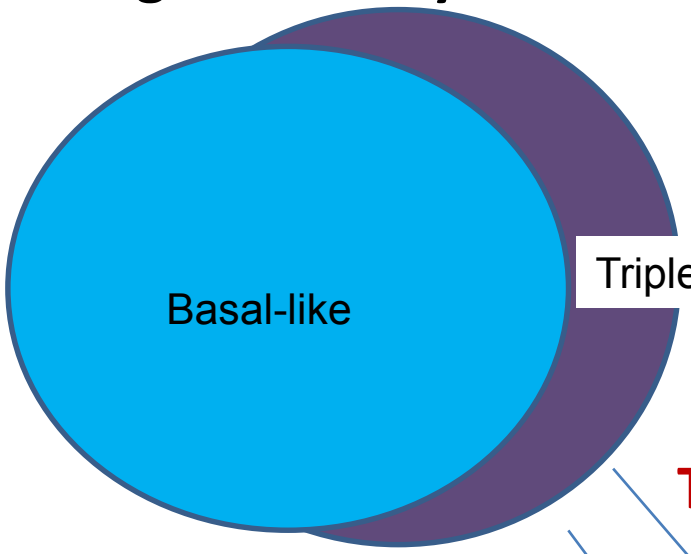


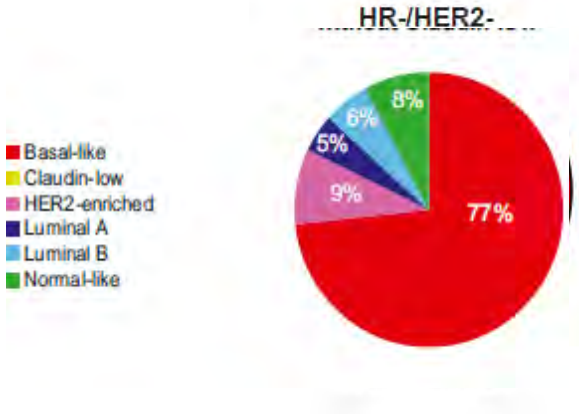
- Low ER (and related genes) expression
- Low HER2 cluster expression

→ usually “triple negative”

- High basal cluster
  - basal cytokeratins
  - EGFR
  - c-kit
  - others…
- Very proliferative
- Often p53 mutant (>90%)
- Evidence of genomic instability

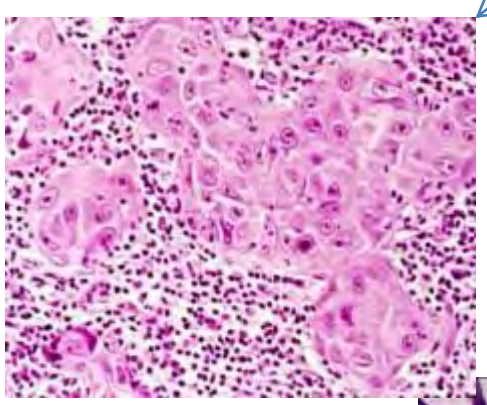
Triple negative BC by IHC and molecular subtypes: a 80% concordance



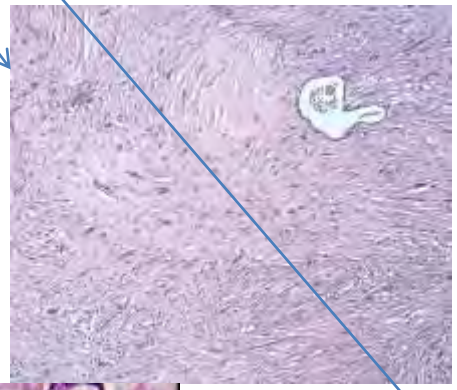


- ER and PgR absent
- HER2 negative
- ~80% overlap between TNBC & intrinsic « basal-like »

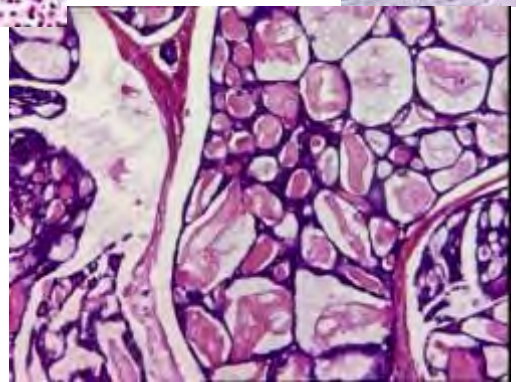
TNBC subtypes of excellent prognosis



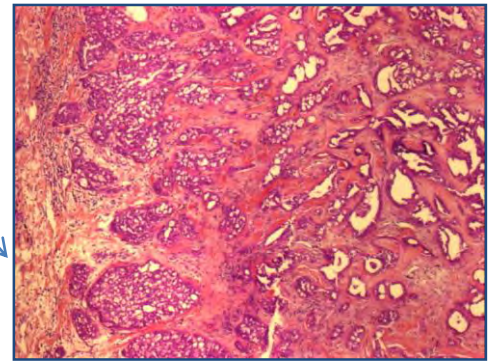
Medullary



Low grade squamous



Adenoid cystic



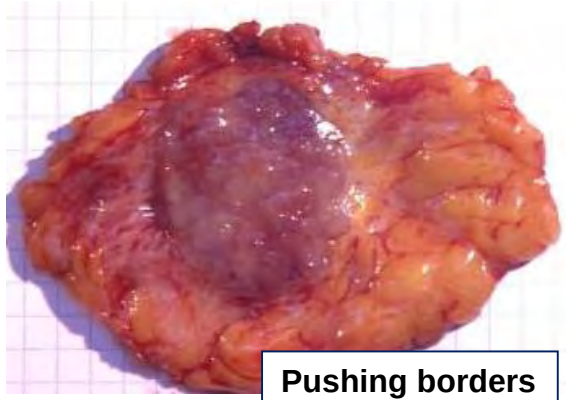
Secretory carcinoma

Triple-Negative Breast Carcinomas: Prototypical Features

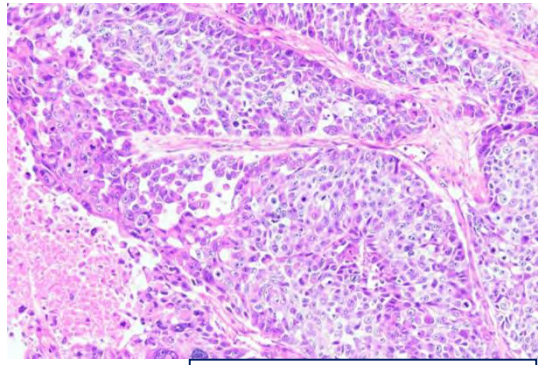
- Clinical features
  - Younger patients (47-55 years)
  - African American women
  - Interval cancers
  - BRCA-1 mutations
  - Prevalence of brain and lung metastases
  - Early metastasis (2-3 years)

Reis-Filho JS, et al. *Histopathology.* 2008;52(1):108-118.
Diaz LK, et al. *Adv. Anat Pathol.* 2007;14(6):419-430.

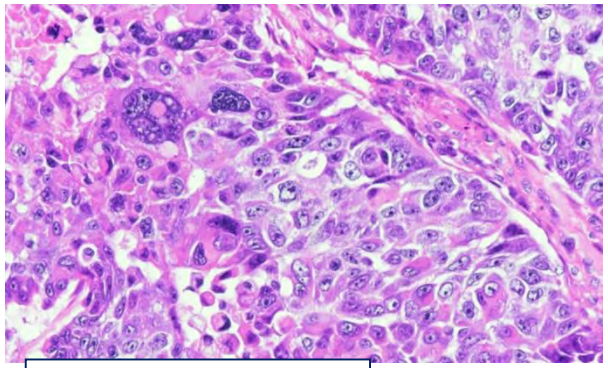
90% of Triple negative breast tumors: invasive ductal NST



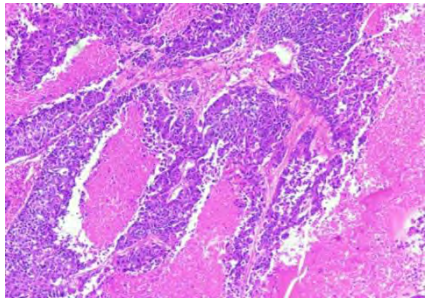
Pushing borders



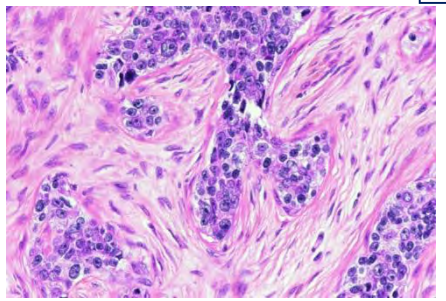
Poor differentiation



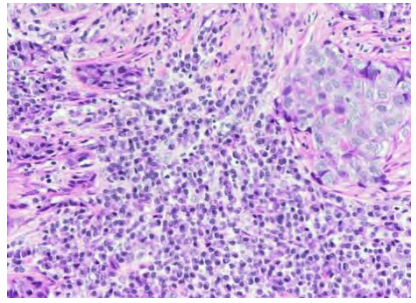
Atypia, proliferation



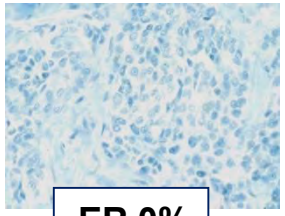
Large areas of necrosis



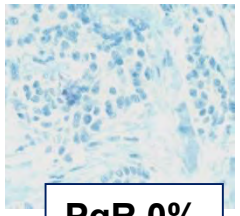
Myofibroblastic stroma



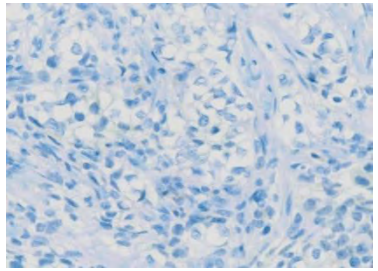
Lymphocytic stroma



ER 0%



PgR 0%



HER2 negative

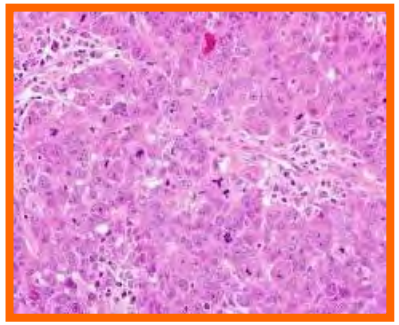
TN Tumors Are Heterogeneous

- IDC NOS, high grade
- ILC high grade, pleomorphic
- Metaplastic, high grade
- Myoepithelial carcinoma
- High-grade (oat-cell) neuroendocrine
- Apocrine
- Adenoid-cystic
- Juvenile Secretory
- Carcinoma with rich lymphoid stroma
- Metaplastic, low grade
  - Low-grade adenosquamous
  - Fibromatosis-like

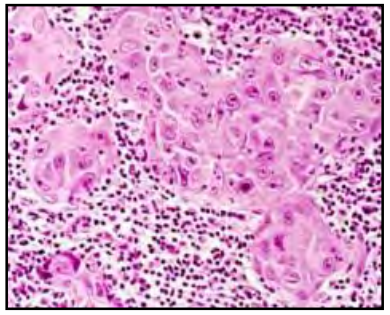
Poor prognosis

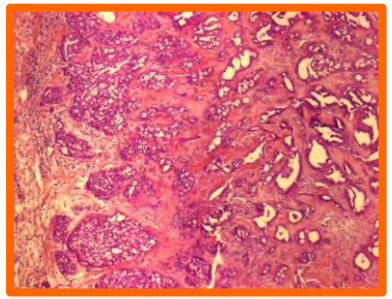
Good prognosis

Identify special types with better prognosis

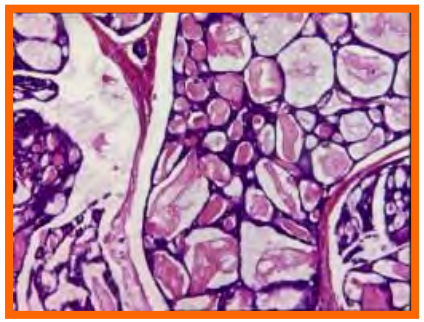


Amplicons chr 10, 12
10p+, 9p+, 16q+, 4p-



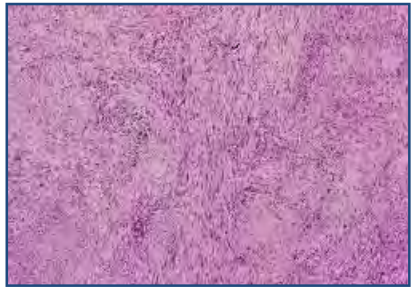


t(12;15) (ETV6; NTRK3)

