Breast cancer pathology and molecular biology

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Conflict of Interest

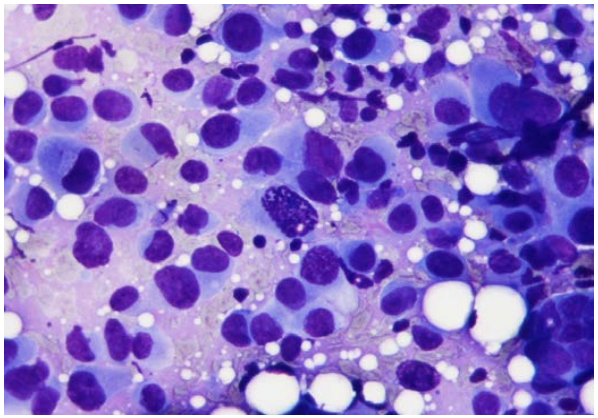
- I have no financial relationships to disclose

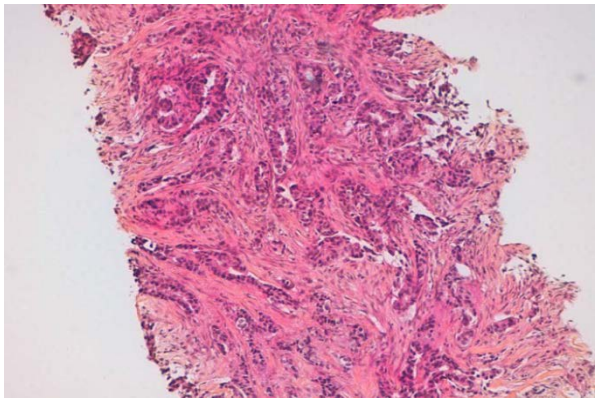
Topics

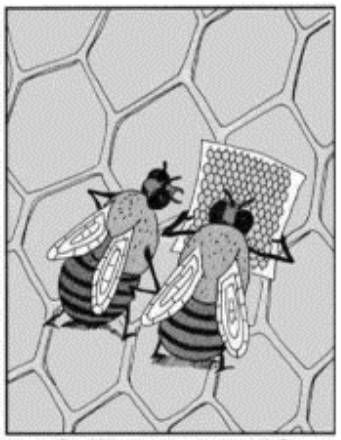
- Pathological features of breast carcinoma
- Standard prognostic and predictive factors of invasive breast carcinoma
- Molecular classification of breast carcinoma
- Molecular markers of invasive breast carcinoma

Invasive breast carcinoma

- BC is a heterogeneous disease
- Tumours with similar morphology show variable behaviour, outcome and response to therapy







So, Where are we exactly?

Major Questions in Each Individual Patient:

? Risk of relapse
? Risk of death due to breast cancer
? Expected relative and absolute benefits of different systemic therapies

Prediction is difficult, especially about the future

Niels Bohr, 1885-1962

Why do we need a classification?

Aim 1: **Diagnosis**

Aim 2: **Prognosis**

Aim 3: **Prediction**

Summary of prognostic and predictive factors for invasive breast cancer

	Prognostic	Predictive
Patient age	√√	
Nodal status	√√√	
Tumor size	√√√	
Lymphovascular invasion	√√	
Histological grade	√√	√√
Histologic type	√	√
Steroid receptors	√	√√√
Her2/neu	√	√√√

Eifel P, Axelson JA, Costa J, Crowley J, Curran WJ Jr, Deshler A, et al. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. J Natl Cancer Inst. 2001;93(13):979–89.

Nodal status

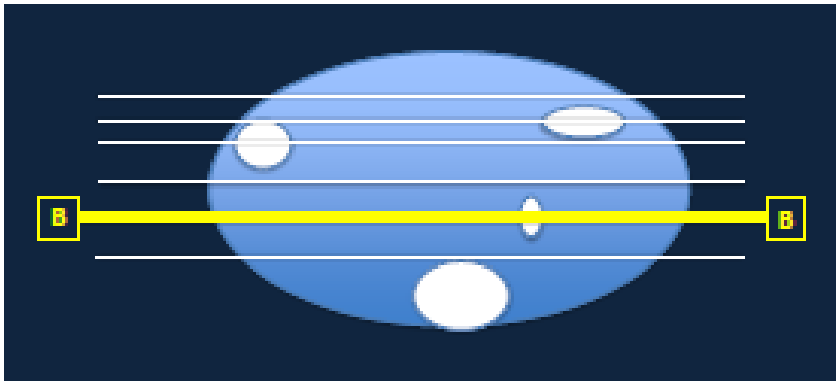
The Effect of Tumor Size and Lymph Node Status on Breast Carcinoma Lethality

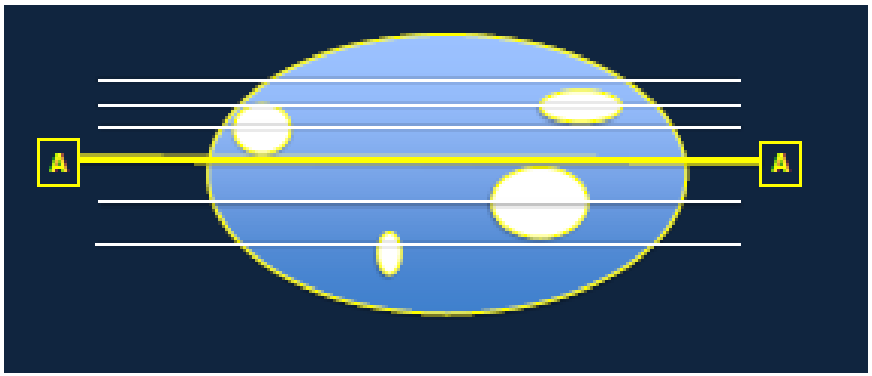
Cancer 2003;98:2133-43.

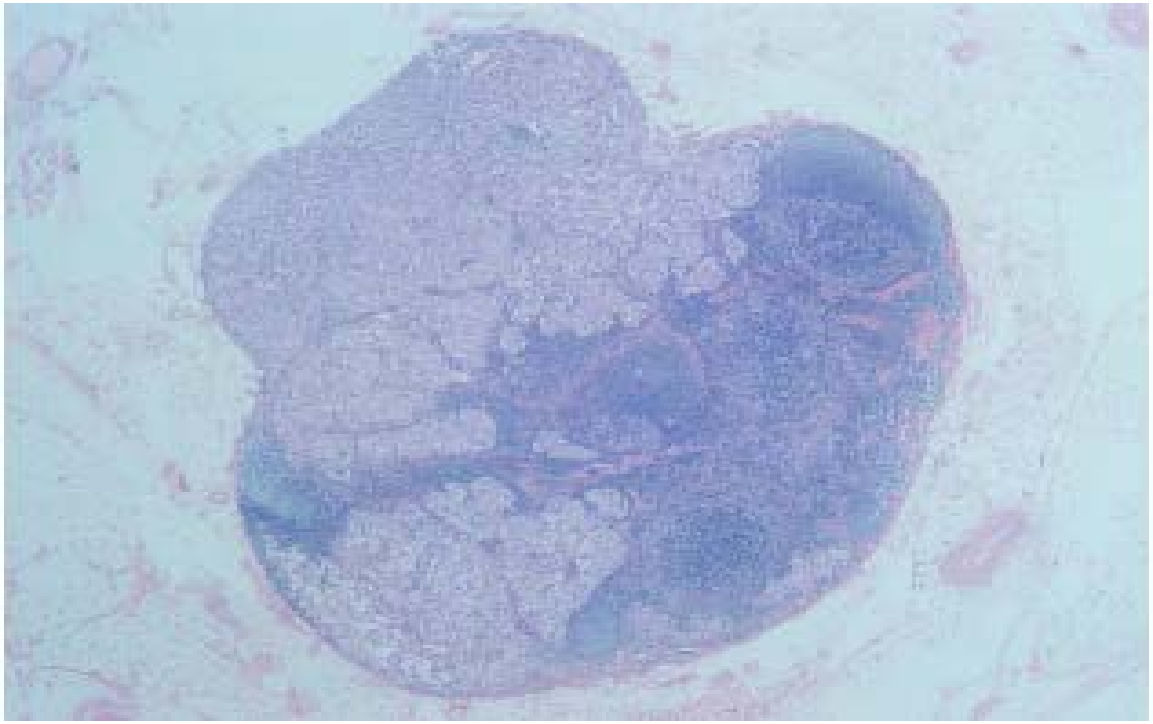
For women with equivalent lymph node status, tumor size was associated with increased lethality, such that each milimeter of tumor diameter was associated with an additional 1% chance of death

For women with tumors of equivalent size, lethality increased with increasing number of positive lymph nodes, such that there was an extra 6% chance of death associated with each positive lymph node

Nodal status







Lymph node involvement

Annals Surgery 1971

Significance of Axillary Macrometastases and Micrometastases in Mammary Cancer

A. G. Huvos, M.D., R. V. P. Hutter,* M.D., J. W. Berg,** M.D.

From the Department of Pathology, Memorial Hospital for Cancer and Allied Diseases, New York, New York 10021

- pN1

MACROMETASTASIS

size >2 mm

- pN1mic

MICROMETASTASIS

size >0.2 mm and <2 mm

>200 cells in one LN section

- pN0

pN0(i-)

pN0(i+)

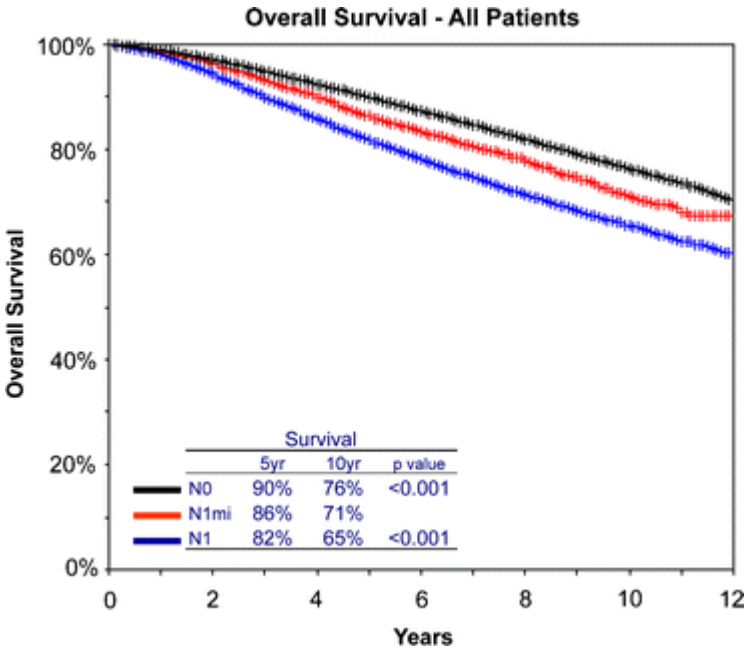
ISOLATED TUMOR CELLS (ITCs)

single cells and clusters <0.2 mm, even in H/E-stained slides

pN0(mol-) and pN0(mol+)

AJCC 2010

SEER micrometastasis study



209,720 patients (SEER)
1992-2003 pN0
pN1mi (0.3-2 mm)
pN1 (>2 mm)

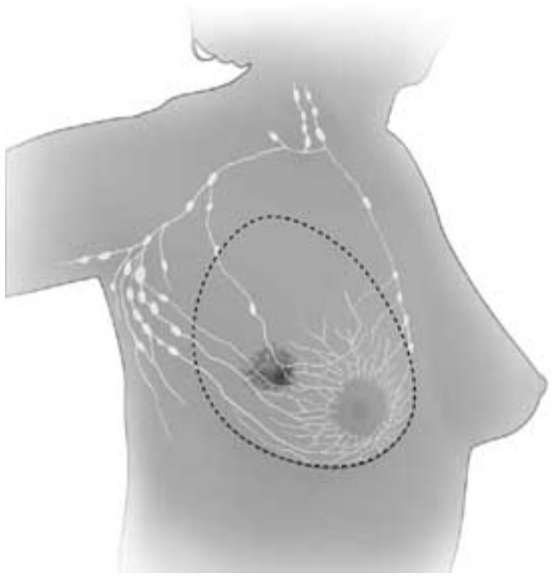
•N1mi significant at multivariate analysis ($p<0.0001$) vs N0 (HR1.35)
vs N1 (HR 0.82)

Chen SL et al Ann Surg Oncol. 2007, 12:3378-84

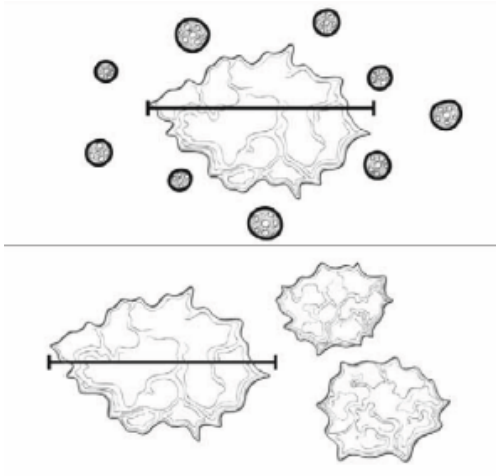
Sentinel lymph node (SLN) biopsy

- 1st LN draining tumor bed → 1st site of local mets
- Pathologically negative SN have been shown to predict negative axillary status with a 98% degree of accuracy
- Standard method in breast cancer patients cN0

Rao R, Euhus D, Mayo HG, Balch C. Axillary node interventions in breast cancer: a systematic review. JAMA. 2013;310(13):1385–94.
Thompson AM. New standards of care in the management of the axilla. Curr Opin Oncol. 2012;24(6): 605–11.
Zarebczan Dull B, Neuman HB. Management of the axilla. Surg Clin North Am. 2013;93(2):429–44.
Noguchi M, Morioka E, Ohno Y, Noguchi M, Nakano Y, Kosaka T. The changing role of axillary lymph node dissection for breast cancer. Breast Cancer. 2013;20(1):41–6.
Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA. 2011;305(6):569–75.