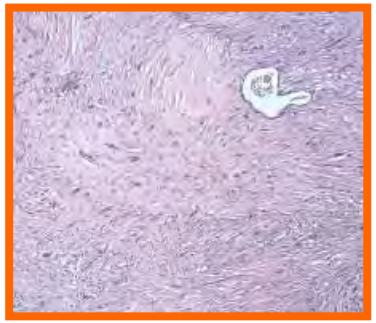


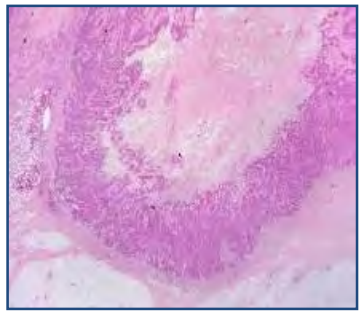
t(6;9) (q22-23; p23-24) (*MYB* ;*NFIB*)

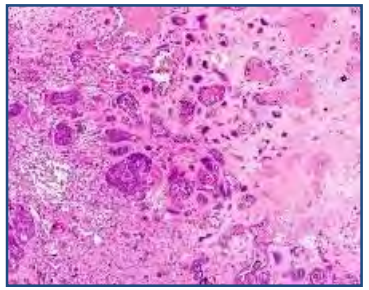
Basal like carcinoma

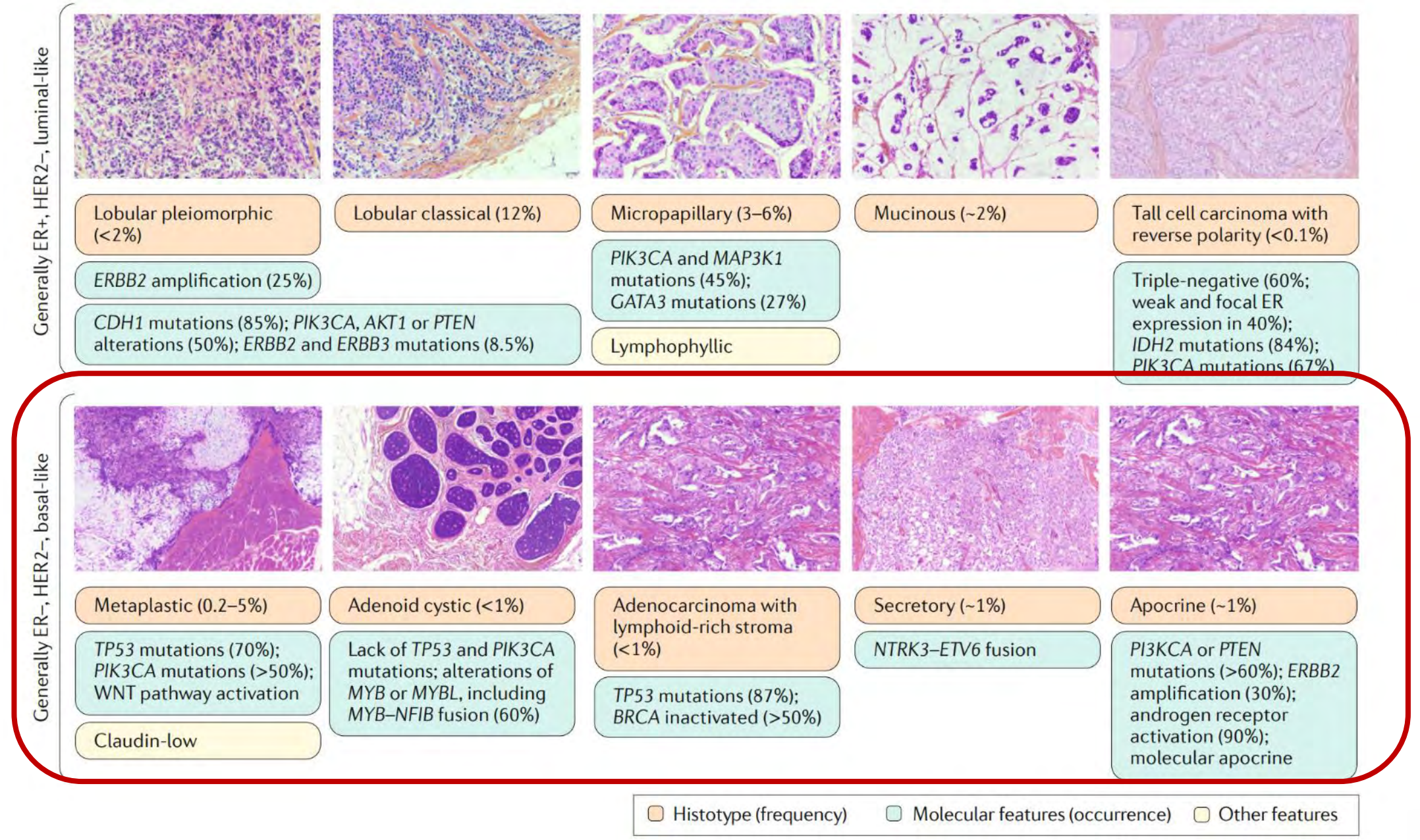


EGFR amplification
WNT pathway alterations





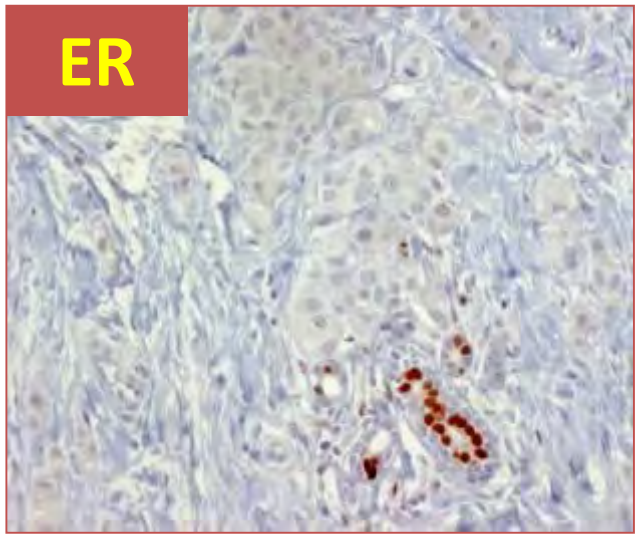


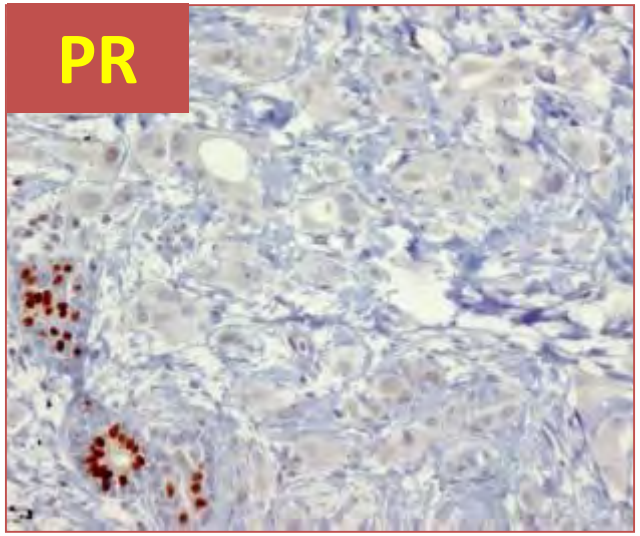


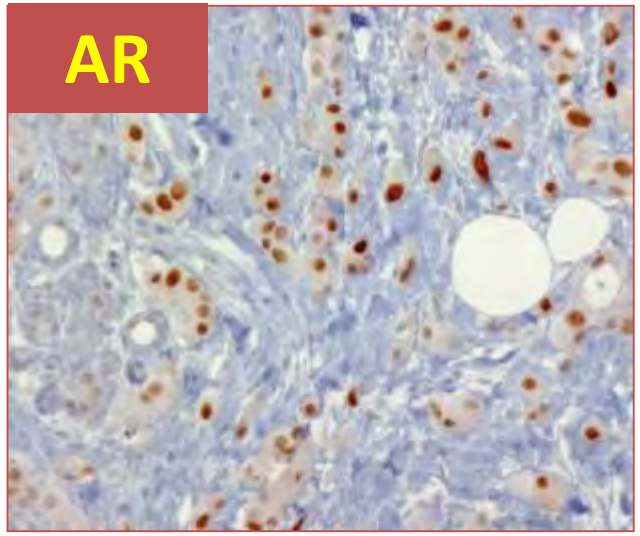
Harbeck N, Penault-Llorca et al Nature Review disease Primer (2019) 5:66

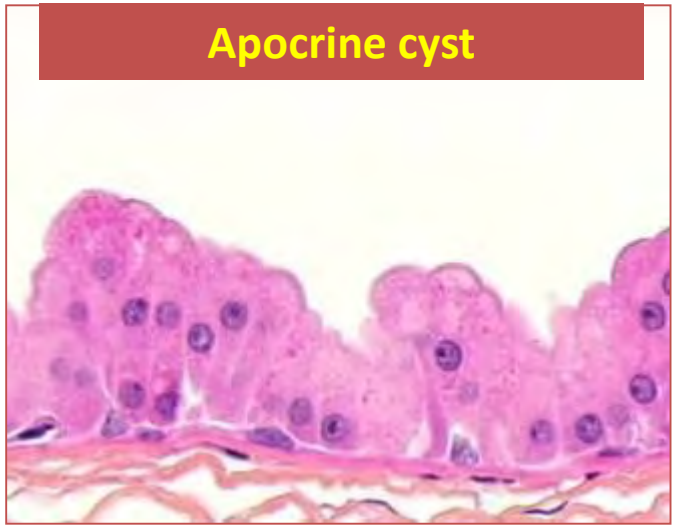
Uncertain prognosis: Apocrine carcinoma

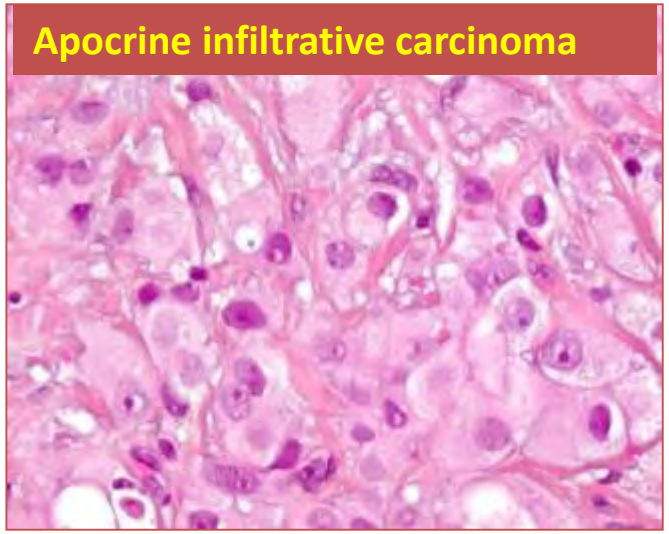
in ½ cases: HER2+











Bicalutamide-abiraterone acetate

HER2 POSITIVE

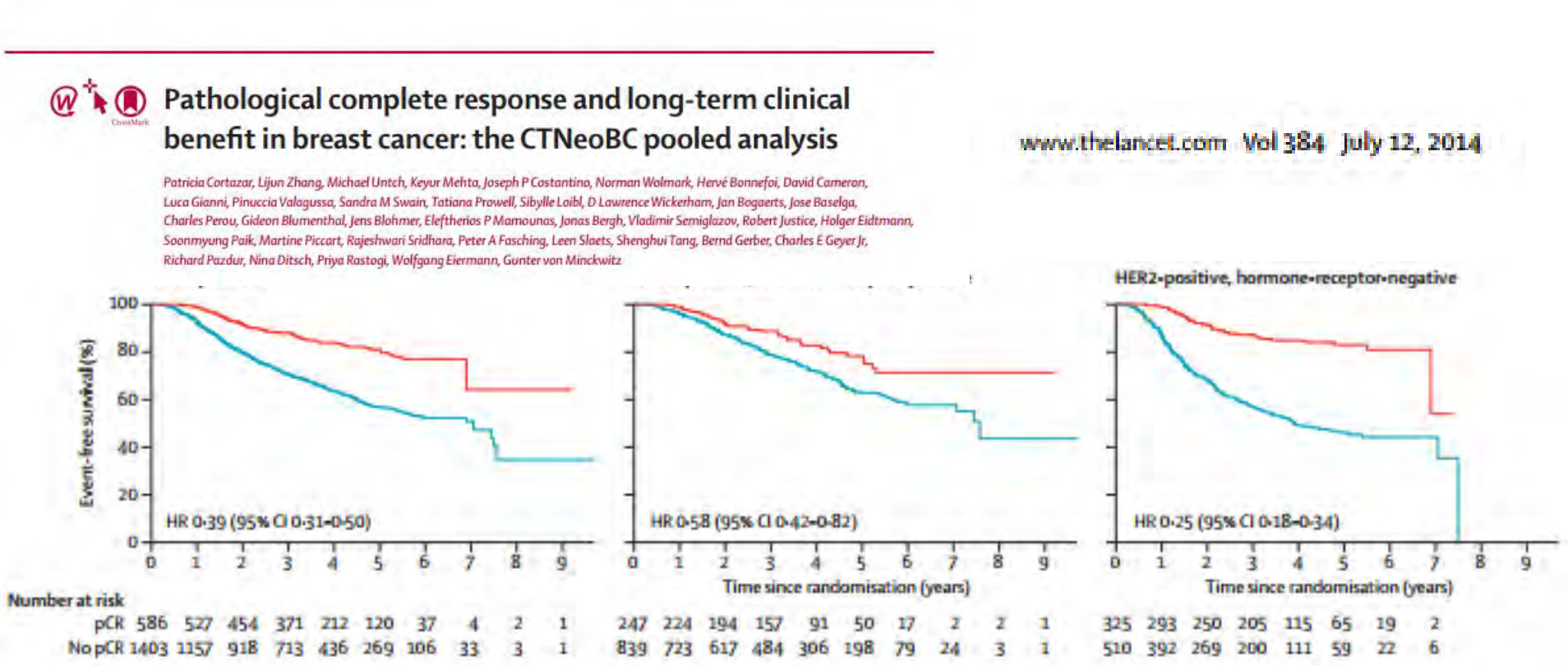
Surrogate definition of intrinsic subtypes of breast cancer