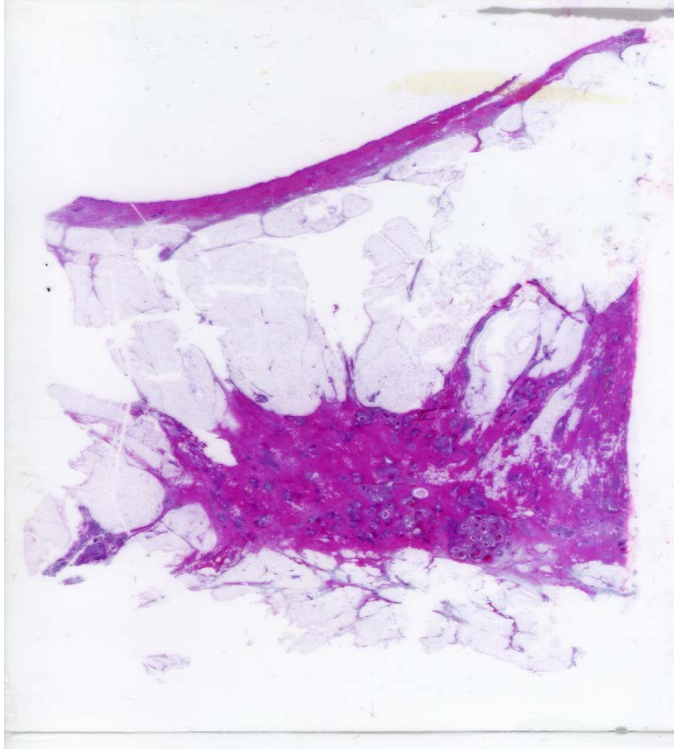


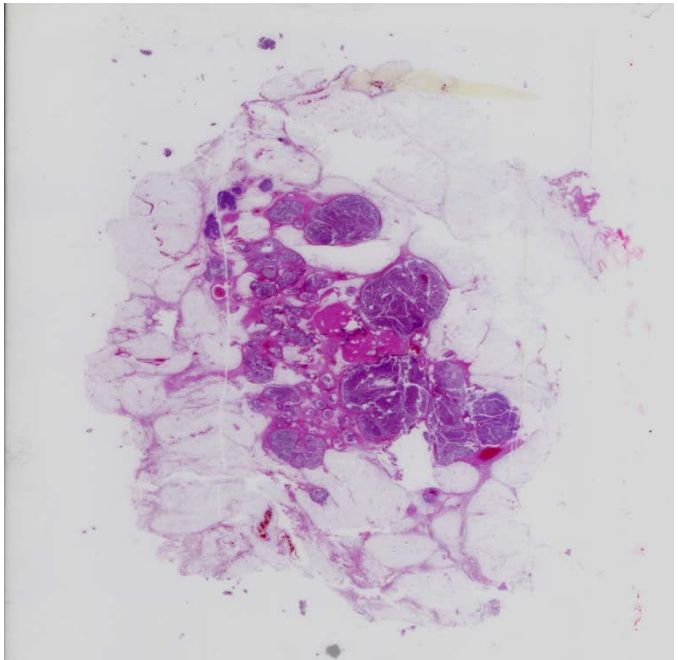
Tumor size



Invasive carcinoma with surrounding intraductal carcinoma

Multiple invasive carcinomas
size of the largest is used for T-staging





Tumor grade

- Different grading systems
- Nottingham combined histologic grade (the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system)
- Subjectivity
- Adherence to strict criteria is necessary for reproducibility so that grading can be used as a prognostic marker

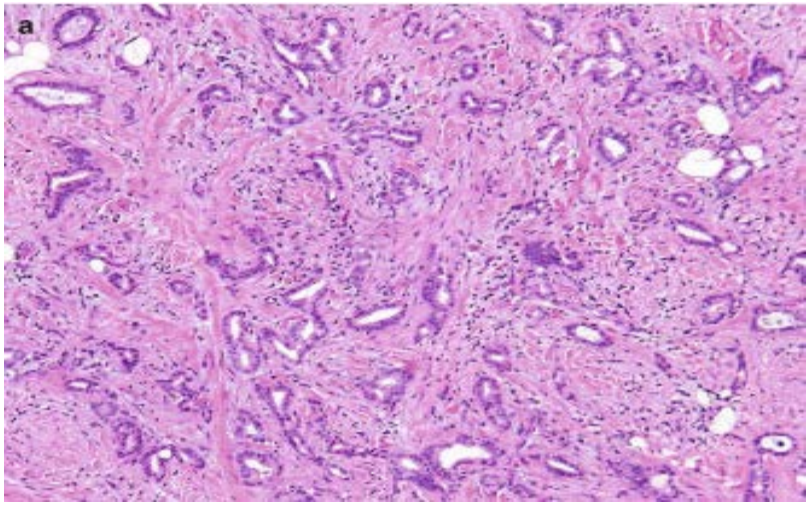
Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. II, Histological type. Relationship with survival in a large study with long-term followup. Histopathology. 1992;20:479–89.

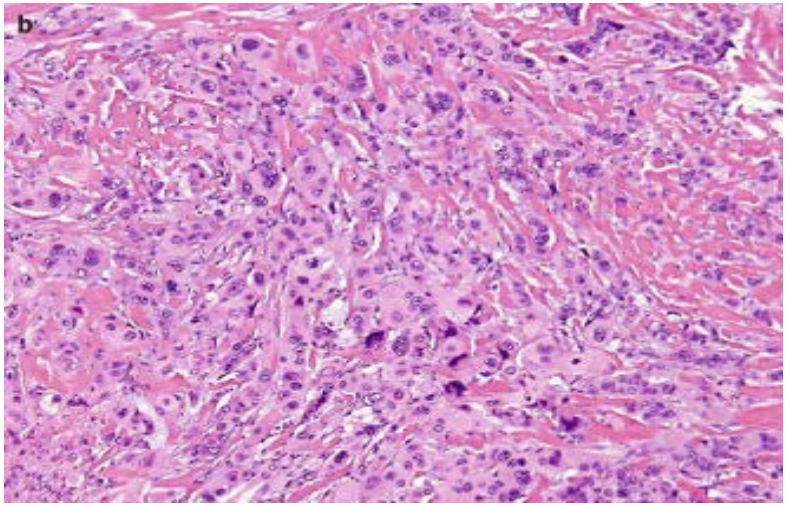
Breast cancer grade scoring Nottingham combined histologic grade (the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system)

Tubuli	> 75 %	1
	10 – 75 %	2
	< 10 %	3
Nuclei	small monomorphous	1
	intermediate size and variability	2
	large and polymorphous	3
Mitosis	number in 10 HPF	1 - 3

a *HPF* high-power field

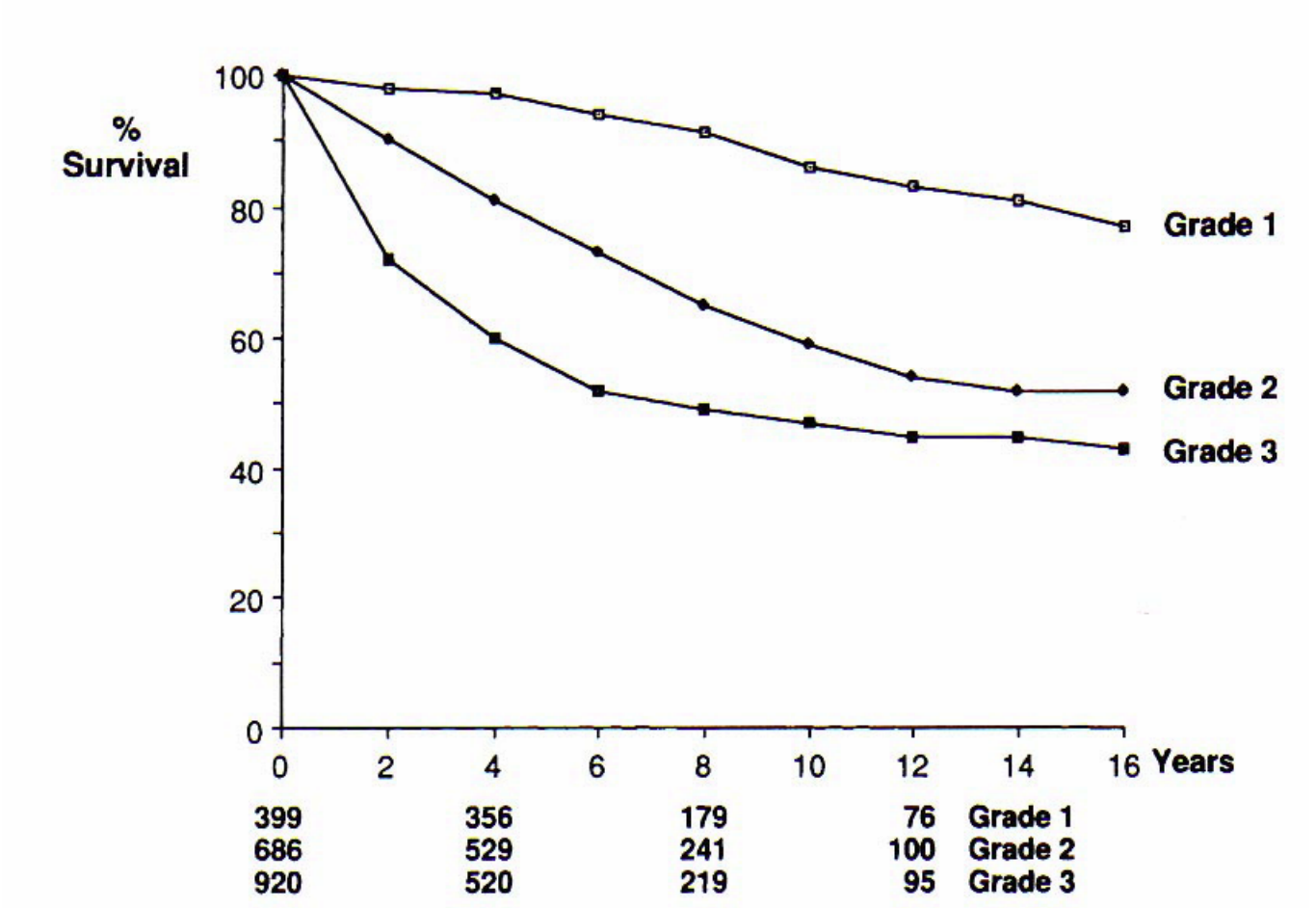
Grade 1	total score	3 – 5
Grade 2	total score	6 – 7
Grade 3	total score	8 – 9





Elston CW and Ellis IO The Breast, Churchill Livingstone 1998

Histologic grade and survival

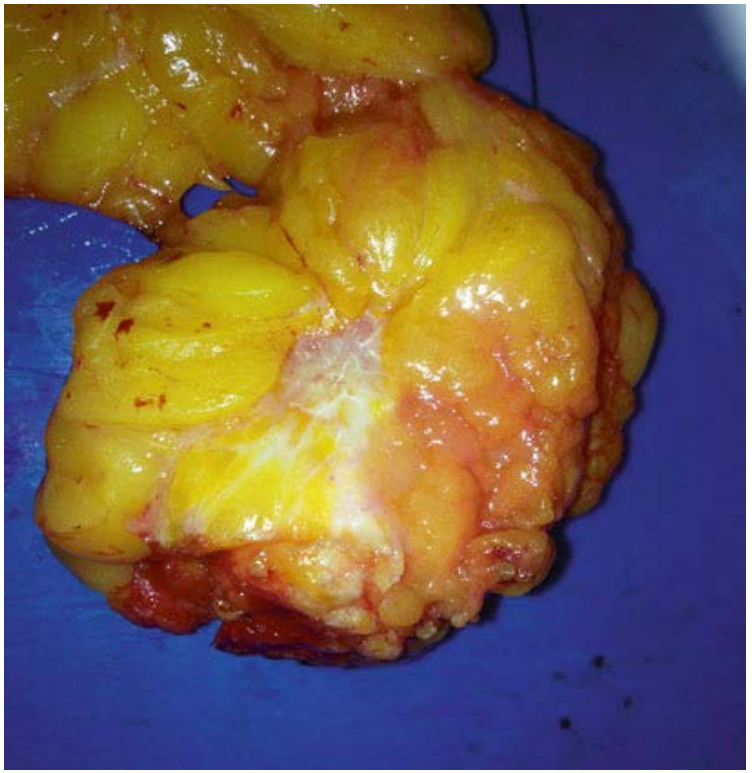


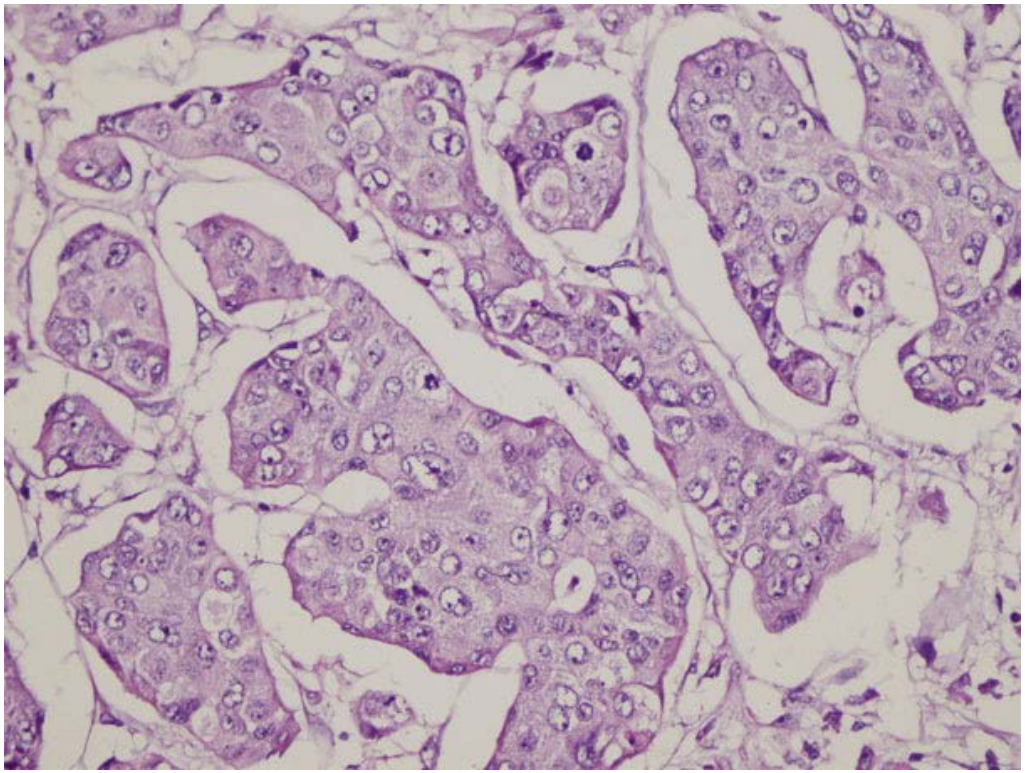
Elston CW and Ellis IO The Breast, Churchill Livingstone 1998