«HER2 enriched»

- HER2 positive ➔ 3+ by IHC or amplified by FISH
- And ER and PgR negative

HER2+ diseases

- Rare +++ lobular, tubular carcinoma
- ~ 50% are ER+ ➔ completely different disease



HER2+, prognostic value of pCR in HR-

Hindawi Publishing Corporation
Journal of Oncology
Volume 2013, Article ID 854121, 9 pages
http://dx.doi.org/10.1155/2013/854121

2 different HER2+ groups /HR status

Review Article

Predictive Factors of Response in HER2-Positive Breast Cancer Treated by Neoadjuvant Therapy

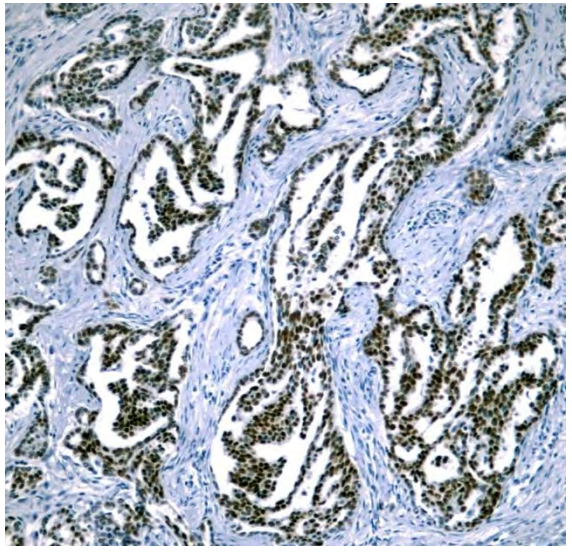
Less pCR in HER2+, ER +

Table 3: Rates of pCR according to HR status.

Study (ref.)	Neoadjuvant regimen	pCR rate HR+	pCR rate HR−
NeoSphere [18]	(i) Docetaxel + trastuzumab—(arm A)	20%	36.8%
	(ii) Docetaxel + trastuzumab + pertuzumab (arm B)	26%	63.2%
	(iii) Trastuzumab + pertuzumab (arm C)	5.9%	27.3%
	(iv) Docetaxel + pertuzumab (arm D)	17.4%	30%
Neo-ALTTO [12]	(i) Weekly P + trastuzumab	22.7%	36.5%
	(ii) Weekly P + lapatinib	16.1%	33.7%
	(iii) Weekly P + trastuzumab + lapatinib	41.6%	61.3%
CHER-LOB [14, 19]	(i) CT + trastuzumab	25%	26.6%
	(ii) CT + lapatinib	22.7%	35.7%
	(iii) CT + trastuzumab + lapatinib	35.7%	56.2%
Buzdar et al. [4]	(i) CT + trastuzumab	61.5%	70%
	(ii) CT alone	27.2%	25%
NOAH [20]*	(i) CT + trastuzumab	18%	48%
	(ii) CT alone	17%	22%
REMAGUS 02 [9]	(i) CT + trastuzumab	20.5%	32%
	(ii) CT alone	20.5%	19%
NSABP B-41 [15]	(i) CT + trastuzumab	46.7%	65.5%
	(ii) CT + lapatinib	48%	60.6%
	(iii) CT + trastuzumab + lapatinib	55.6%	73%

LUMINAL BREAST CANCER

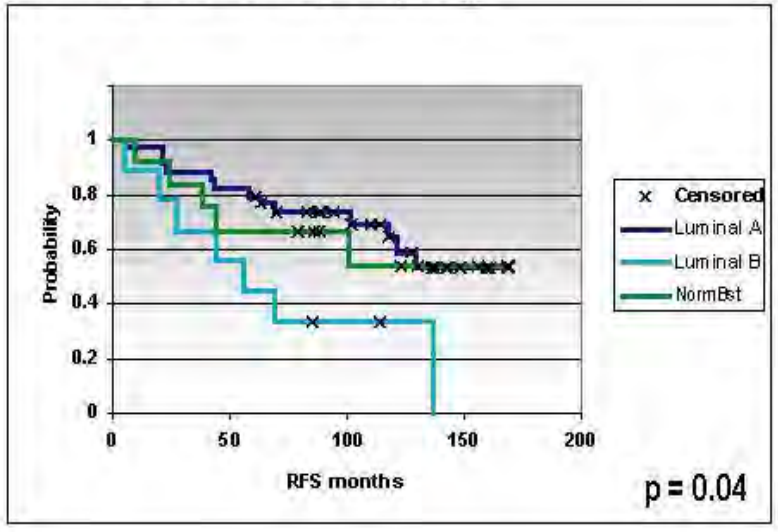
Luminal breast cancer



Luminal A

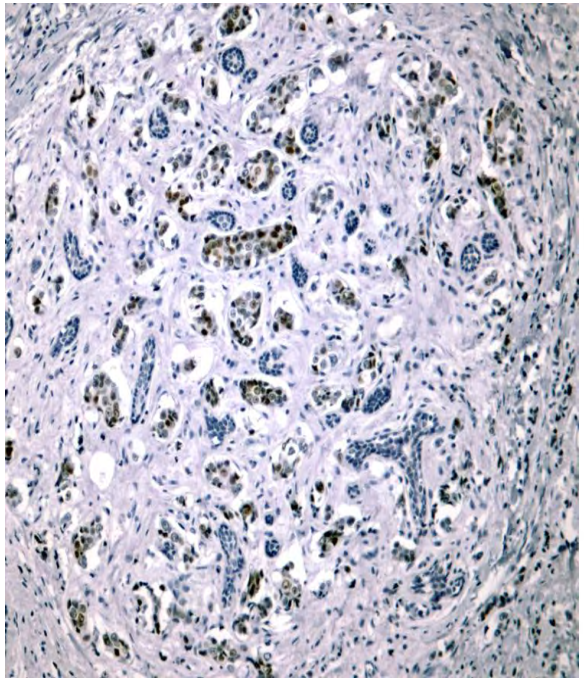
- ER+
- And all
  - PR +
  - Ki67 low
  - HER2 -
  - Low molec risk

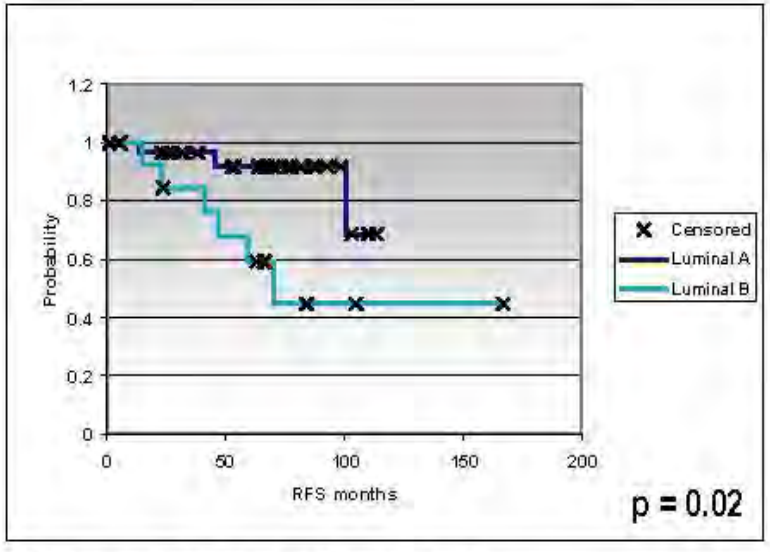
60 Sample ER+ Tamoxifen-Treated Test Set
Ma et al., Cancer Cell 5, 1-10 (2004).



Luminal B

- ER+
- And at least
  - PR low
  - Ki67 high
  - High molec risk





45 Tamoxifen Treated Test Set #2
Chang et al., PNAS 102, 3738-43 (2005) + UNC

Luminal B HER2 +

- ER+, HER2 3+
- Whatever PR
- Whatever Ki67

Luminal BC

LUMINAL A

- Grade 1
- ER^+
- PR^+ (> 20%)
- Ki67 low (< 20%)
- NOS, tubular, cribriform, mucinous mol low risk, simplex genomic profile
- Low activation PI3K/AKT
- Hormonosensitivity

Intermediate category

LUMINAL B

- Grade 3
- ER^+
- $PR^{+/-}$ (≤ 20%)
- Ki67 high (≥ 20%)
- $HER2^{+/-}$
- NOS, micropapillary
- Mol high risk, complex genomic profile
- Activation growth factor R
- Hormonosensitivity, chemosensitivity

→ Heterogeneous tumours defined by the expression of ER

→ **Current detection method is IHC** (issues on threshold, standardization)

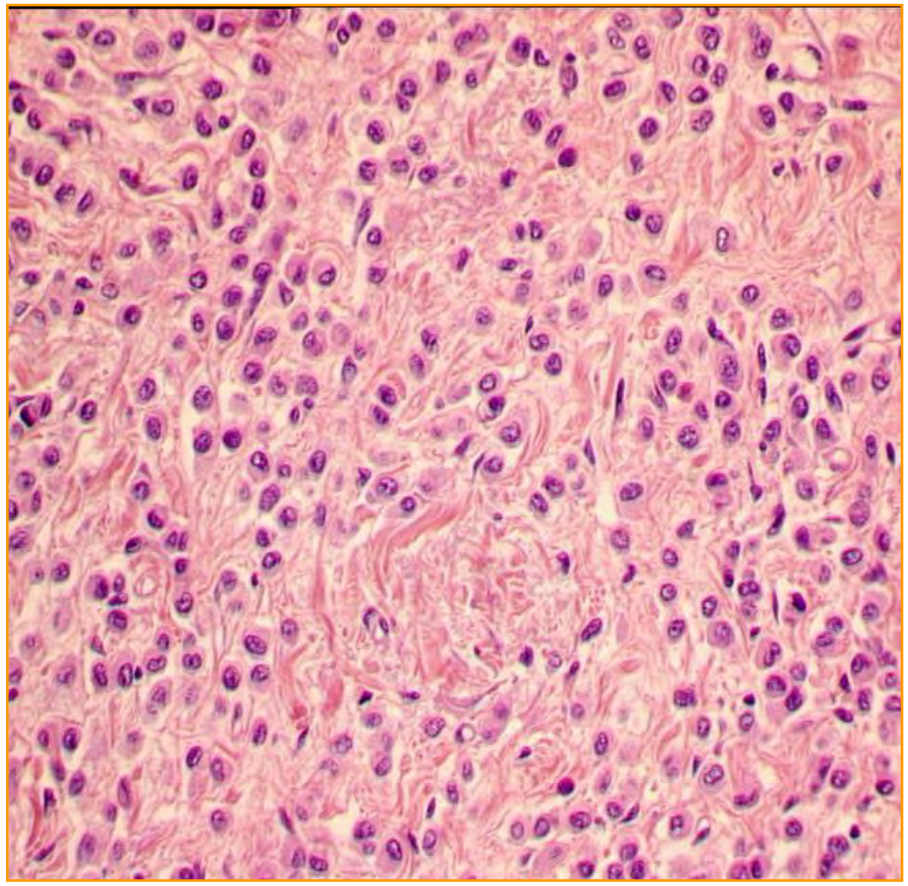
→ ER^+ tumours and $HER2^+$ classified as luminal B

→ Major role of proliferation

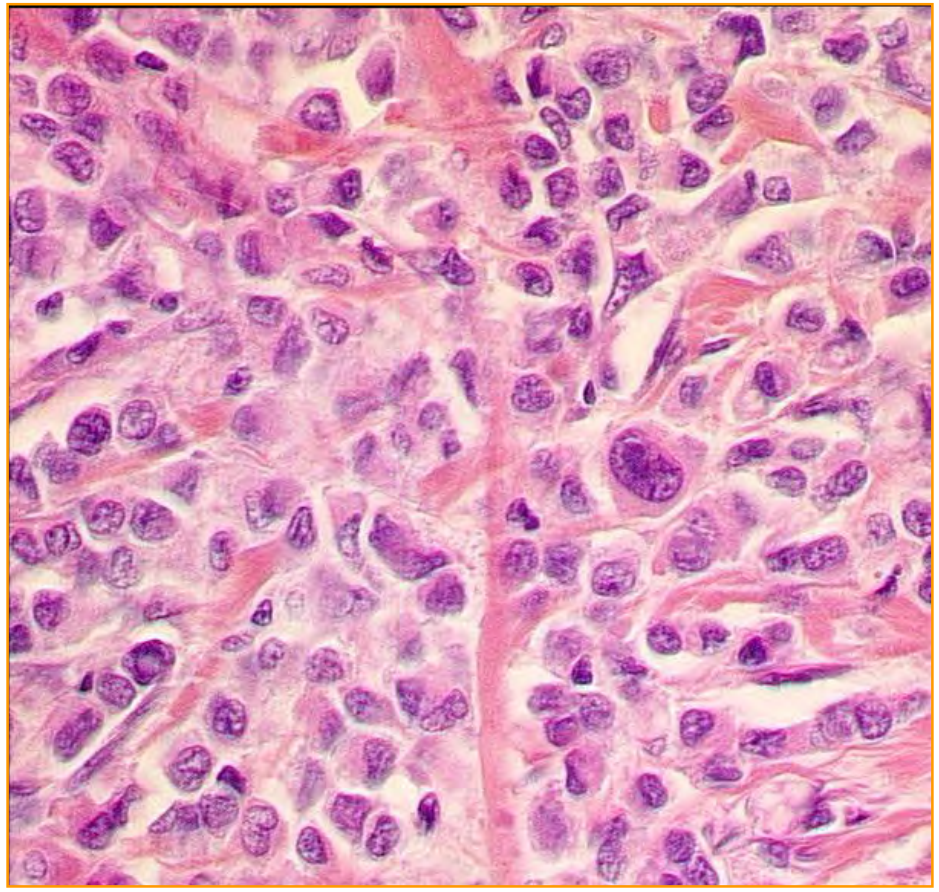
→ **Potential over/undertreatment / late recurrences**

LOBULAR CARCINOMA

Classical



Pleomorphic



12-14% of BC, poor limitation

Frequent metastasis to serous tissues (pleura, peritoneum, pericardia

Lobular carcinoma

- E-cadherin Inactivation in 95% of cases
- ER+ > 90% of cases
- Low proliferation

→ Low chemosensitivity

- HER2 score 3+ < 5% of cases
- *HER2* Mutations :
  - 6% classical ILC
  - 15% ILC high grade

→ Targeted anti-HER2 therapies

- ***PIK3CA* Mutations in 48% of the cases**
- Mutations *TP53*, *GATA3*, *FOXA1*, *RUNX1* ~ 5 -10% of the cases
  PTEN/AKT pathway activation mutually exclusive with mutuellement *PIK3CA* mutations.
- 3 or 2 transcriptomic groups have been identified
  - « reactive-like » (good prognostic), « Immune-related » &« proliferative »

  or « immune-related » & « hormone – related »

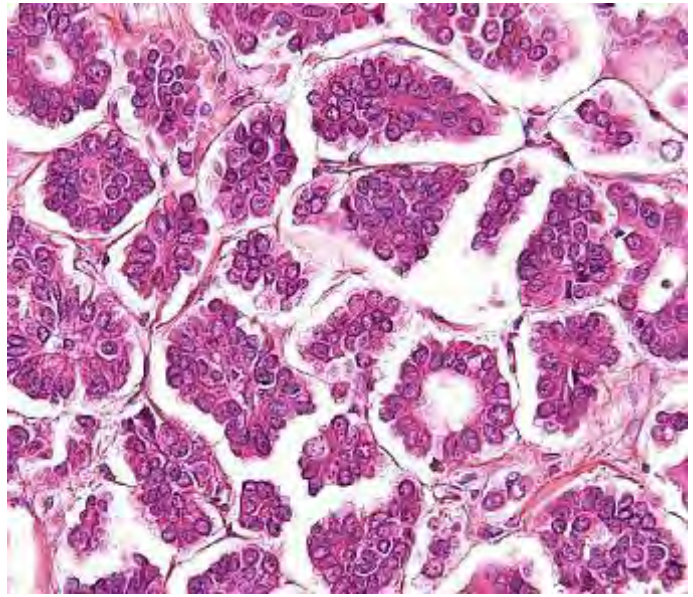
mTOR inhibitor
PIK3CA i

Michaut et al Scientific report 2016
Ciriello *et al* Cell 2015
Deniziaut *et al* Oncotarget 2016

TCGA. Nature 2012.
Huang-Chun *et al*. Breast Cancer Res Treat 2015

Micropapillary carcinoma a very aggressive luminal tumor

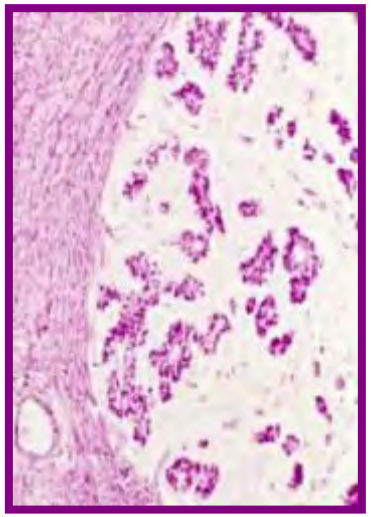
- Embolies -70-80%) and frequent node invasion (pure 60%, mixed 40%)
- SBR II or III Recurrent abnormalities in 8p11-22, involving FGFR1, NGR1 / neuregulin
- HR + 70-90%
- HER2 + 35-50%
- C-MYC amplification



Specific/frequent molecular alterations

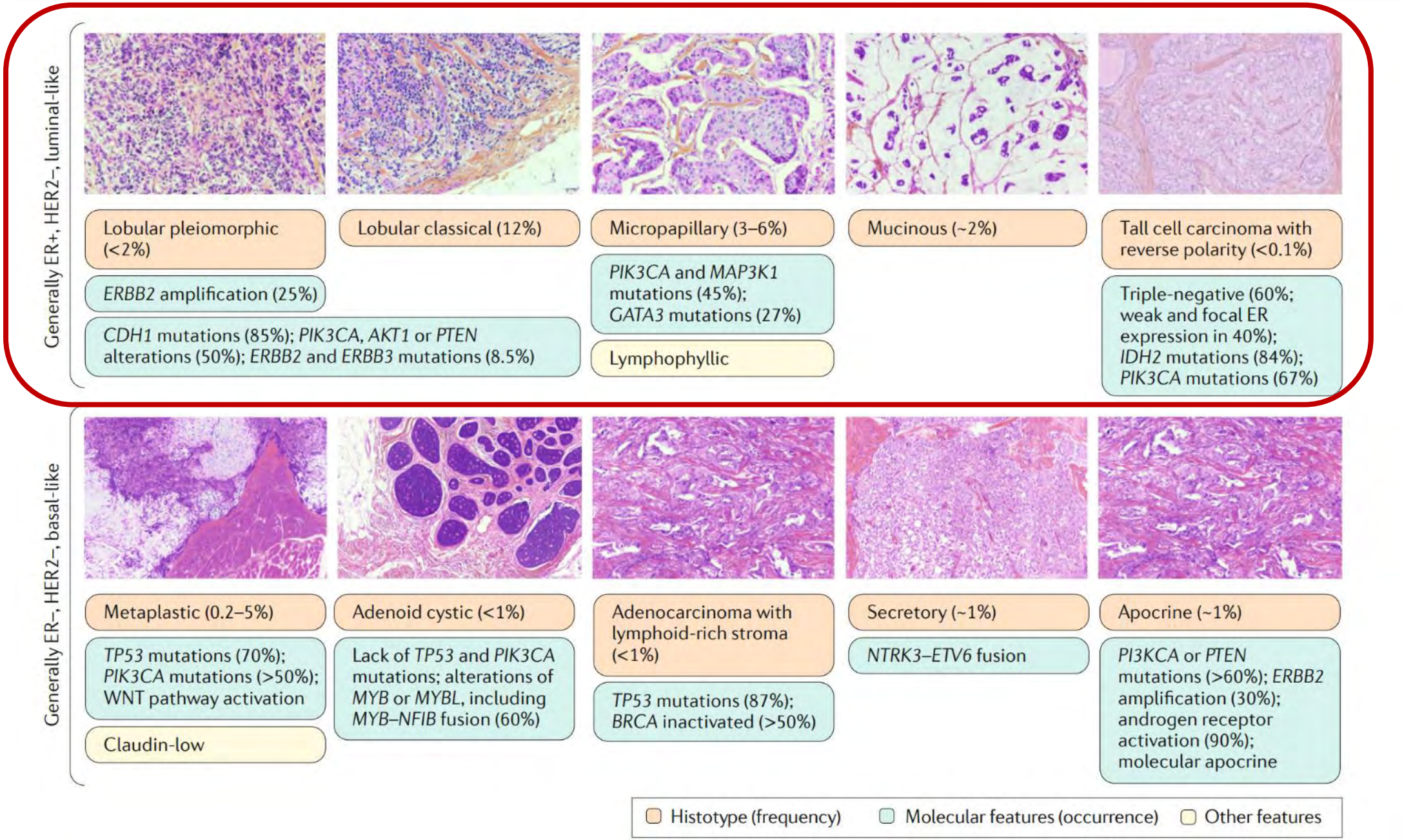
- **Mucinous carcinomas** (2%)

➔Characterized by **increased frequency of GATA3** (23%) mutations, and **decreased frequency of PIK3CA** (8%) and TP53 (8%) alterations compared to IDC.



- **One third of all BC primary tumors do not present any reported driver mutation**.

LUMINAL KEY MESSAGES

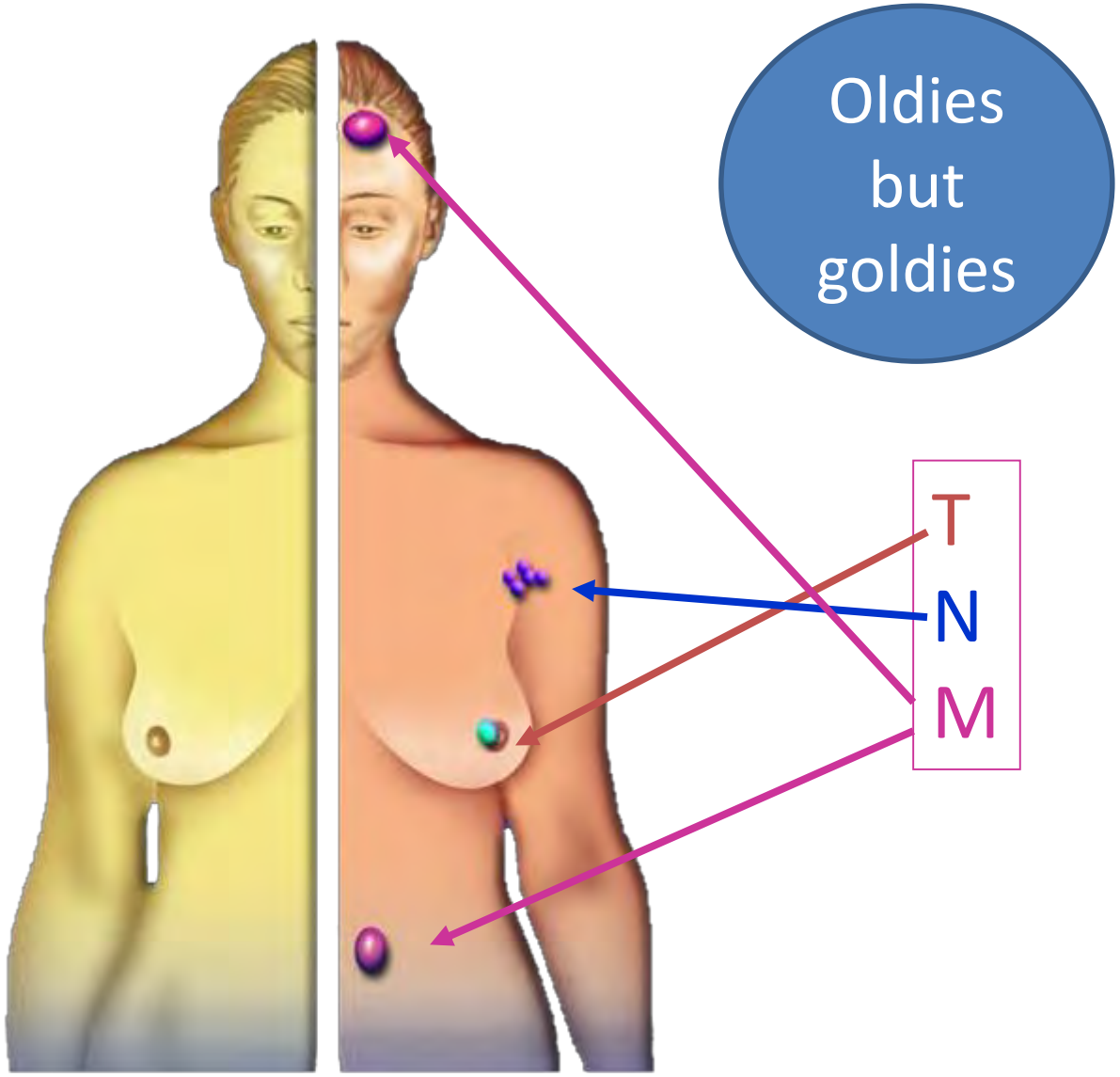


Harbeck N, Penault-Llorca et al Nature Review disease Primer (2019) 5:66

CLASSICAL PARAMETERS ARE IMPORTANT, BUT…….