Histologic type

- Invasive ductal carcinoma of no special type -75%

Gross Features





Hstologic appearance

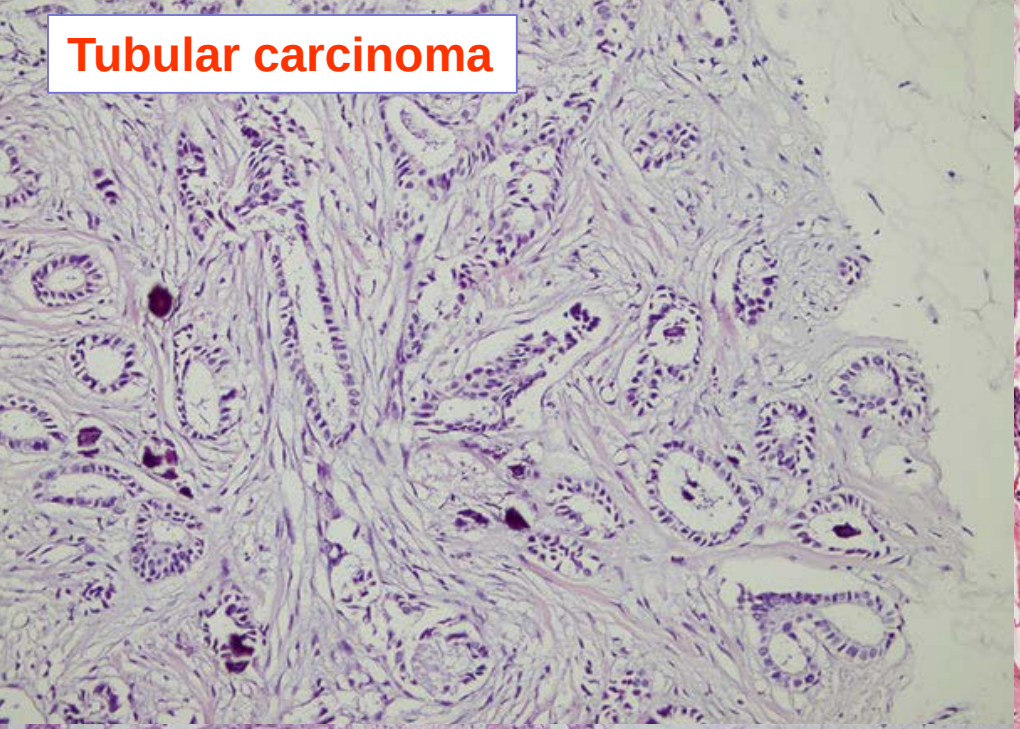
20 Histological types: morphology matters!

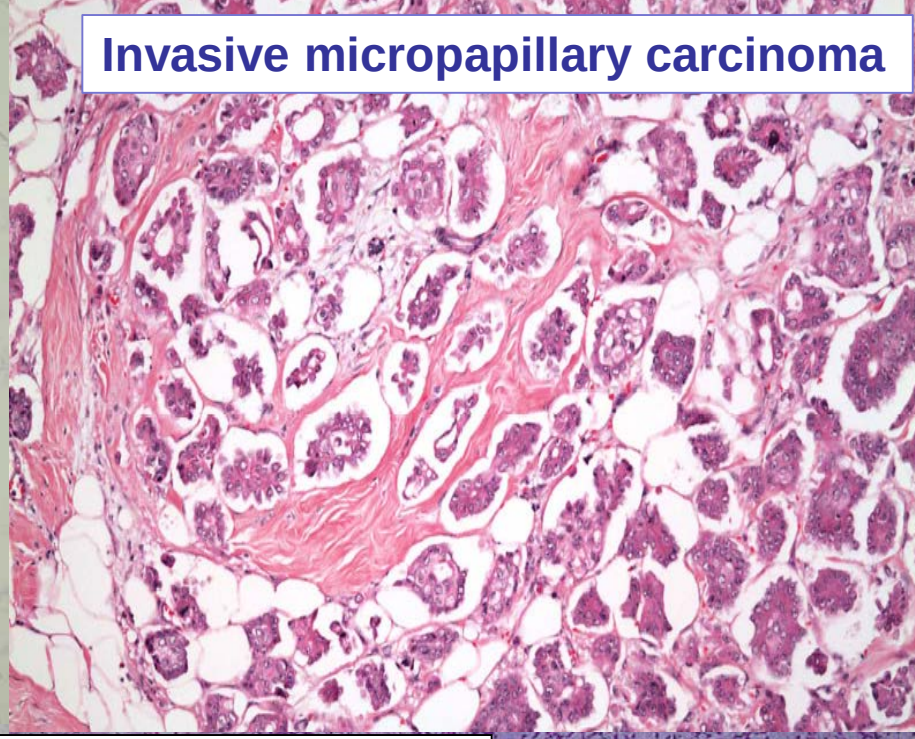
- The identification of special histologic types enables further refinement of the prediction of clinical outcome

Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, vande Vijver MJ, editors. World Health Organization classifi cation of tumors. Pathology and genetics of tumors of the breast and female genital organs. 4th ed. Lyon: IARC Press; 2012.
56. Ellis IO, Galea M, Broughton N, Locker A, Blamey RW, Elston CW. Pathological prognostic factors in breast cancer. II, Histological type. Relationship with survival in a large study with long-term followup. Histopathology. 1992;20:479–89.

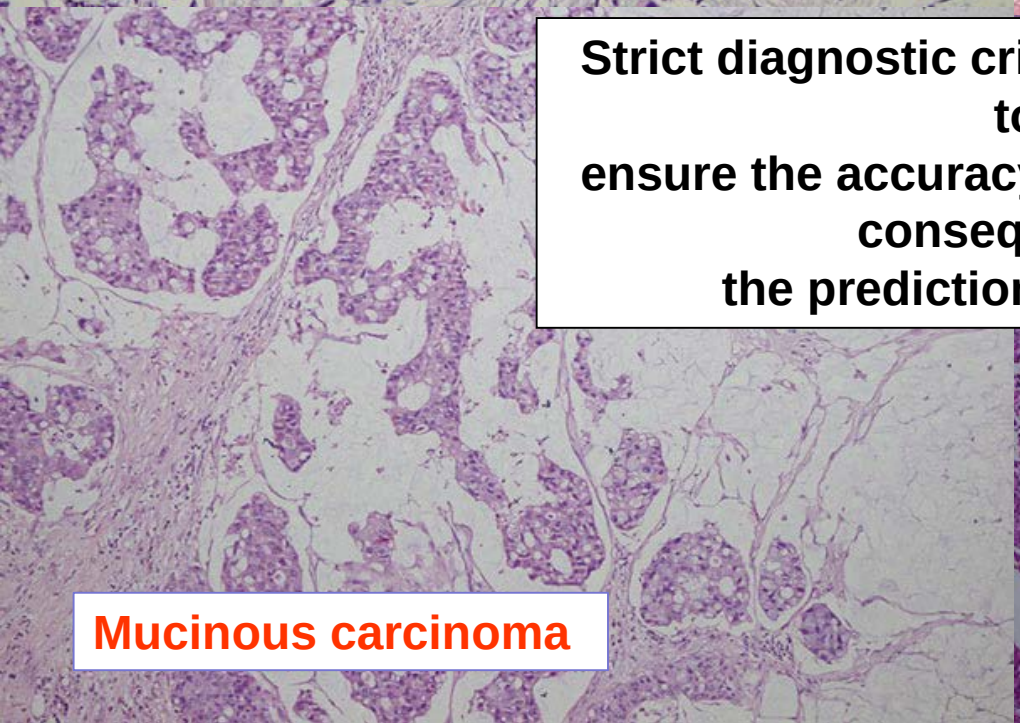
Special histological types of breast carcinoma

1 Invasive lobular carcinoma
2 Tubular carcinoma
3 Cribriform carcinoma
4 Carcinoma with medullary features
5 Metaplastic carcinoma
6 Carcinoma with apocrine differentiation
7 Salivary gland/skin adnexal-type tumors
8 Adenoid cystic carcinoma
9 Mucoepidermoid carcinoma
10 Polymorphous carcinoma
11 Mucinous carcinoma and carcinoma with signet ring cell differentiation
12 Carcinoma with neuroendocrine features
13 Invasive papillary carcinoma
14 Invasive micropapillary carcinoma
15 Secretory carcinoma
16 Oncocytic carcinoma
17 Sebaceous carcinoma
18 Lipid-rich carcinoma
19 Glycogen-rich clear cell carcinoma
20 Acinic cell carcinoma



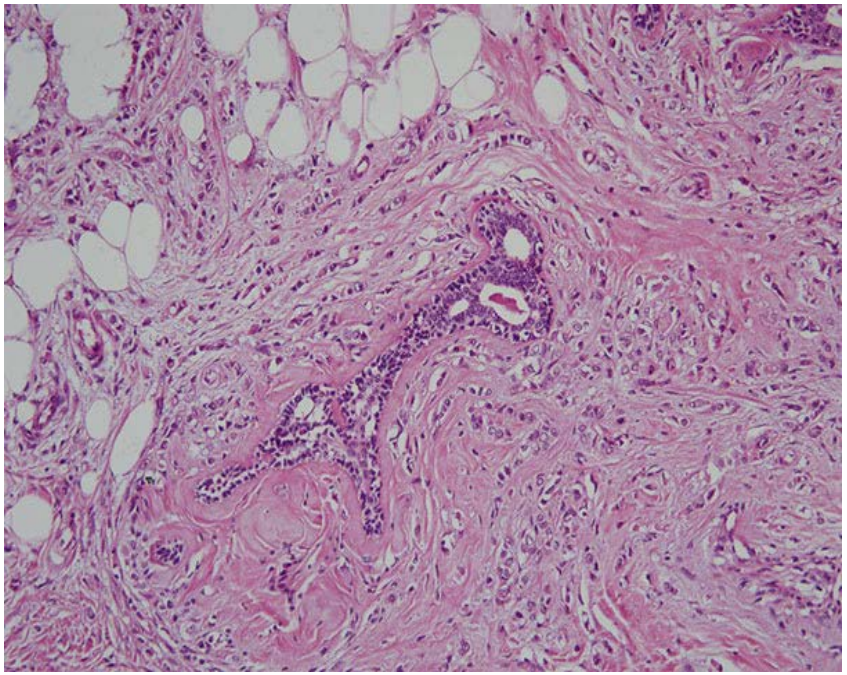


Strict diagnostic criteria must be used to
ensure the accuracy of diagnosis and, consequently,
the prediction of outcome



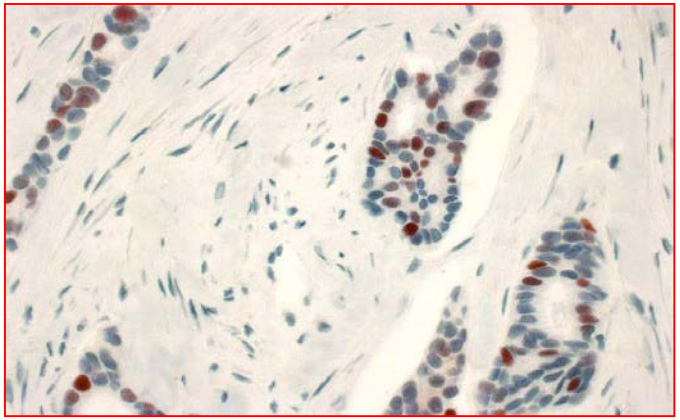
Invasive lobular carcinoma

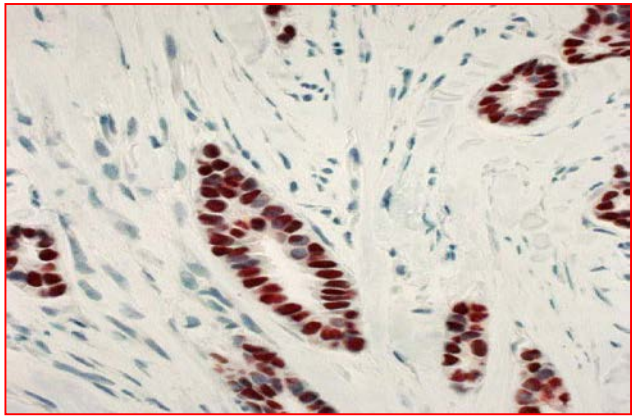
- bilateral and multifocal
- older patients
- larger in size
- positive for steroid receptors and negative for Her2/neu
- E-cadherin negative