Classical prognosis and predictive factors

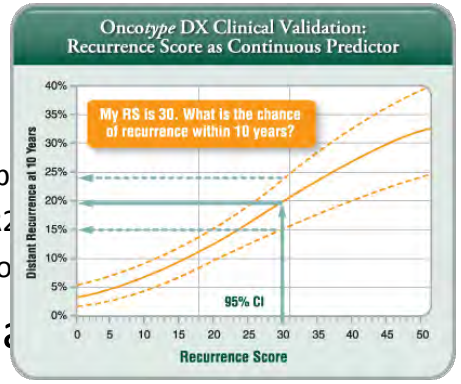
- Age
- Grade
- Histological subtypes
- ER/PR and HER2 status
- Ki67 +/- mitotic index
- Vascular invasion
- **Tumor margins**

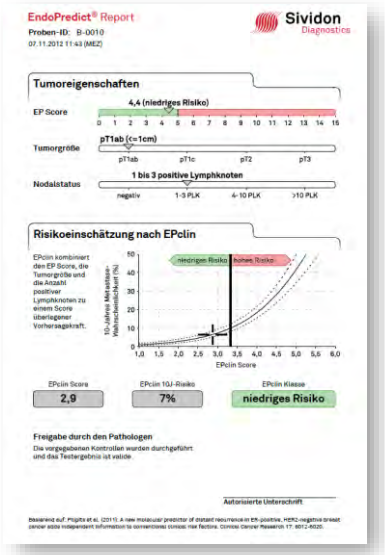


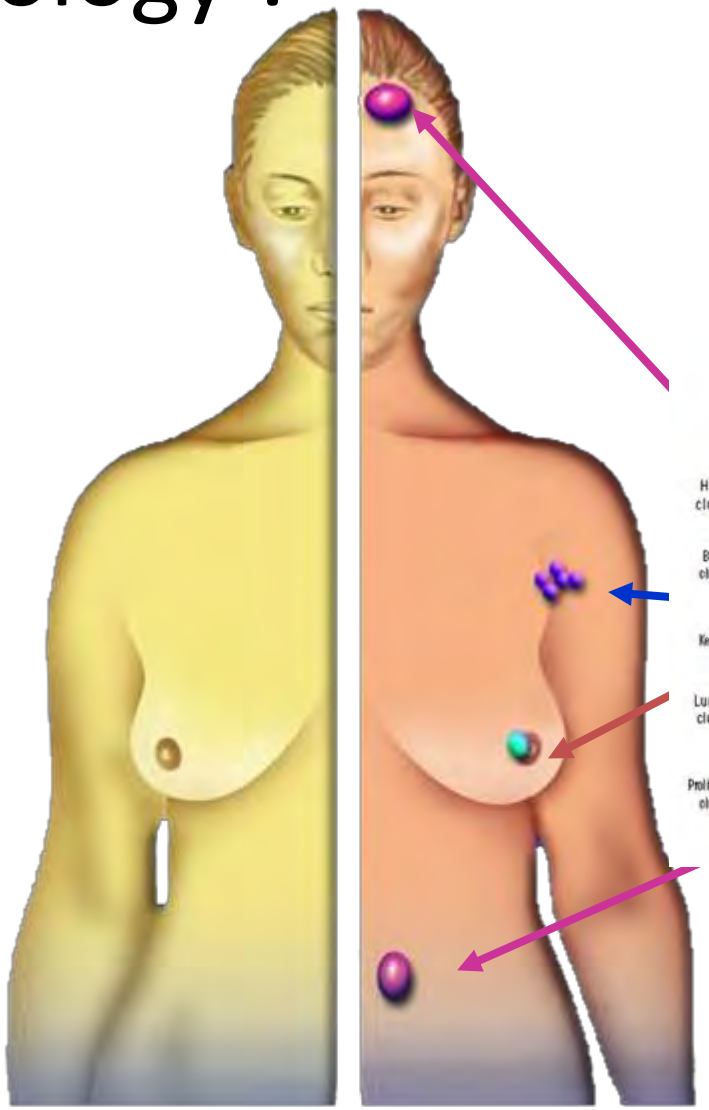
TREATMENT DESCALATION IN HR+ HER2-
➔MOLECULAR SIGNATURES

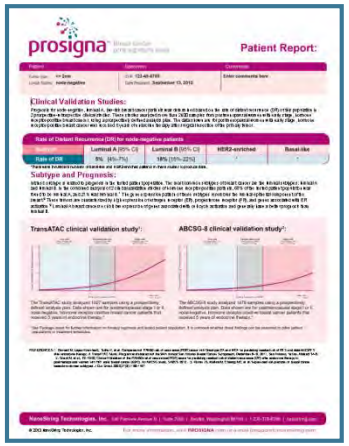
Yes , we have molecular biology !

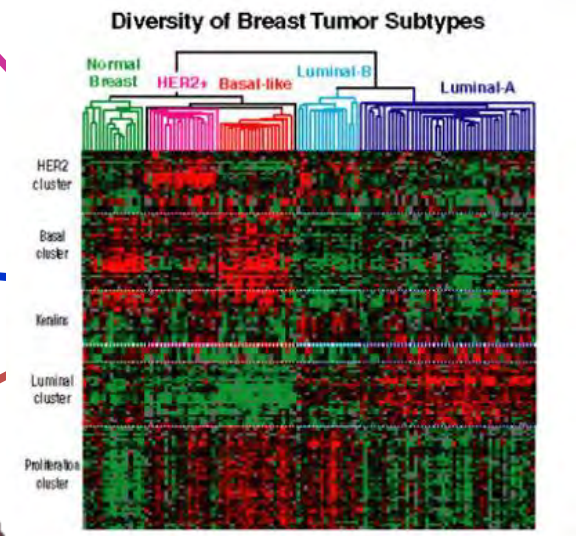
- Age
- Grade
- Histological sub
- ER/PR and HER2
- Vascular invasio
- Tumor ma











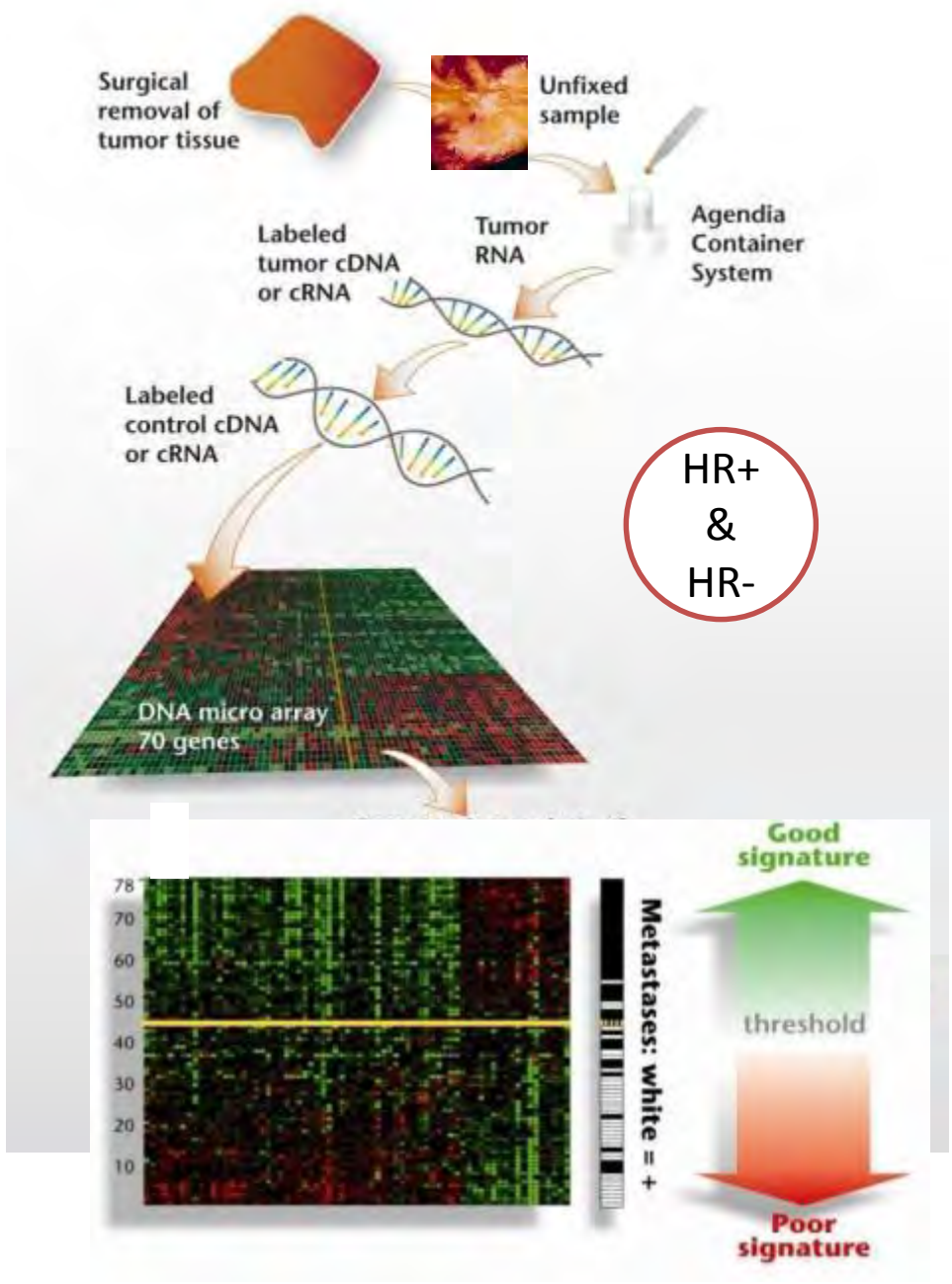
4 signatures, 4 different worlds

	Oncotype DX	MammaPrint	Prosigna	EndoPredict
Gene number	16 + 5 reference	70	50 + 8 reference	8 + 3 reference
Patient Type	Pre or postmenopausal HR+, HER2 Node -/+ (1-3) early stage	Pre or postmenopausal ER+/- Node -/+ early stage tumor <5cm	Postmenopausal HR+, HER2- Node -/+ (1-3) Stage I to IIIA BC	Postmenopausal HR+, HER2- Node -/+
Individual Risk	Yes	No	Yes	Yes
Classification	Continuous score 0-100; reports individualised	Low, High	Continuous score reported as Low, Inter, High	Low, High
Prognostic	Yes level 1A	Yes level 1A	Yes level 1B	Yes level 1B
Predictive of chemotherapy benefit	Yes level 1A	No clinical evidence	No clinical evidence	No clinical evidence
Technology	Quantitative RT-PCR	Microarray	direct mRNA hybridization	Quantitative RT-PCR

Paik et al. N Engl J Med. 2004, 51:2817-26; Paik J Clin Oncol 2006, 24:3726-3734; Filipits et al. Clin Cancer Res. 2011; 4. Bueno-de-Mesquita et al. Lancet Oncol. 2007;
5. Mook et al. Breast Cancer Res Treat. 2009; 6. Sapino et al. J Mol Diagn. 2013; 7. Dowsett et al. J Clin Oncol. 2013; 8. Gnant et al. Ann Oncol. 2013

Centralized tests

MammaPrint (Agendia, NL)



HR+ ET HR - / HER2- , T < 5cm, N ≤ 3

Fresh frozen=> FFPE

DNA array

70 GENES

CELL CYCLE/ PROLIFERATION
SIGNAL TRANSDUCTION
INVASION, METASTASIS, ANGIOGENESIS

« CENTRALIZED » TEST

RECENTLY ADAPTATED TO FFPE

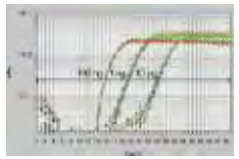
Group of genes (« signatures »)

EARLY RECURRENCE (Dg < 5 ans)

PROGNOSTIC

GOOD SIGNATURE :
LOW RISK

POOR SIGNATURE :
HIGH RISK



OncotypeDX (Genomic Health, USA)

HR+ / HER2- , T1-3, N-/N+
FFPE specimens
qRT-PCR

21 GENES

PROLIFERATION, OESTROGENE, HER2, INVASION (16 GENES) + REFS (5 GENES)

« CENTRALIZED » TEST

(recurrence score) RS

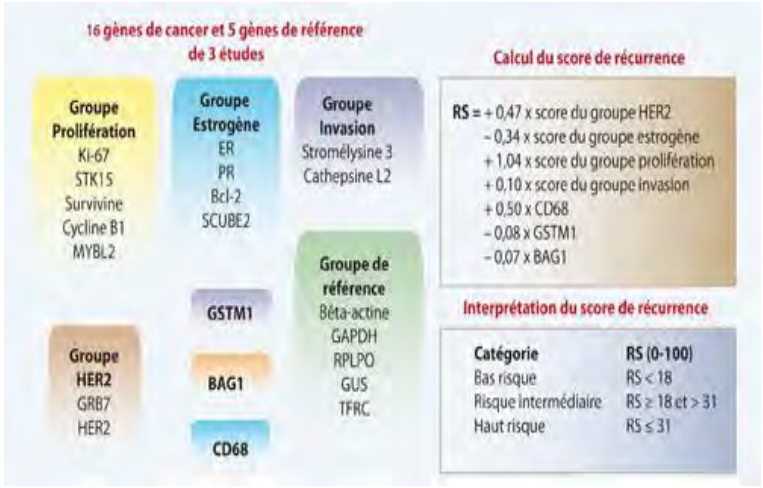
Late recurrence (10 years)
Benefit from adjuvant TT
PROGNOSTIC AND PREDICTIVE

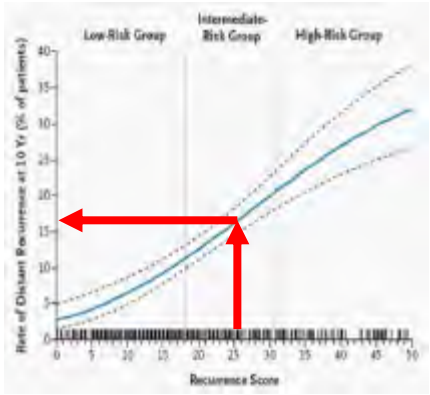
LOW RISK 1-25:

HORMONOTHERAPY

HIGH RISK >26:

+ HORMONOTHERAPY / + CHEMOTHERAPY

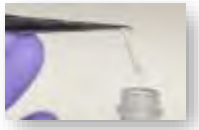


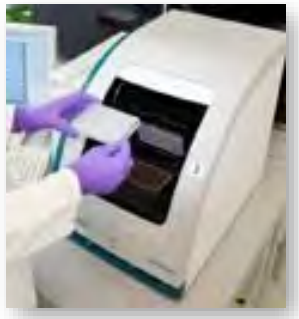


First generation signatures	Prognostic	Predictive	Technical validation
MammaPrint® All BC, N0-N1-3 70 genes signature 2 categories (low & high risk)	+++	++	YES Gene expression profile Central Lab
Oncotype Dx® ER+, HER2- BC, N0-N1-3 21 genes signature Recurrence score RS 3 categories	+++	+++	YES RT-PCR Central Lab
Clinical validation			
MammaPrint®: LOEIA Prospective validation for prognostic value of low genetic in clinically high risk: 5yrs DMFS >94% (48%N+) 14% reduction in CT prescription up to 46% in high clinical risk			
Oncotype Dx®: LOEIA prospective validation for RS LO1B validated retrospectively in prospective clinical trials (prediction chemotherapy benefit), prospective clinical validation ongoing for prediction			

<26 prognosis

Decentralized tests





EndoPredict (Sividon, GE)

HR+ / HER2- , T1-2, N0

FFPE

qRT-PCR

8 GENES SIGNATURE

PROLIFERATION, OESTROGENES

UBE2C
BIRC5
DHCR7

STC2
AZGP1
IL65T
RBBP8
MGP

« LOCAL » TEST

(SPECIAL EQUIPMENT IS REQUIRED)

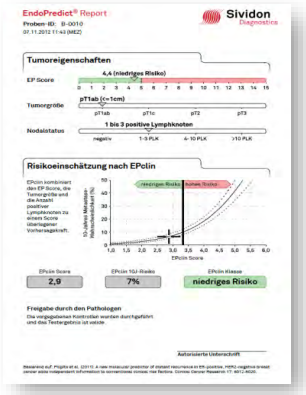
SCORE OF RECURRENCE EP SCORE

LATE AND EARLY RECURRENCES (5 & 10 YEARS)

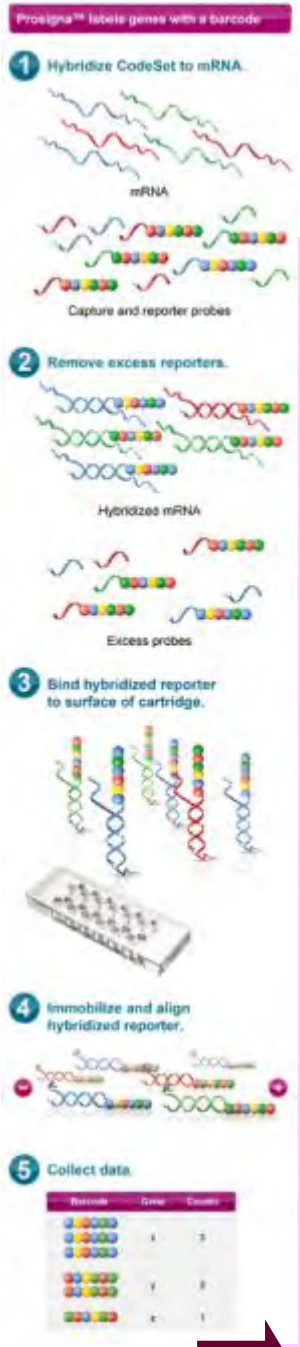
PROGNOSIS

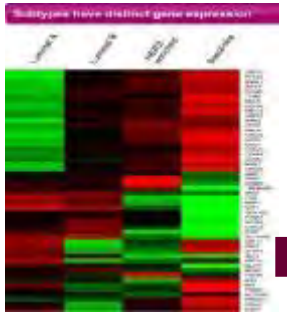
LOW RISK

HIGH RISK



Prosigna (PAM50)
(NanoString Technology, USA)





IDENTIFICATION OF « MOLECULAR3 SUBTYPES »
(LumA, LumB, HER2-enrichi, Basal)

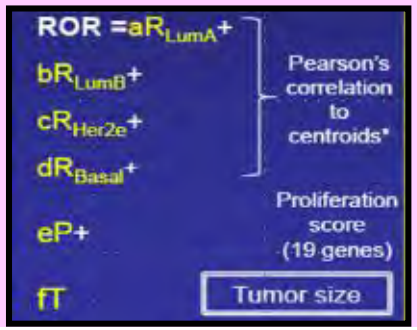
Two risk scales
N0
N 1-3
Tumor size
<= 2cm
>2 cm

FFPE
DNA ARRAY WITH BARCODES
(1 gene = 1 barcode)

50 GENES

« LOCAL » TEST
(SPECIAL EQUIPMENT IS REQUIRED)

LATE AND EARLY RECURRENCES
(5 & 10 YEARS)
PROGNOSIS



LOW RISK (ROR)

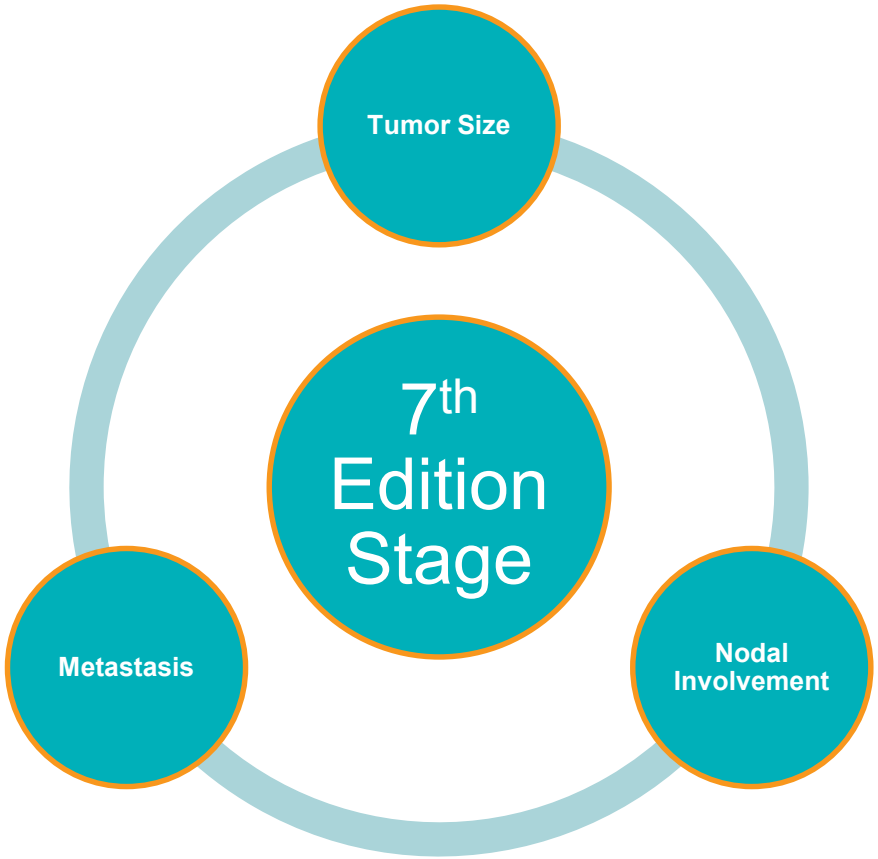
Intermediate risk

HIGH RISK (ROR)

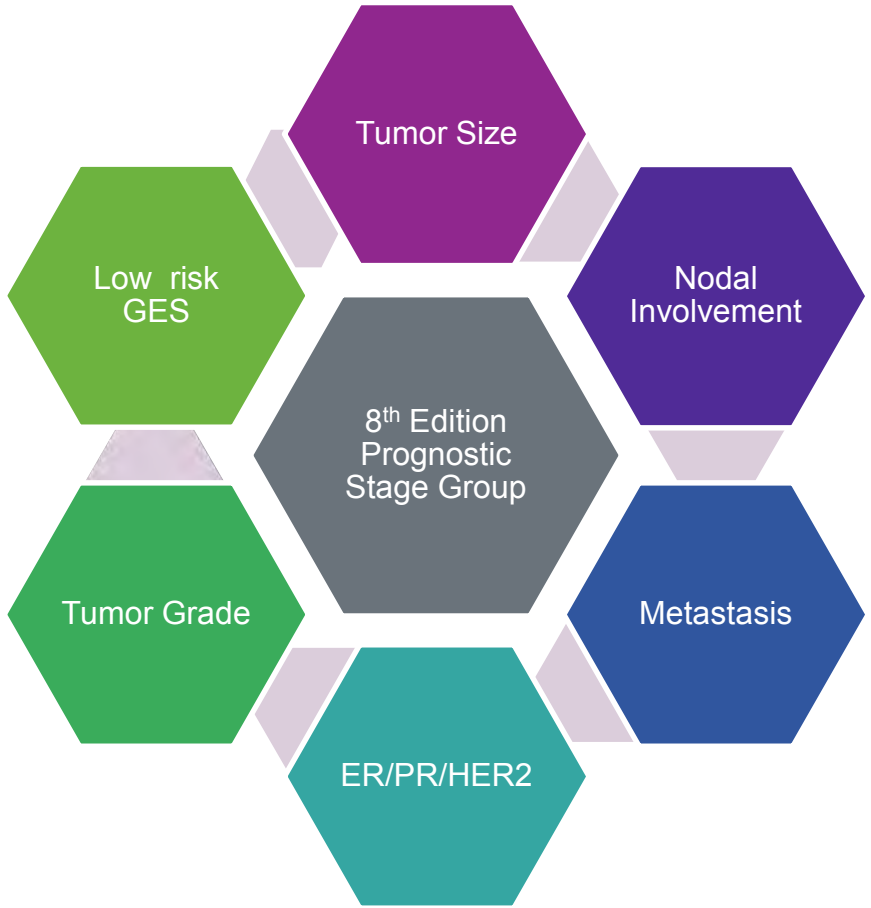
Second generation signatures	Prognostic	Predictive	Technical validation
Prosigna® ER+, HER2- BC, N0-N1-3 **50 genes signature** Includes size and N	++	++	YES N-Counter® technology Dedicated instrument
Endopredict® ER+, HER2- BC, N0-N1-3 **8 genes signature** Includes size and N	++	++	YES RT-PCR Dedicated instrument
Clinical validation			
Prosigna®: LOE1BValidated retrospectively in prospective clinical trials of HT Prognosis Late recurrences (after 5 years)			
Endopredict®: LOE1BValidated retrospectively in prospective clinical trials of HT Prognosis Late recurrences (after 5 years)			

NEW AJCC TNM AND SIGNATURES

8th Edition – *"Genomic panels…have become as or more important than the anatomic extent of disease to define prognosis"**