Hormone Receptors

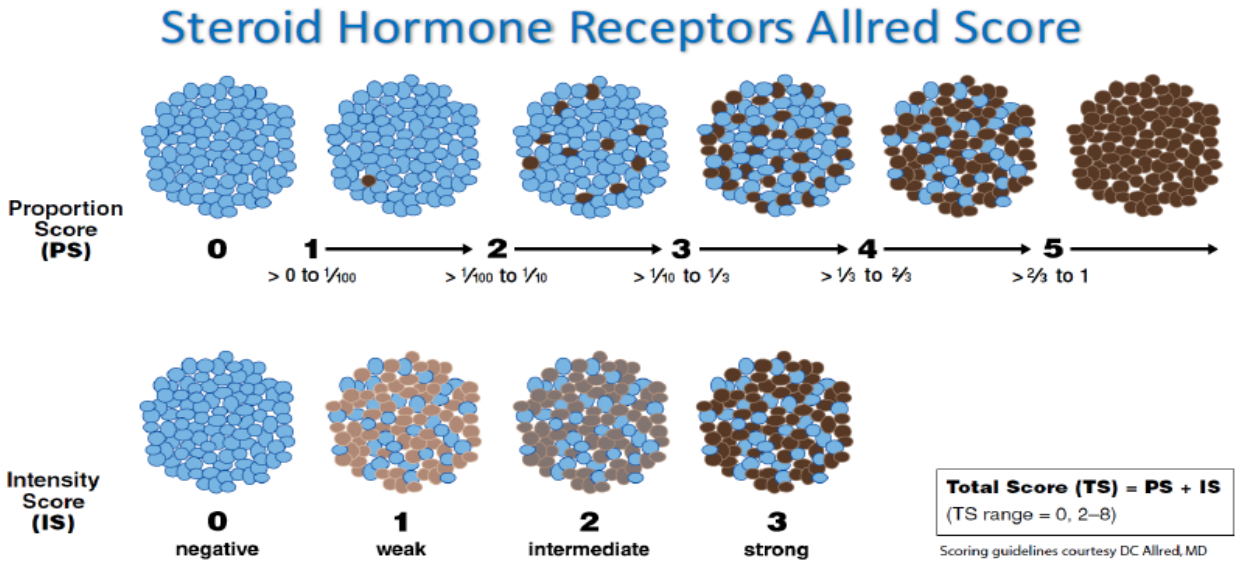
- Weak prognostic factors
- Predictive factors of the response to hormonal therapy
- Evaluation of ER and PR - a mandatory component of the pathologic evaluation of breast carcinomas





Hormone Receptors

- IHC evaluation - standard of practice
- Most guidelines recommend reporting both the proportion of positively stained nuclei and the intensity of nuclear staining



1. Scoring Guidelines for Immunohistochemical Staining of Estrogen-receptor

0–1	No effect of HT
2–3	Small (20%) chance of benefit of HT
4–6	Moderate (50%) chance of benefit of HT
7–8	Good (75%) chance of benefit of HT

Published Ahead of Print on April 19, 2010 as 10.1200/JCO.2009.25.6529
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.25.6529

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

The interlaboratory variance in ER and PR data is as high as 30 %

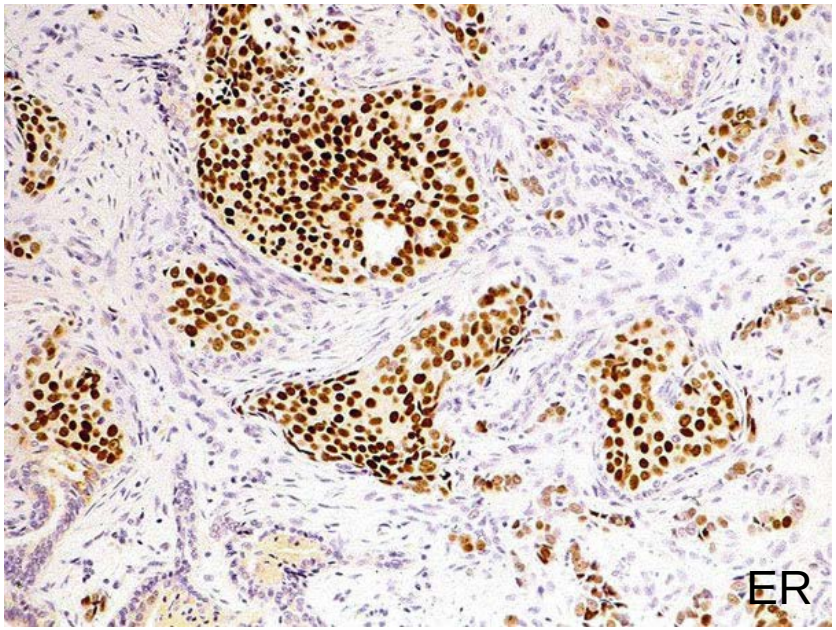
American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

M. Elizabeth H. Hammond, Daniel F. Hayes, Mitch Dowsett, D. Craig Allred, Karen L. Hagerty, Sunil Badve, Patrick L. Fitzgibbons, Glenn Francis, Neil S. Goldstein, Malcolm Hayes, David G. Hicks, Susan Lester, Richard Love, Pamela B. Mangu, Lisa McShane, Keith Miller, C. Kent Osborne, Soonmyung Paik, Jane Perlmutter, Anthony Rhodes, Hironobu Sasano, Jared N. Schwartz, Fred C.G. Sweep, Sheila Taube, Emina Emilia Torlakovic, Paul Valenstein, Giuseppe Viale, Daniel Visscher, Thomas Wheeler, R. Bruce Williams, James L. Wittliff, and Antonio C. Wolff

From Intermountain Healthcare, University of Utah School of Medicine, Salt Lake City, UT; Washington University School of Medicine, St Louis, MO; American Society of Clinical Oncology, Alexandria, VA; University of Michigan Comprehensive Cancer Center, University of Michigan Health System; St Joseph Mercy Hospital; Gemini Group, Ann Arbor; Advanced Diagnostics Laboratory, Redford, MI; Presbyterian Hospital, Charlotte, NC; Indiana University

1	Samples from all patients with breast carcinoma should be tested. Large, particularly multiple-core, biopsies of the tumor are preferred for testing if they are representative of the tumor (grade and type) at resection
2	The time from tissue acquisition to fixation should be as short as possible. Samples for ER and PR testing are fixed in 10 % formalin for 6–72 h. Cold ischemia time, fixative type, and the time the sample was placed in fixative must be recorded
3	Storage of slides for more than 6 weeks before analysis is not recommended
4	Validation of any test must be performed before the test is offered
5	Validation must be performed using a clinically validated ER or PR test method. Revalidation should be performed whenever there is a significant change to the test system, such as a change in the primary antibody clone or introduction of new antigen retrieval or detection systems
6	Positive for ER or PR if ≥1 % of tumor cell nuclei are immunoreactive
7	Negative for ER or PR if <1 % of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PR (positive intrinsic controls are observed)
8	Uninterpretable for ER or PR if no tumor nuclei are immunoreactive and internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining

- Clinical data indicate that ER positivity as low as 1 % can identify patients who would benefit from hormonal therapy



Harvey JM, Clark GM, Osborne CK, Allred DC. Predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 2000;17: 1474–81.
Rhodes A, Jasani B, Barnes DM, Bobrow LG, Miller KD. Reliability of immunohistochemical demonstration of oestrogen receptors in routine practice: interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. J Clin Pathol. 2000;53:125–30.
Umemura S, Itoh J, Itoh H, Serizawa A, Saito Y, Suzuki Y, et al. Immunohistochemical evaluation of hormone receptors in breast cancer: which scoring system is suitable for highly sensitive procedures? Appl Immunohistochem Mol Morphol. 2004;12: 8–13.
Leake R, Barnes D, Pinder S, Ellis I, Anderson L, Anderson T, et al. Immunohistochemical detection of steroid receptors in breast cancer: a working protocol on behalf of the UK Receptor Group, UK NEQAS, the Scottish Breast Cancer Pathology Group, and the Receptor and Biomarker Study Group of the EORTC. J Clin Pathol. 2000;53:634–5.

Immunohistochemistry of Estrogen and Progesterone Receptors Reconsidered

Experience With 5,993 Breast Cancers

Mehrdad Nadji, MD, Carmen Gomez-Fernandez, MD, Parvin Ganjei-Azar, MD, and Azorides R. Morales, MD

Status of ER and PR in 5,497 Cases of Infiltrating Mammary Carcinoma in Histologic Specimens

Receptor	No. (%)
ER+	4,100 (75)
PR+	3,016 (55)
ER+/PR+	3,016 (55)
ER+/PR–	1,084 (20)
ER–/PR–	1,397 (25)
ER–/PR+	0 (0)

ER, estrogen receptor; PR, progesterone receptor; +, positive; –, negative.

Relationship of ER and PR to Histologic Subtypes of Mammary Carcinoma*

Type of Carcinoma	ER+	PR+
Infiltrating ductal, not otherwise specified (n = 4,396)	3,255 (74)	2,330 (53)
Tubular (n = 237)	237 (100)	225 (95)
Colloid (n = 184)	184 (100)	133 (72)
Papillary (n = 44)	44 (100)	35 (80)
Apocrine (n = 40)	0 (0)	0 (0)
Medullary (n = 96)	0 (0)	0 (0)
Metaplastic (n = 120)	0 (0)	0 (0)
Infiltrating lobular (n = 380)	380 (100)	293 (77)

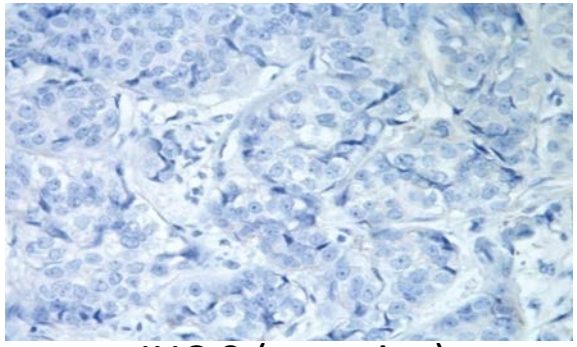
ER, estrogen receptor; PR, progesterone receptor; +, positive.

Her2/Neu

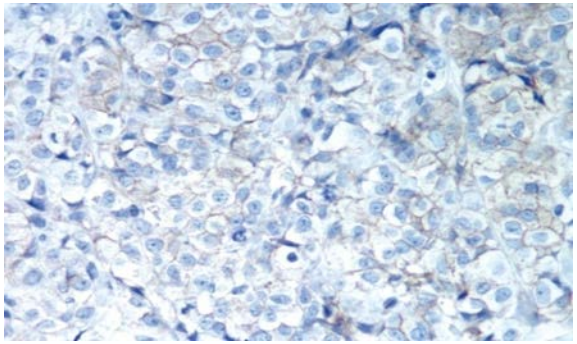
- Positive in 15–25 %
- Poor prognostic factor
- Predictive factor of the response to anti-HER2 therapy

- Her2 testing
  - -IHC
  - -ISH (FISH, CISH, SISH)

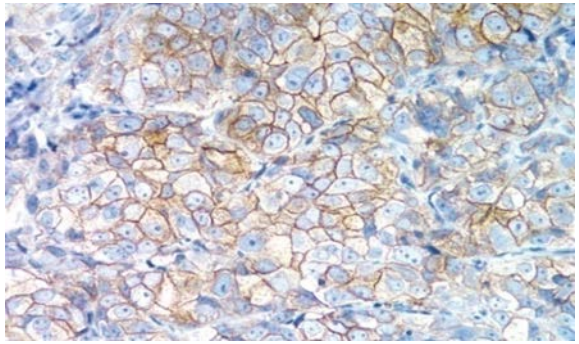
IHC scoring: semi-quantitative interpretation of HER2 expression



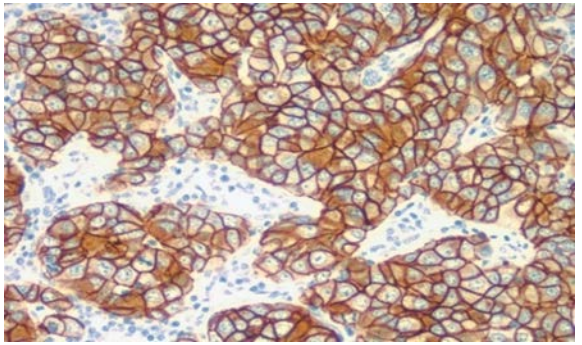
IHC 0 (negative)



IHC 1+ (negative)

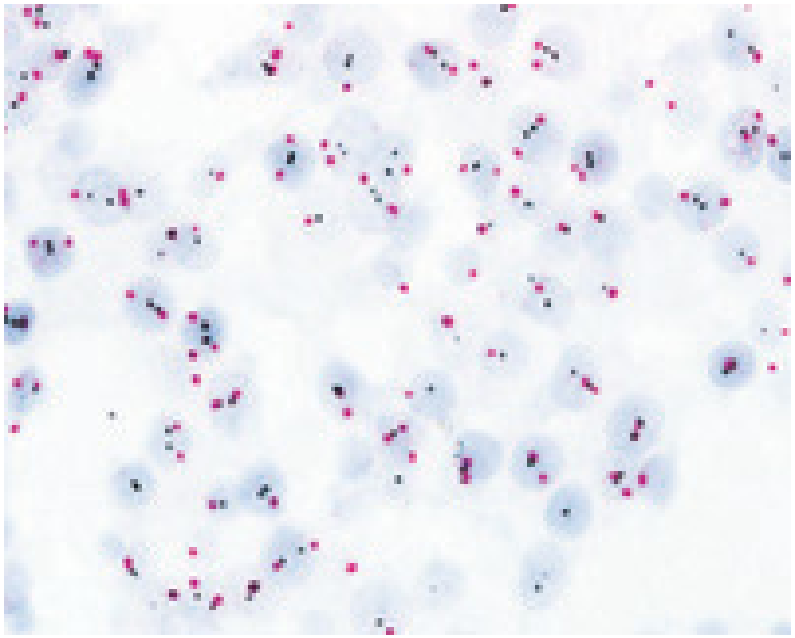


IHC 2+ (equivocal)