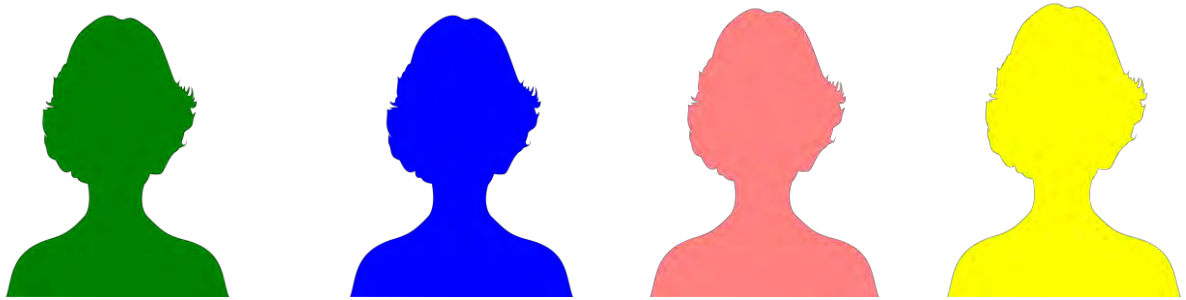
2010-



2018 and

*AJCC 8th Edition, pgs 617, 621, 624

Low risk molecular signature result in lower stage than would be recorded using biologic and anatomic factors alone



Stage IB	Stage IIA	Stage IIB	Stage IIIA
• T1, Gr 1, PR-, N0, M0, ER+, HER2- • T1, Gr 3, PR+, N0, M0, ER+, HER2- • T2, Gr 1-2, PR+, N0, M0, ER+, HER2-	• T1, Gr 3, PR-, N0, M0, ER+, HER2- • T2, Gr 1, PR-, N0, M0, ER+, HER2- • T2, Gr 3, PR+, N0, M0, ER+, HER2-	• T2, Gr 2, PR-, N0, M0, ER+, HER2-	• T2, Gr 3, PR-, N0, M0, ER+, HER2-

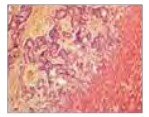
8th ed. Prognostic Stage using T,N,M, grade, ER, PR, HER2

If **low risk GES**, all of these patients are classified as Stage IA

EMERGING BIOMARKERS (FOR METASTATIC DISEASE)

Metastatic breast cancer

Tumor biopsy



ER IHC

20% of discordances
pos. vers neg. 24%
neg. vers pos. 14%

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33% of discordance
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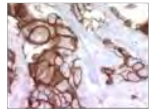
HER2 IHC



8% of discordances
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HER2 FISH

Tumor *BRCA* testing PARPi

Tumor *BRCA* testing PARPi

Luminal

HER2+

Triple negative

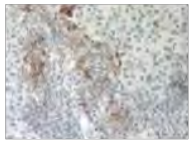
PIK3CA mutations

40% in luminal BC (stable between primary and mets)
PIK3CA inhibitors

ESR1 mutations

20-40% acquired in luminal BC with prior AI therapy
Resistance to IA

PDL-1



Immune cells >> tumor cells
TNBC>HER2+>luminal
IC≥1% for IO treatment

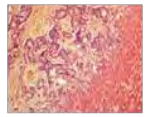
Liquid biopsy

Blood samples

Germinal *BRCA* testing PARPi

Metastatic breast cancer

Tumor biopsy



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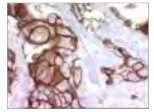

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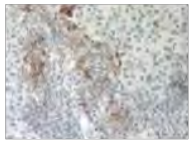

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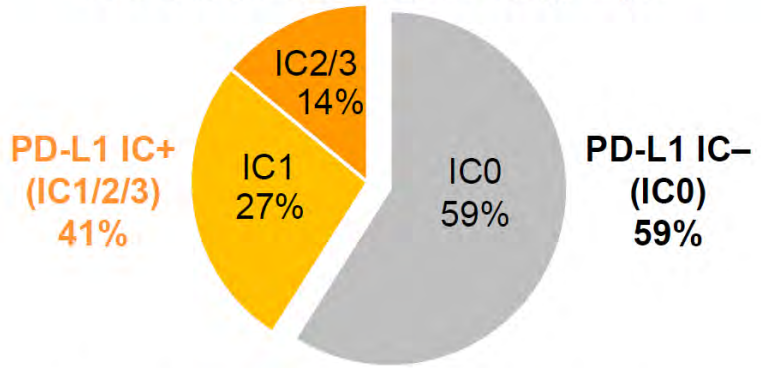
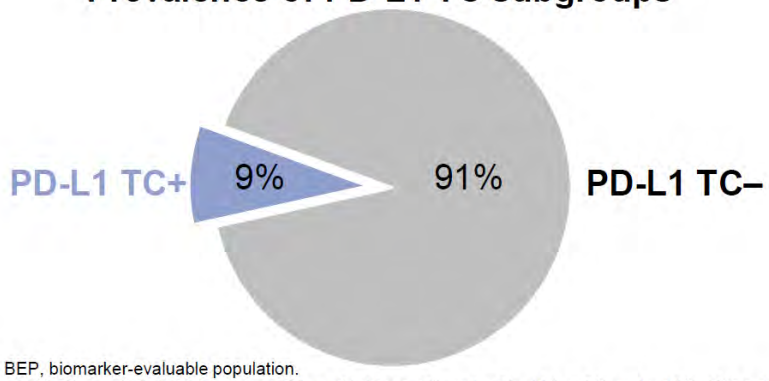
In IMpassion130, PD-L1 in TNBC is expressed mainly on tumor-infiltrating immune cells

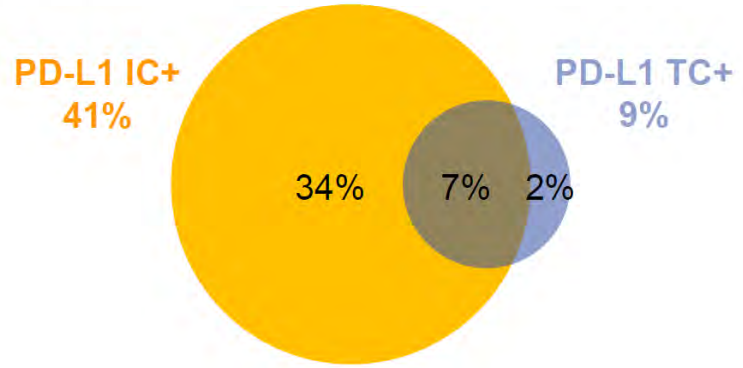
Prevalence of PD-L1 IC subgroups



Prevalence of PD-L1 TC subgroups



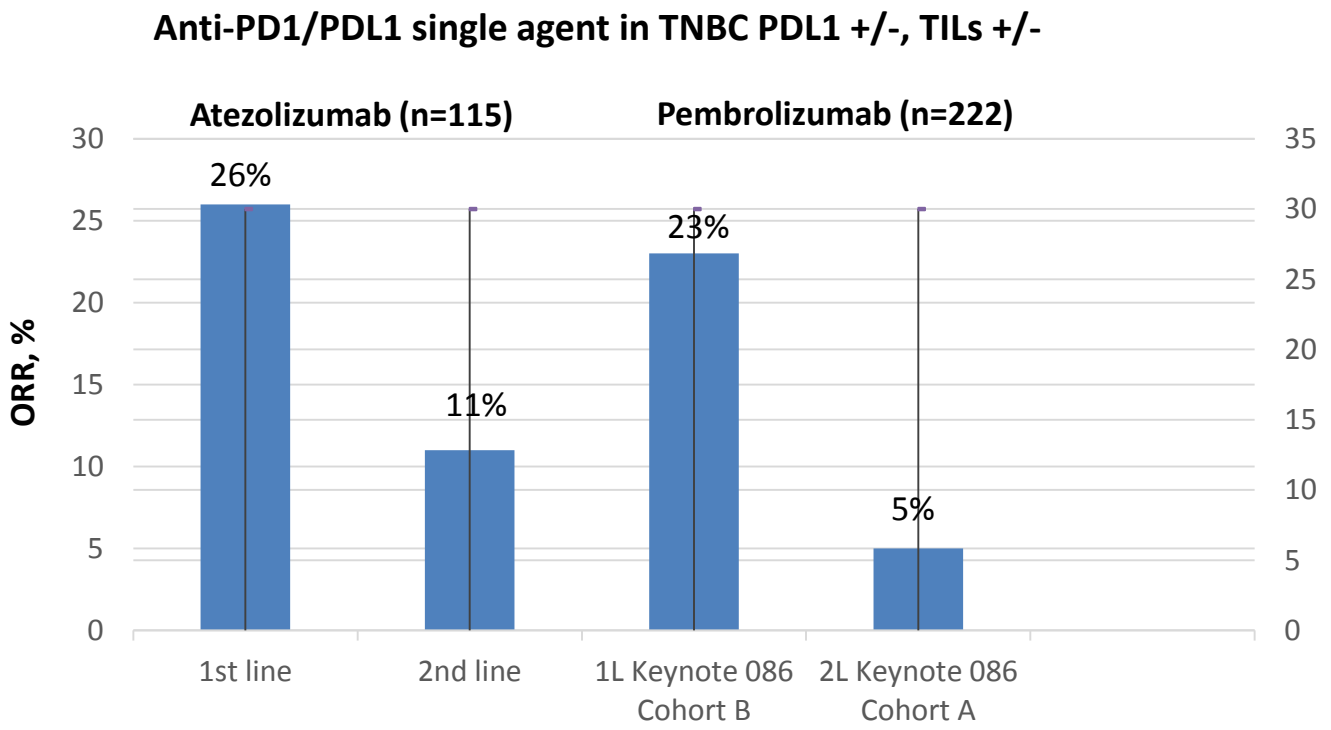
The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population



BEP, biomarker-evaluable population.
BEP (TC): n = 900. PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

Response to Immunotherapy Alone

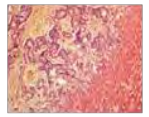


TNBC, Triple negative breast cancer

Schmid P, et al. AACR 2017, Abstract 2986. Adams S, et al. J Clin Oncol. 2017;35(Suppl 4):Abstract 1088. Adams S, et al. J Clin Oncol. 2017;35(Suppl 4):Abstract 1008. Loi S, et al. Ann Oncol. 2017;28(Suppl 5):Abstract LBA13.

Metastatic breast cancer

Tumor biopsy



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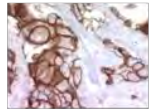

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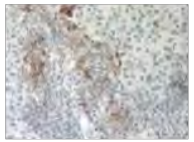

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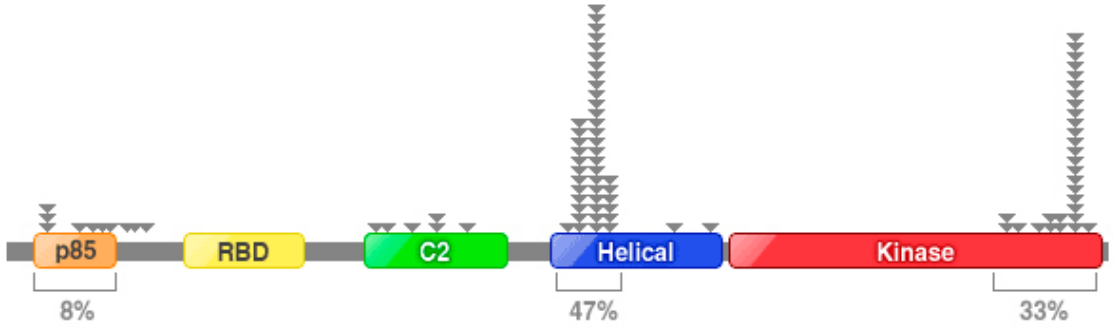
PIK3CA

- **Recurrent mutations**
  - **exon 9: E542K, E545K, Helicase domain**
  - **exon 20: H1047R, Kinase domain**
  - **Frequent: 30 to 40% of BC**
- **Prognostic role?**
- **Predictive role for specific PIK3CA inhibitors**



SCIENCE, 2004, 304:554

Metastatic breast cancer

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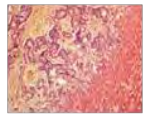

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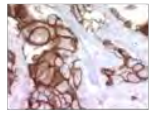

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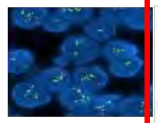

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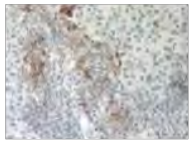

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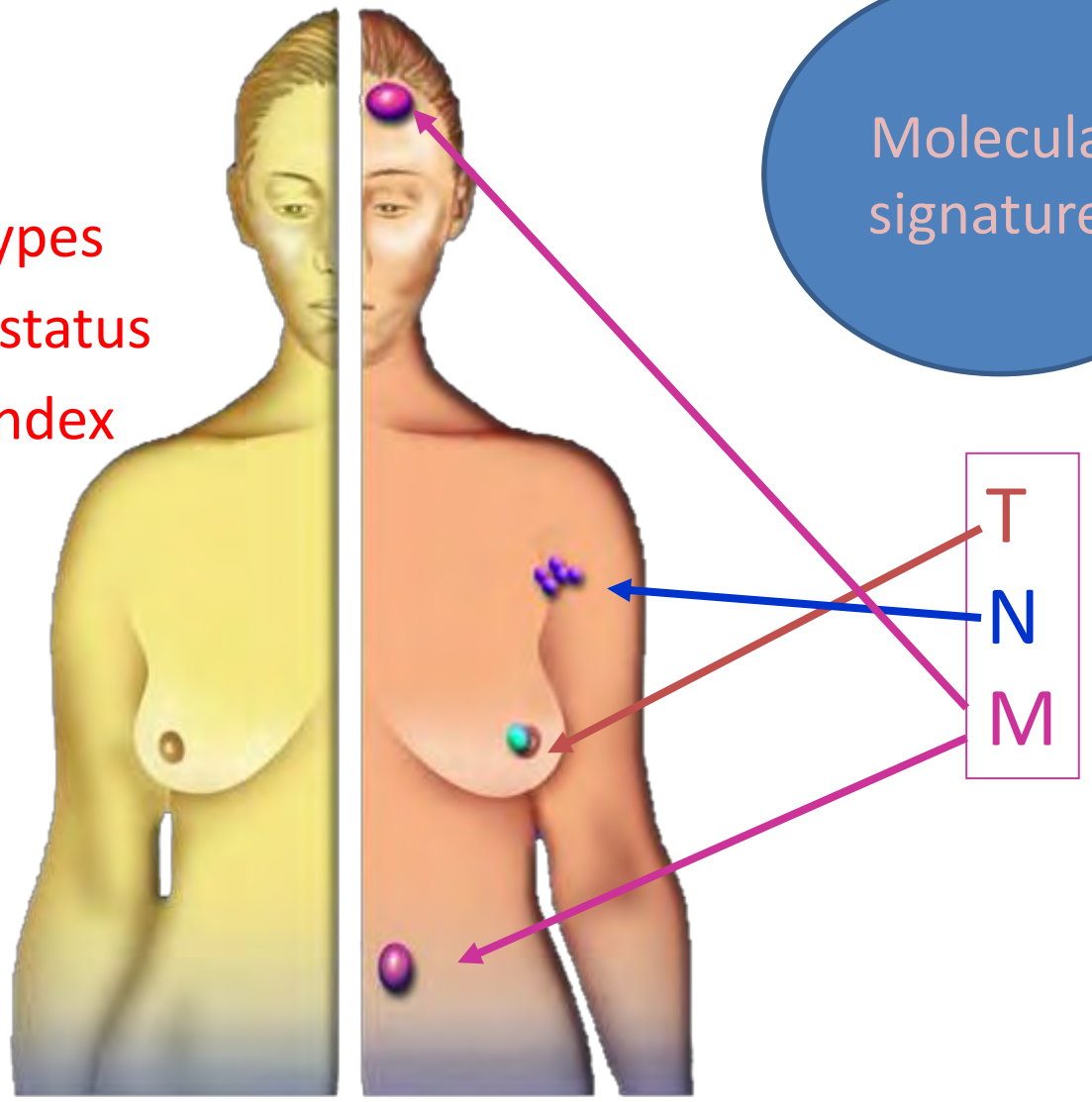
CONCLUSION

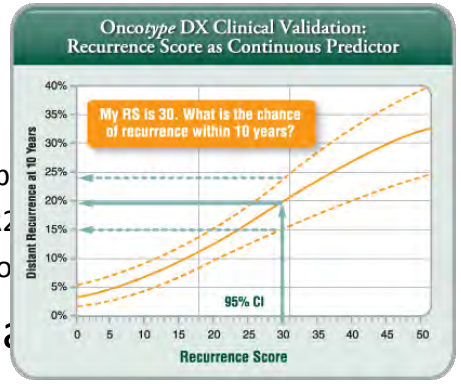
Classical prognosis and predictive factors

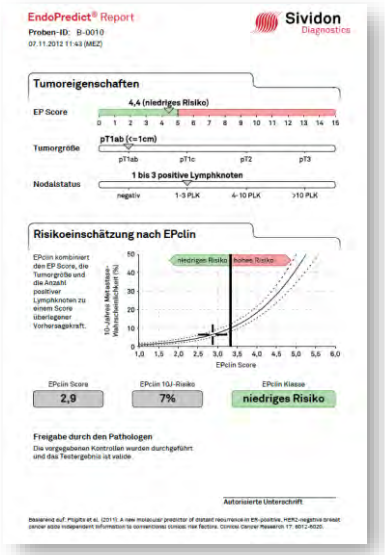
- Age
- Grade
- Histological subtypes
- ER/PR and HER2 status
- Ki67 +/- mitotic index
- Vascular invasion
- **Tumor margins**

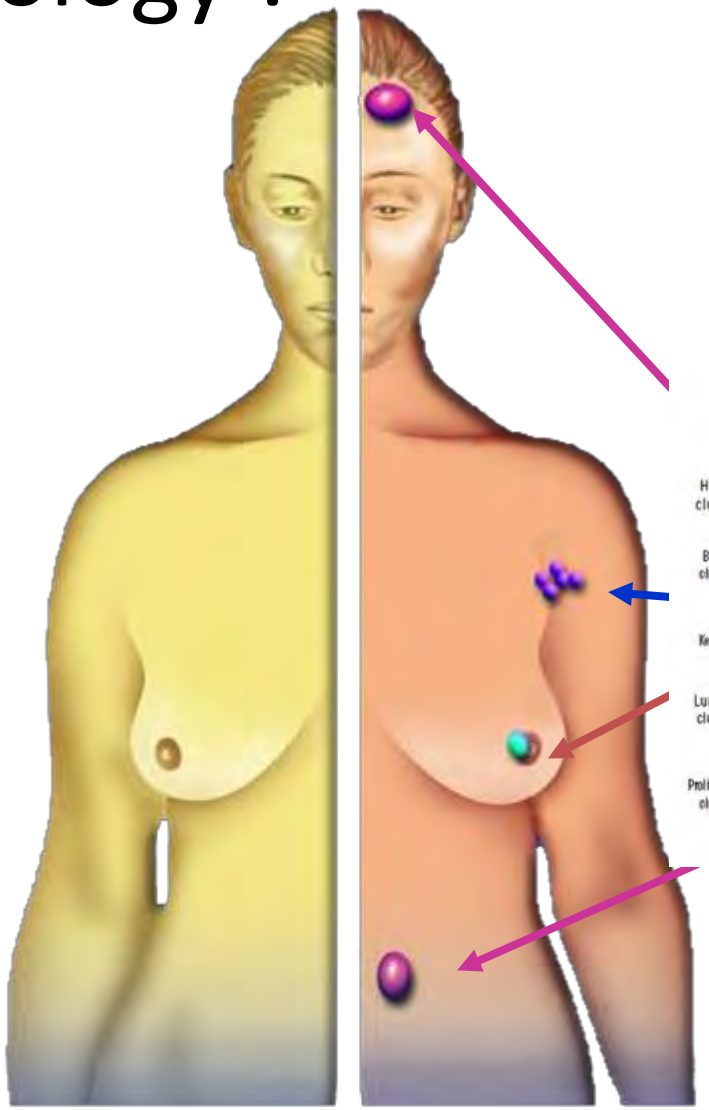


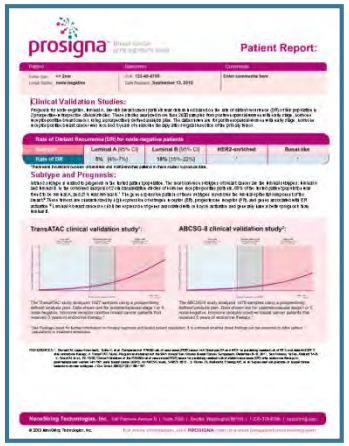
Yes , we have molecular biology !

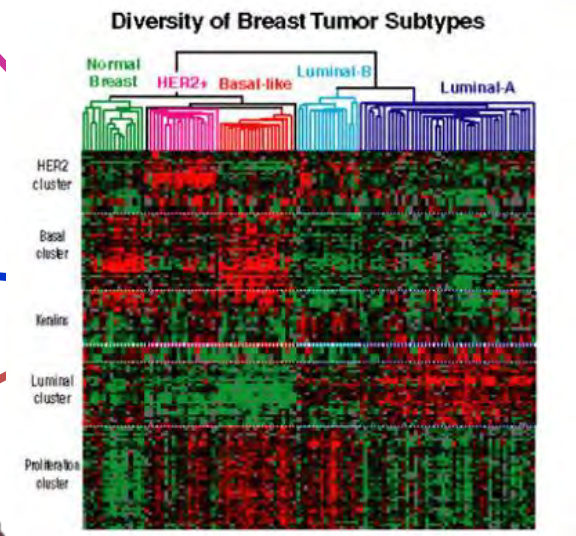
- Age
- Grade
- Histological sub
- ER/PR and HER2
- Vascular invasio
- Tumor ma



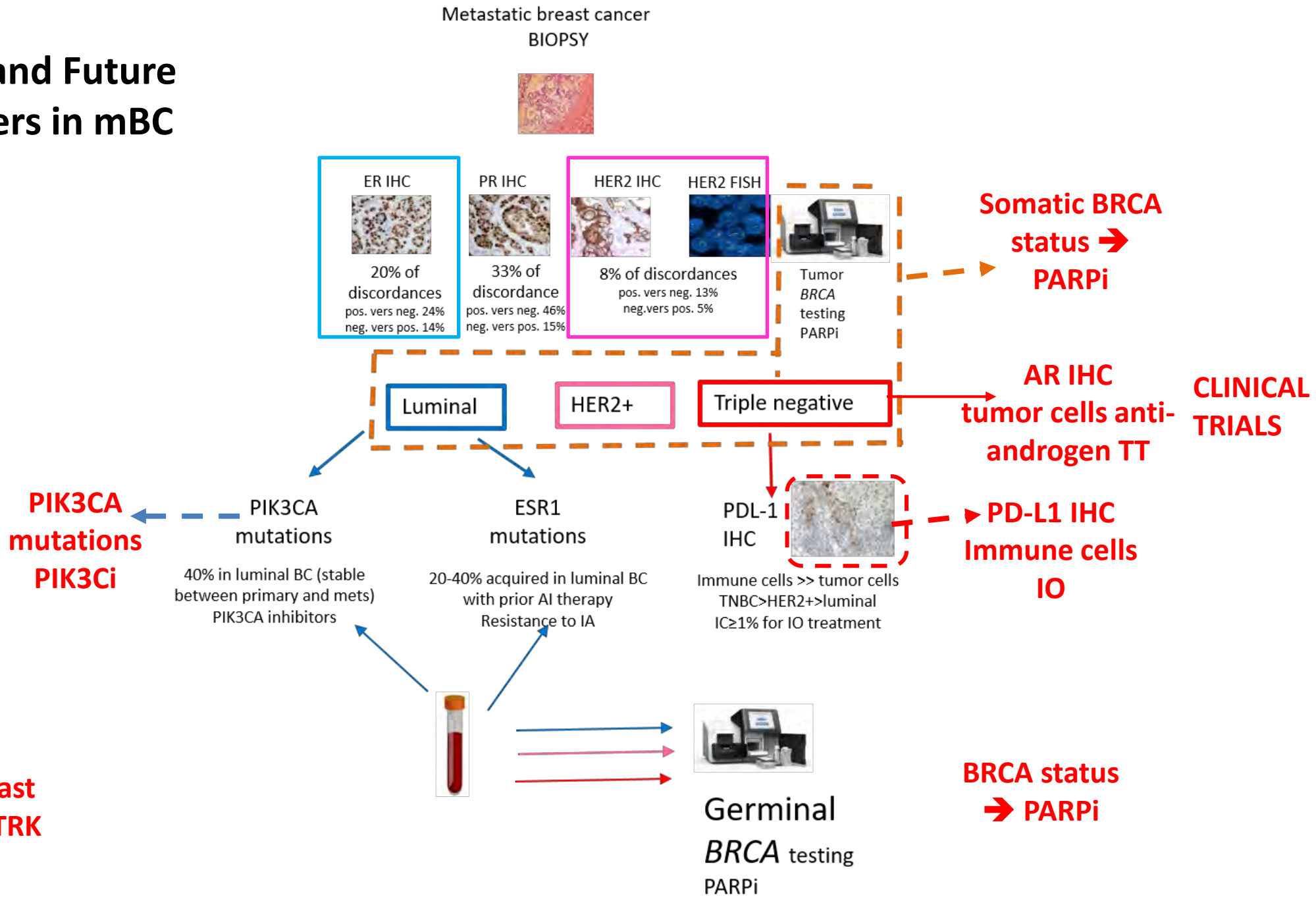








Present and Future biomarkers in mBC



NTK fusions enriched in secretory breast cancers → NTRK inhibitors

THANK YOU!