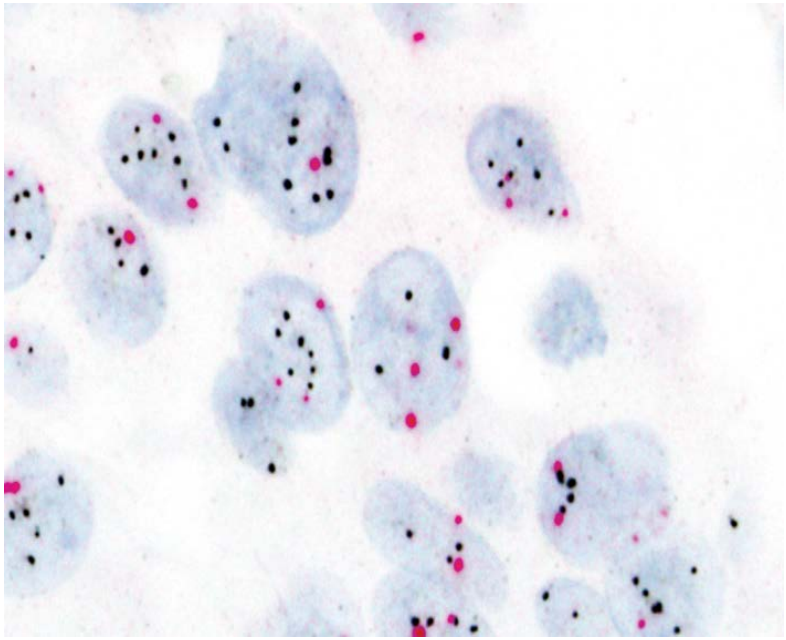


IHC 3+ (positive)

HER2 ISH



<4 Her2/neu gene copies per nucleus, or a ISH gene ratio <2.0



>6 gene copies per nucleus, or a ISH gene ratio (ratio of Her2/neu gene signals to chromosome 17 signals) ≥2

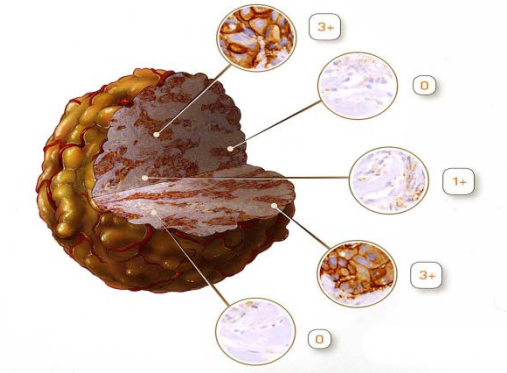
Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol. 2013;31(31):3997–4013.

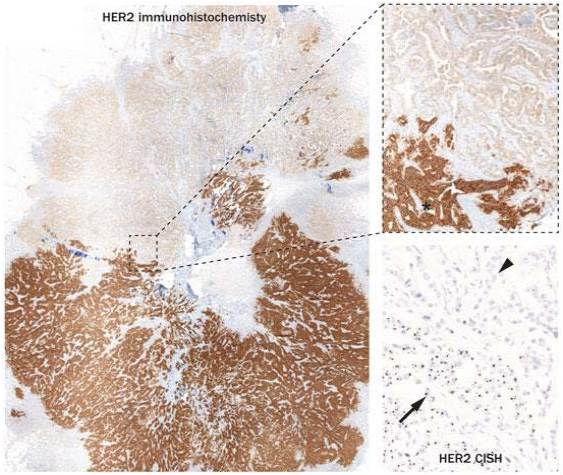
Her2/neu testing

-All primary invasive breast cancers

-All metastasis

-All recurrences





Studije 2010.g.	Amir N≈ 70 Prospektivno	Locatelli N = 250 Retrospektivno (samo jetra)	Karlsson N = 470 Retrospektivno	Lindstrom N=118 - 459 Retrospektivno
ER + → ER -	12 %	11 %	36 %	26 %
ER - → ER +	14 %	25 %	22 %	7 %
HER 2 - → HER 2 +	5 %	6 %	nd	7 %
HER 2 + → HER 2 -	12 %	32 %	nd	3 %

Tumor proliferation: Ki67

Int. J. Cancer: **31,** 13-20 (1983)

PRODUCTION OF A MOUSE MONOCLONAL ANTIBODY REACTIVE WITH A HUMAN NUCLEAR ANTIGEN ASSOCIATED WITH CELL PROLIFERATION

Johannes GERDES[1], Ulrich SCHWAB[2], Hilmar LEMKE[2] and Harald STEIN[1,3]

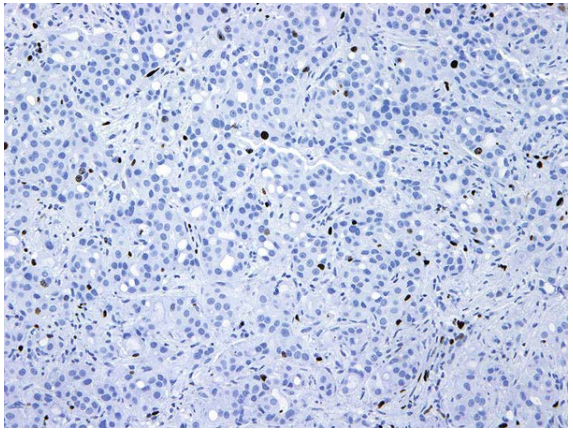
[1] *Institute of Pathology, Christian Albrecht University, Hospitalstrasse 42, D-2300 Kiel; and* [2] *Institute of Biochemistry, Christian Albrecht University, Olshausenstrasse 40-60, D-2300 Kiel, Germany.*

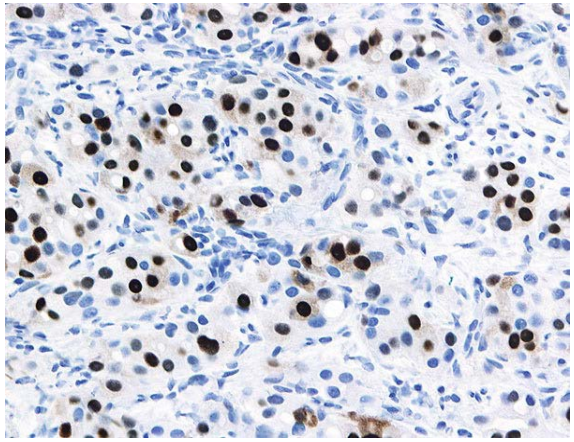
The production of a mouse monoclonal antibody, Ki-67, is described. The Ki-67 antibody recognized a nuclear antigen present in proliferating cells, but absent in resting cells. Immunostainings with Ki-67 revealed nuclear reac-

MATERIAL AND METHODS

Cells and specimens

Human peripheral blood lymphocytes and mono-





Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group

Mitch Dowsett, Torsten O. Nielsen, Roger A'Hern, John Bartlett, R.Charles Coombes, Jack Cuzick, Matthew Ellis, N.Lynn Henry, Judith C. Hugh, Tracy Lively, Lisa McShane, Soon Paik, Frederique Penault-Llorca, Ljudmila Prudkin, Meredith Regan, Janine Salter, Christos Sotiriou, Ian E. Smith, Giuseppe Viale, Jo Anne Zujewski, Daniel F. Hayes

Manuscript received March 14, 2011; revised September 1, 2011; accepted September 2, 2011.

- **17 of the 18 studies that included more than 200 patients showed statistically significant association between Ki67 and prognosis providing compelling evidence for a biological relationship**

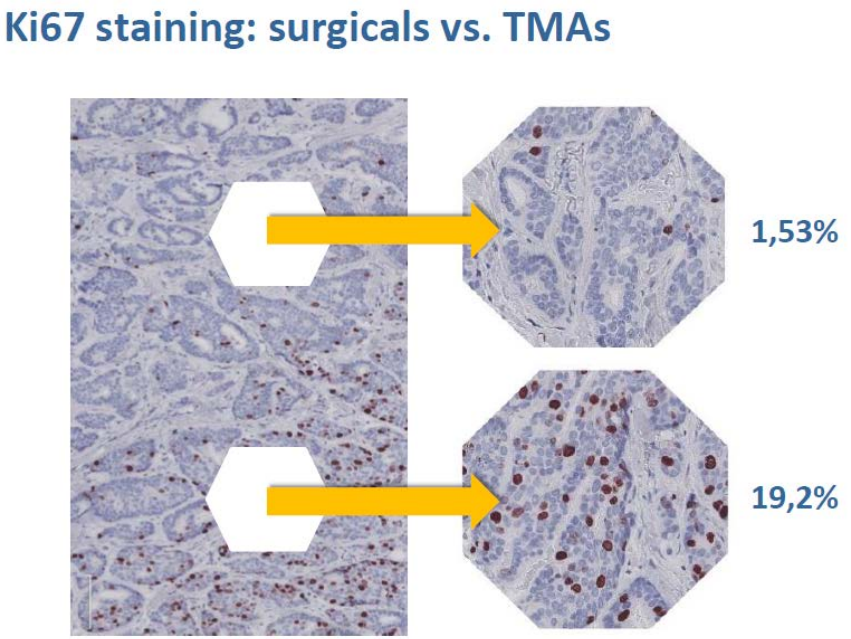
- but the cut-offs to distinguish "Ki67 high" from "Ki67 low" varied from 1% to 28.6%, thereby severely limiting its clinical utility

DowsettM et al; JNCI 2011

Ki-67

- **Limits of procedure**

– Quantification
– Interpretation
– Tumor heterogeneity
– Tissue fixation
    - Artefacts
    - Staining
– Reproducibility



- **Clinical Limits**

– Cut points arbitrary

• Various cut points suggested

• Still under debate

• May vary depending on topic (prognostic or predictive)

– For adjuvant treatment choice

• Cut points from 5 - 34%

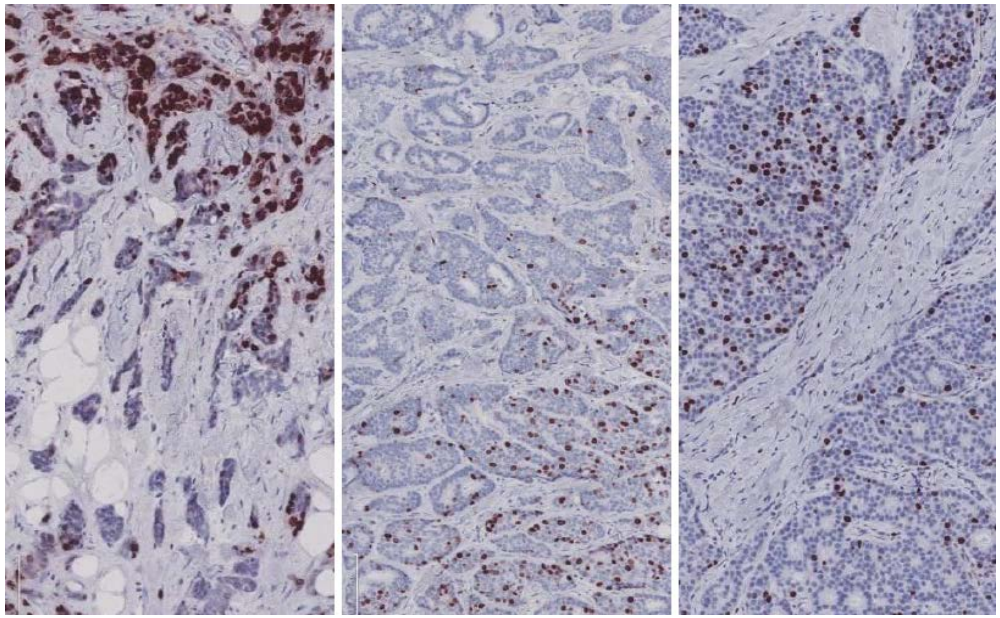
• Most frequently 10 – 20%

• St.Gallen 2013

– 20% (Panel decision)

• Proliferation rates are a continuum and are not bimodal

Ki67 staining: intratumoral heterogeity



St Gallen 2017

"…when is traditional pathology (stage, grade, LVI, ER/PR/HER2) not informative enough?"

Traditional clinicopathological parameters

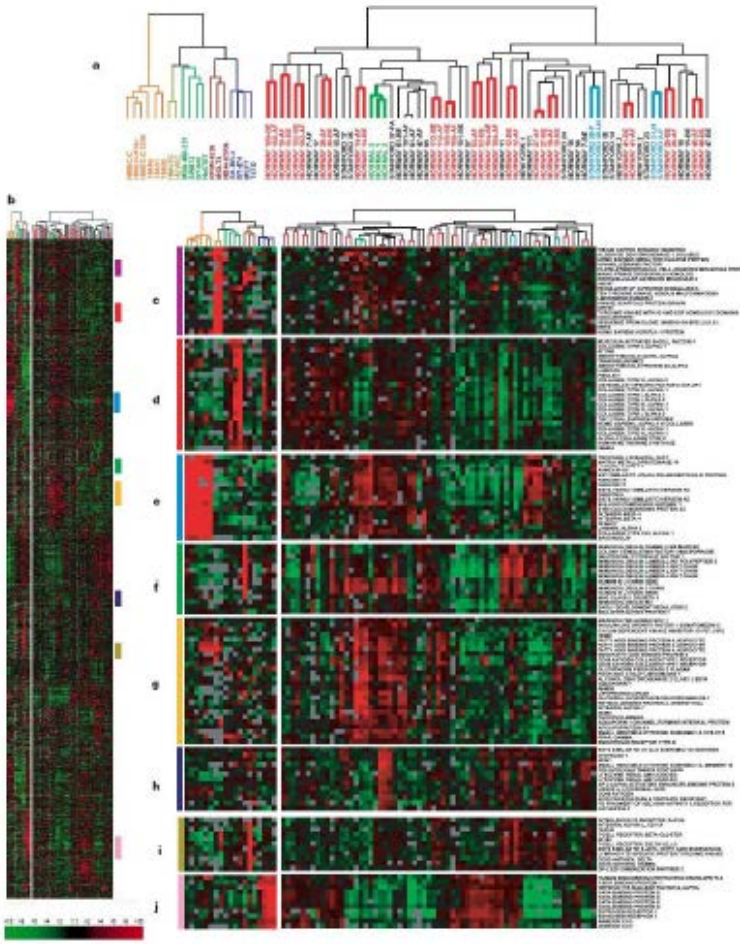
Prognosis of patients with breast carcinoma

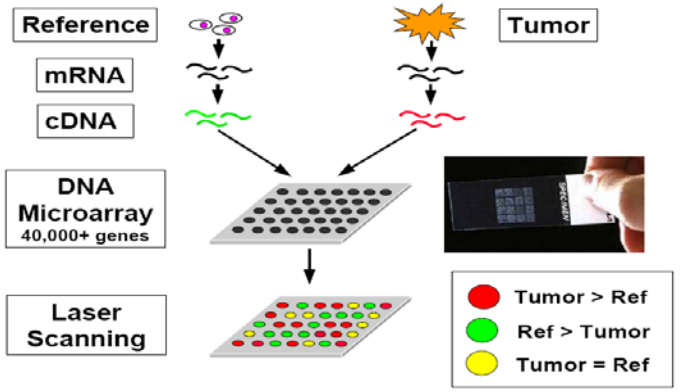
Biology?

Prognosis

- High risk: Chemotherapy
- Low risk: No chemotherapy
- However, clinically indeterminate groups such as LN-/ER+/ HER2- tumours: Additional prognostic tests are needed (**Multigene Prognostic Assays**)

Microarray-based gene expression analysis





Perou et al In 2000
>1700 genes

Each row is a gene
Each column is a sample
Green: <median
Black: =median
Red: >median
Rt panel: cell lines
Left panel: tissue

Dendrogram: similarities in the expression patterns

letters to nature

Molecular portraits of human breast tumours

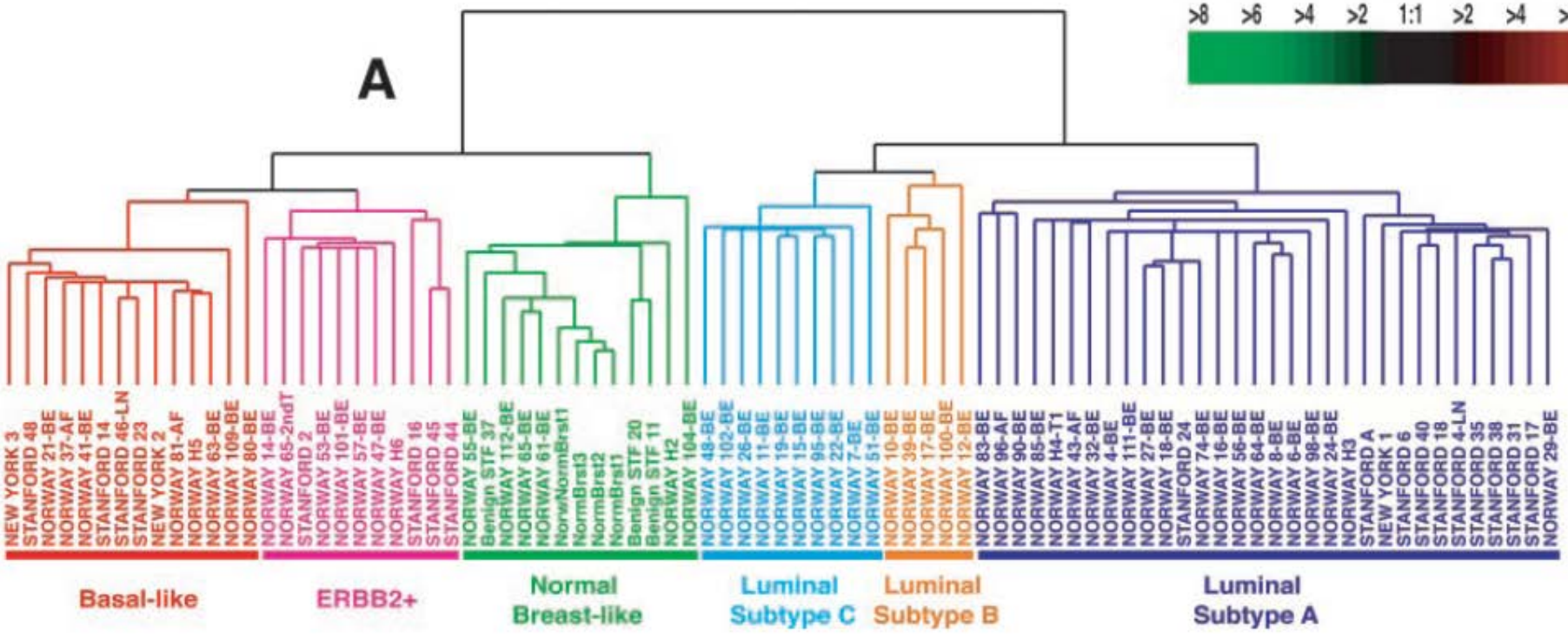
Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*,

Molecular portraits of human breast tumours

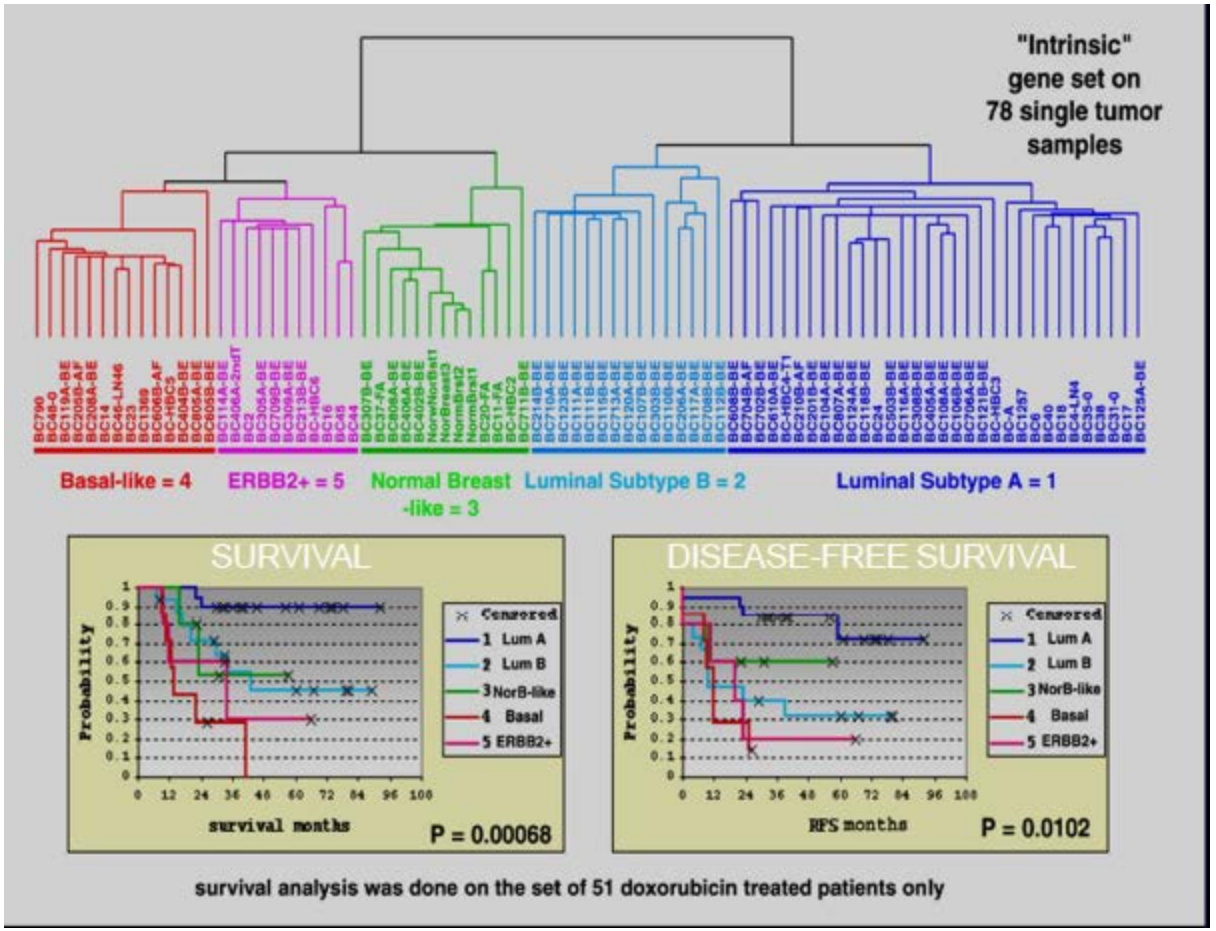
Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*

Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[j], Thor Thorsen[k], Hanne Quist[l], John C. Matese[c], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]



Molecular Subtypes and Prognosis



Sorlie T et al, PNAS 2001

Clinicopathologic surrogate definition

- **Luminal A-like**

  ER+, HER2-, Ki67 low, PgR high

  Low-risk molecular signature (if available)
- **Luminal B-like**

  HER2-negative:

  ER+, HER2- and either Ki67 high or PgR low

  High-risk molecular signature (if available)

  HER2-positive:

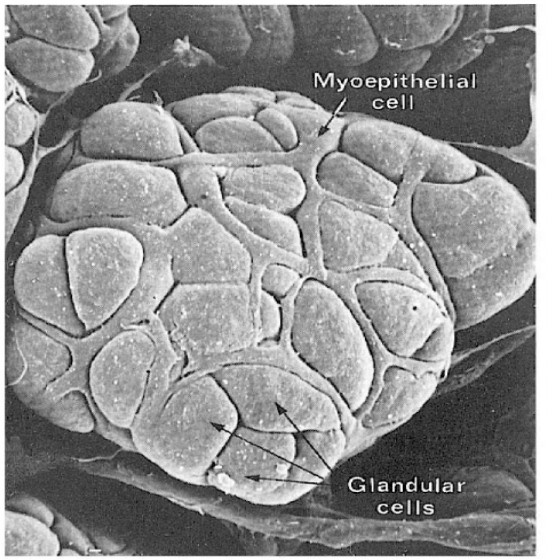
  ER-positive, HER2-positive, any Ki67, any PgR
- **HER2-positive** (non-luminal):

  HER2+, ER and PgR absent
- **Basal-like/Triple-negative**

  ER and PgR absent, HER2-negative

Annals of Oncology 26: v8–v30, 2015

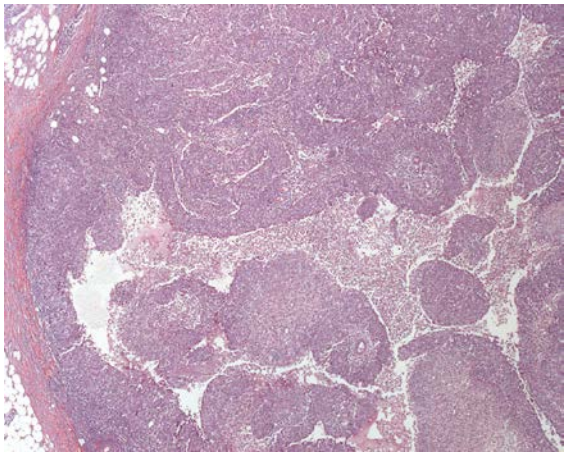
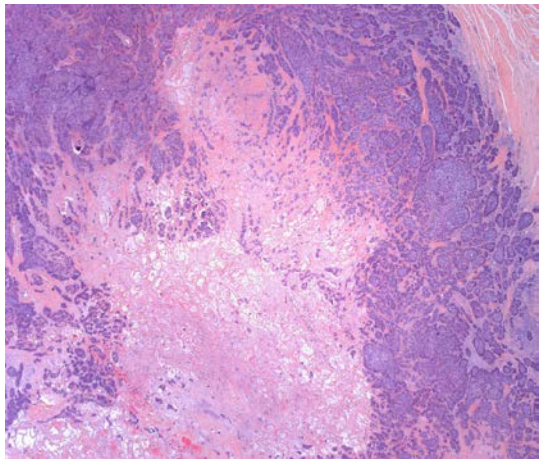
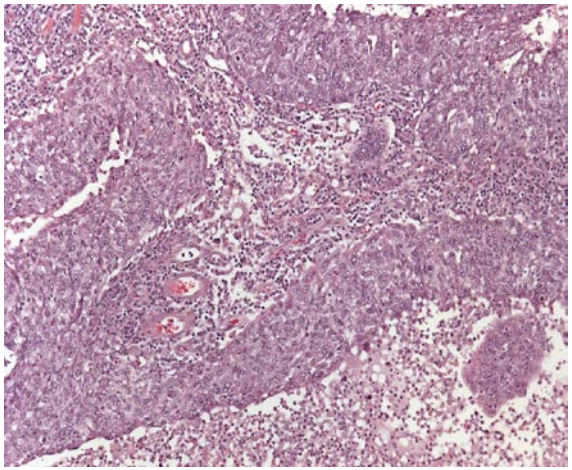
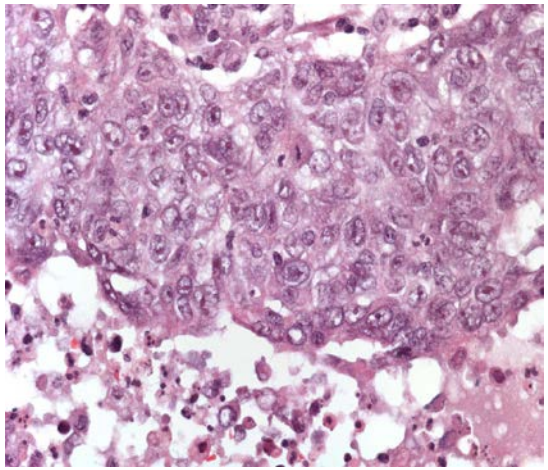
Basal like carcinomas



- Cluster genes characteristically expressed in normal breast basal/myoepithelial cells
- IHC: The basal type of tumors frequently does not express ER, PR, and HER2/neu but also expresses basal cytokeratins 5/6 and 17
- They tend to recur during the first 3 years after diagnosis, and currently there are no specific targeted therapies for them
- Strong association between basal-like carcinomas and BRCA1 mutations carriers

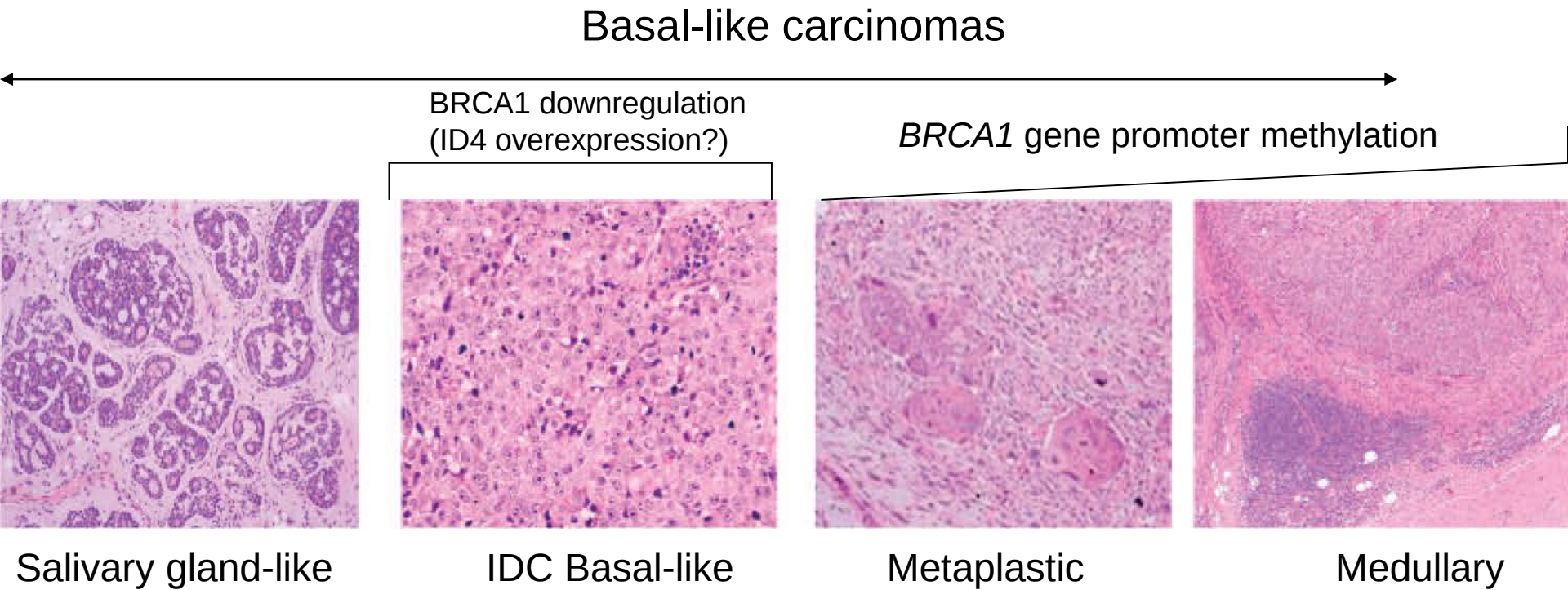
PATHOLOGIC FEATURES OF BASAL-LIKE TUMORS

- High-histologic grade, NOS (75%-100%)

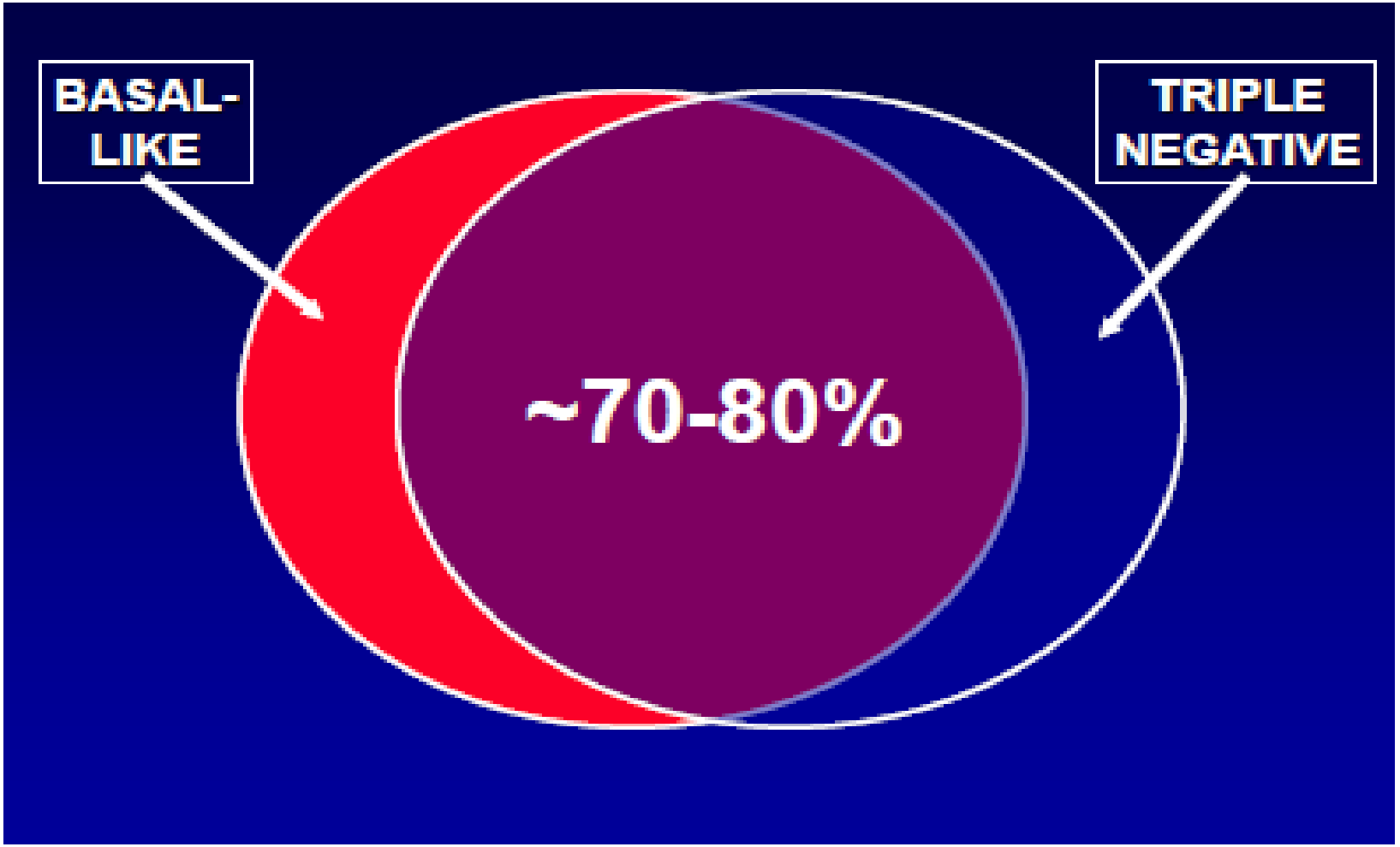





Rakha EA 2006, Foulkes 2004, Kim MJ 2006

The basal-like breast carcinomas and TNBC do not represent a single uniform group of tumors but a spectrum of tumors from low-grade to high-grade with different morphology



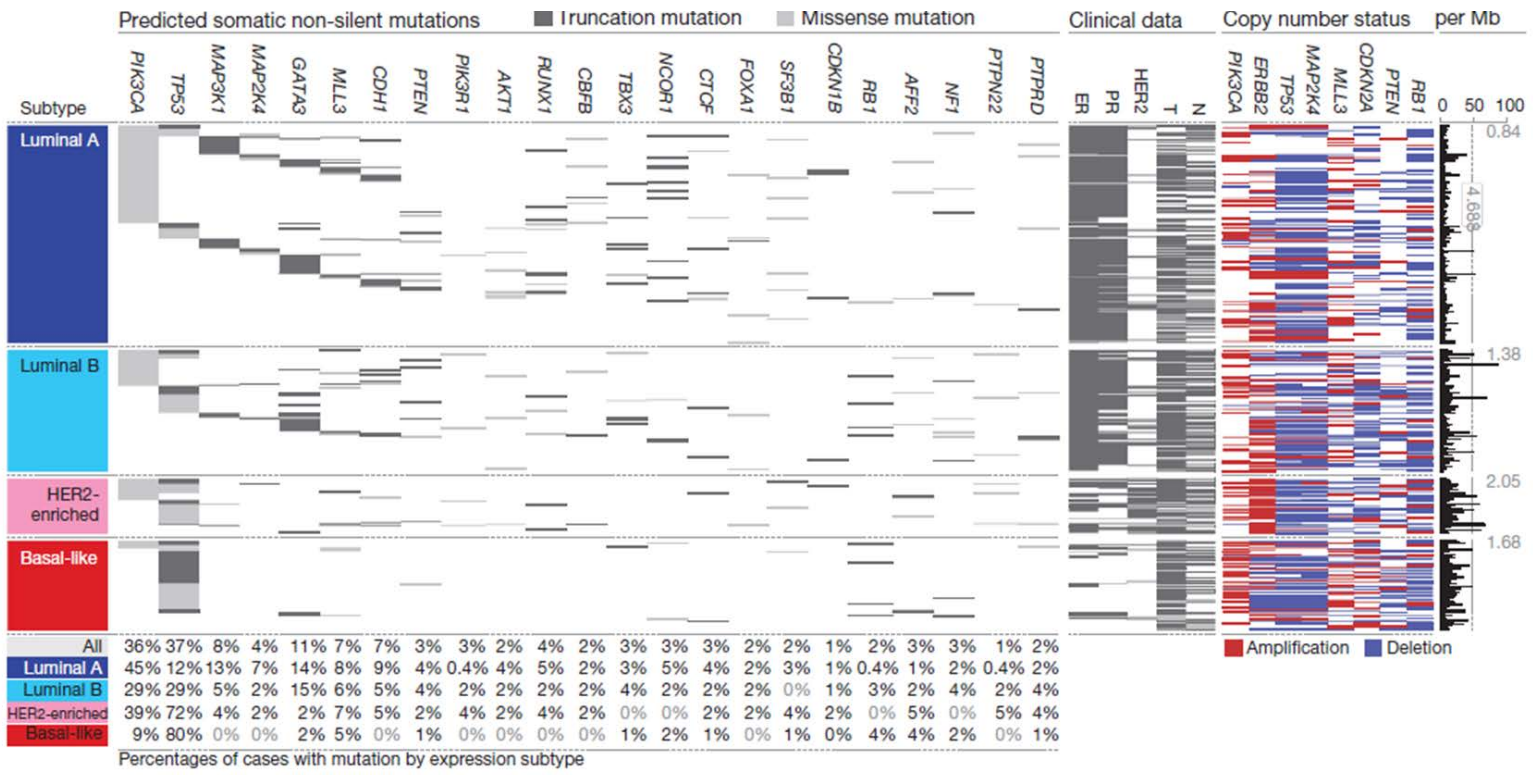
TN is not a synonym for basal-like phenotype!



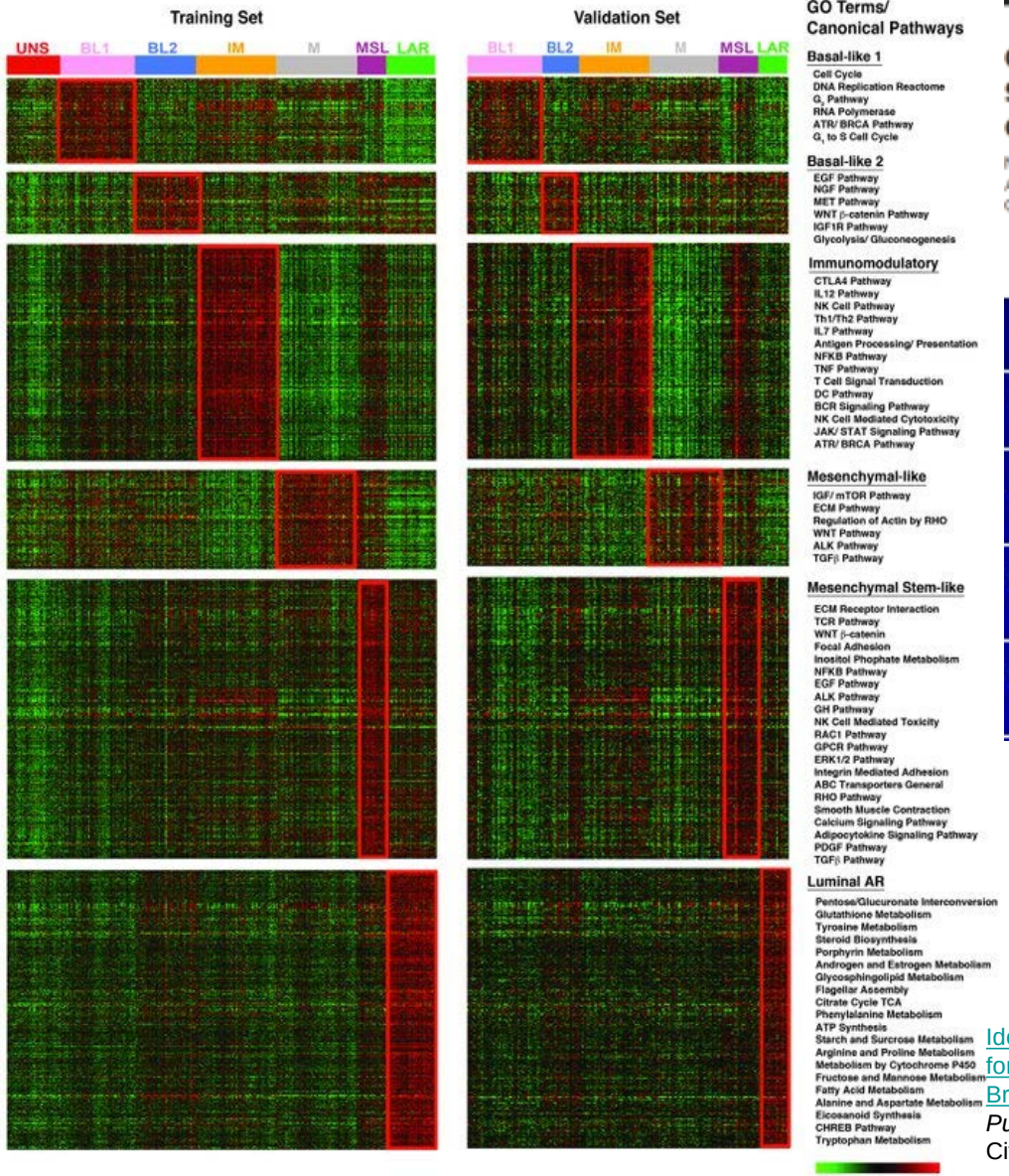
- There is heterogeneity within the molecular subtypes: EVEN THE SUBTYPES HAVE SUBTYPES

Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*



TNBC Subtypes



Biology of Human Tumors

Clinical Cancer Research 2015

Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-Negative Breast Cancer

Matthew D. Burstein[1], Anna Tsimelzon[2], Graham M. Poage[3], Kyle R. Covington[2], Alejandro Contreras[2,4], Suzanne A.W. Fuqua[3], Michelle I Savage[3], C. Kent Osborne[2], Susan G. Hilsenbeck[2], Jenny C. Chang[5], Gordon B. Mills[6], Ching C. Lau[7], and Powel H. Brown[3]

TNBC Subtype	Potential Therapeutic Targets
Luminal AR	AR; MUC1
Mesenchymal	Growth factor receptors (PDGFR, c-Kit)
BL-Immune suppressed	PD1, VTCN1 (immune suppressing molecule)
BL-Immune activated	STAT signal transduction molecules and cytokines

Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies
Brian D. Lehmann ... Yu Shyr, Jennifer A. Pietenpol
Published July 1, 2011
Citation Information: *J Clin Invest.* 2011;121(7):2750-2767. doi:10.1172/JCI45014.

Prognostic multigene signatures

- **Microarray and RT-PCR based assays**

- 21 gene signature (Oncotype Dx)
- 70 gene signature (MammaPrint)
- 76 gene signature (Rotterdam)
- 50 genes: Risk of Recurrence (ROR) score (Prosigna)
- 12 genes (Endopredict) & Epclin
- 5 genes (Molecular grade index)
- 2 gene ratio (H/I™)
- 97 gene: Genomic grade index (MapQuant Dx)
- 14 genes (BreastOncPx)
- 14 gene signature (Celera Metastasis Score™)

Multigene signatures

- **IHC and ISH based assays**

- 4 gene signature (IHC4; ER, PR, HER2 and Ki67)
- 5 gene signature (Mammostrat)
- 9 gene signature (Mammostrat Plus; 5 + ER, PR, HER2 and Ki67)
- 5 gene signature (ProEx™ Br)
- 3 gene signature (eXagenBC™)

- **Signatures based on a biological process**

- Wound-response signature (442 genes)
- Immune signatures (14 genes)
- Invasiveness Gene Signature (186 genes)

ASCO guideline recommendation

Published Ahead of Print on February 8, 2016 as 10.1200/JCO.2015.65.2289
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.65.2289

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Lyndsay N. Harris, Nofisat Ismaila, Lisa M. McShane, Fabrice Andre, Deborah E. Collyar, Ana M. Gonzalez-Angulo, Elizabeth H. Hammond, Nicole M. Kuderer, Minetta C. Liu, Robert G. Mennel, Cathy van Poznak, Robert C. Bast, and Daniel F. Hayes

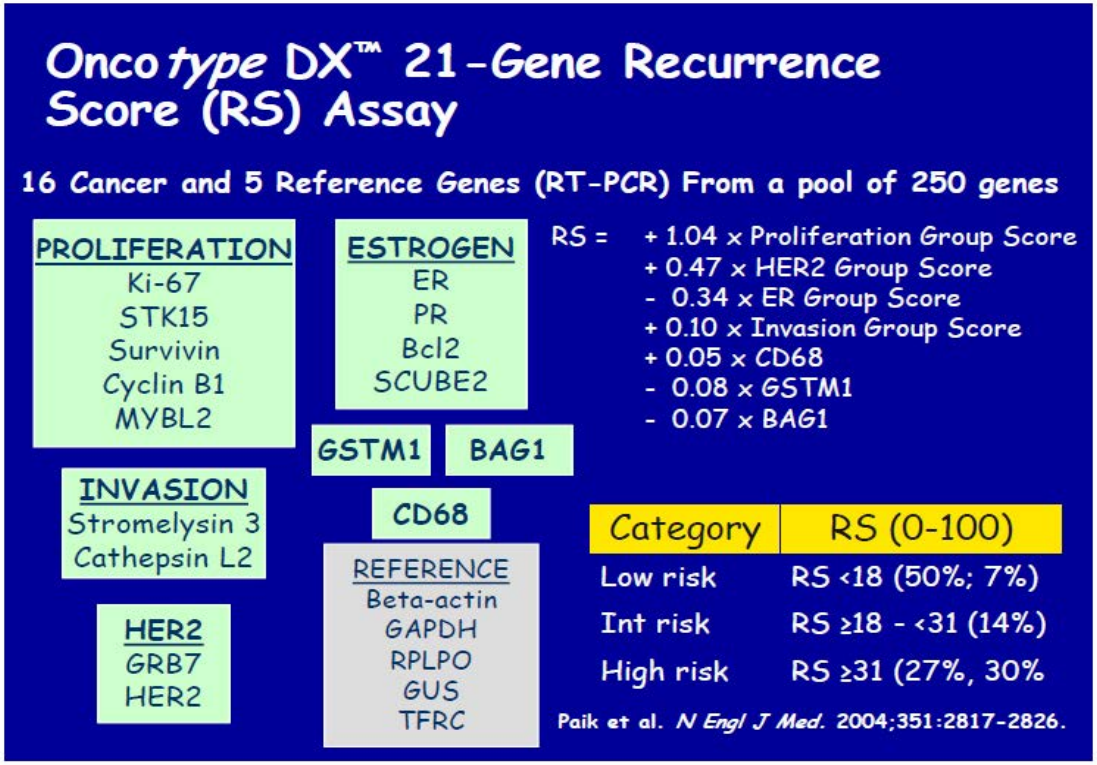
- In addition to ER, PR and HER2, there is sufficient evidence of clinical utility for the biomarker assays [Oncotype DX, EndoPredict, PAM50, Breast Cancer Index, and urokinase plasminogen activator and plasminogen activator inhibitor type 1 in HR+/HER2- Ln-. groups and can be used.
- These assays should not be used to guide treatment

decision in LN+, HER2+ or triple negative cancer

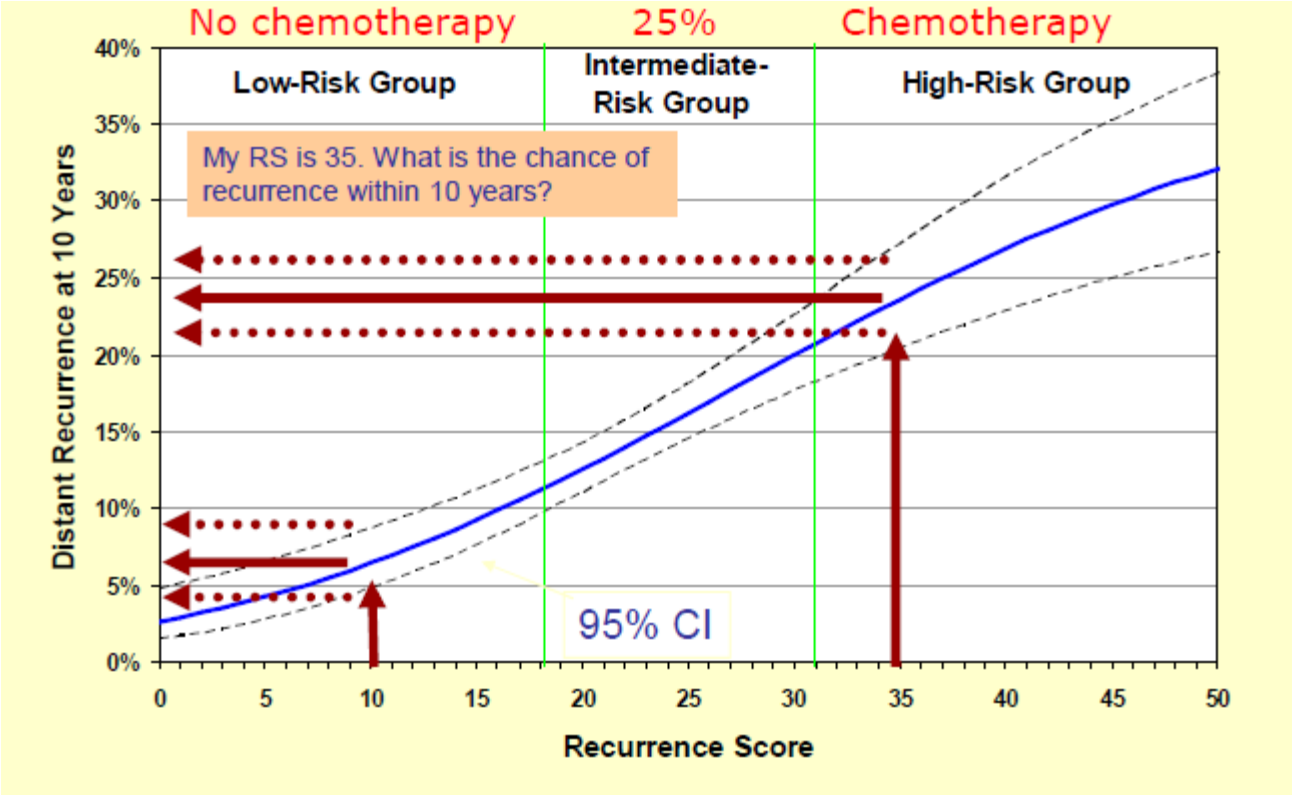
(No other molecular test (including ki67) should be used to direct treatment decision)

Oncotype DX™ 21-Gene Recurrence Score (RS) Assay

- Based on the expression levels of 21 genes, a recurrence score (RS) is generated

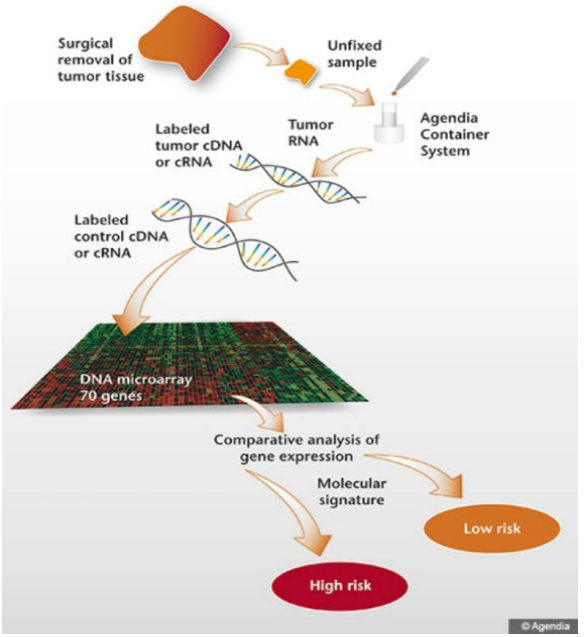


- The test is specifically applied to HR+ breast cancers with 0–3 positive nodes that are to be treated with hormonal therapy
- The general consensus is that hormonal therapy without systemic chemotherapy is sufficient for patients with a low RS.



Gnant M, Harbeck N, Thomssen C. St. Gallen 2011: summary of the consensus discussion. Breast Care (Basel). 2011;6:136–41.
111. van't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, et al. Gene expression profi ling predicts clinical outcome of breast cancer. Nature. 2002;415(6871):530–6.

MammaPrint assay



- 70-gene expression assay developed by The Netherlands Cancer Institute
- It is prognostic for early distant recurrence within the first 5 year after diagnosis and predictive for chemoresponse in poor prognostic patients

Prosigna test

- PAM50-based assay offered by NanoString Technologies (Seattle,WA)
- Based on the expression levels of 50 genes and clinical variables, a risk of recurrence (ROR) score is generated that correlates to one of the four molecular subtypes (lum A, lum B, HER2-enriched, and basal-like)

Multigene Prognostic Tests: Unresolved Issues

Is this approach really better than using a combination of clinical and pathologic factors supplemented by appropriate biomarkers detected by IHC (e.g., ER, PR, HER2 and Ki67)?

Molecular Testing in the Management of Patients with Breast Cancer Current Status and Future Directions. Stuart J. Schnitt, M.D., 2016.

Take Home Messages

- The accurate diagnosis of breast cancer is a critical prerequisite to the therapy decision-making process
- Most of the prognostic factors currently used in clinical practice are based on pathologic evaluation of the primary tumor and lymph nodes (the LN status are more and more detroned)
- ER, PR, and HER2 testing using ASCO/CAP guidelines remain the most important ancillary tests in the management of patients with breast cancer

Take Home Messages

- Among patients with ER+/HER2- (“luminal”) disease, multigene prognostic tests are of value in further defining risk of recurrence and potential benefit from chemotherapy in addition to endocrine therapy
- Ki67 is not highly predictive for utilisation of adjuvant chemotherapy
- New technologies and genomewide approaches have the potential to identify additional prognostic and predictive markers for invasive breast cancer
- The role of the pathologist has changed from that of descriptive pathology of Virchow, to an important team player in the age of personalised medicine.

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