Pathologic and Clinical Aspects of Luminal Subtype Breast Cancer

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OCTOBER 15, 2007

The Man to See
China's President Hu Jintao consolidates his power on the eve of the Party Congress

Long-Distance Love: How To Make It Work

Seinfeld's Back! Marriage, Fatherhood and That *Bee Movie*

TIME

Why Breast Cancer Is Spreading Around The World

9 771064 030005 39

www.time.com

78 BC, 8,102 gene->427 gene

Breast cancer subtypes:

- **normal-like**
- **luminal-like A,B,C**
- **basal-like**
- **Her2 overexpressing**

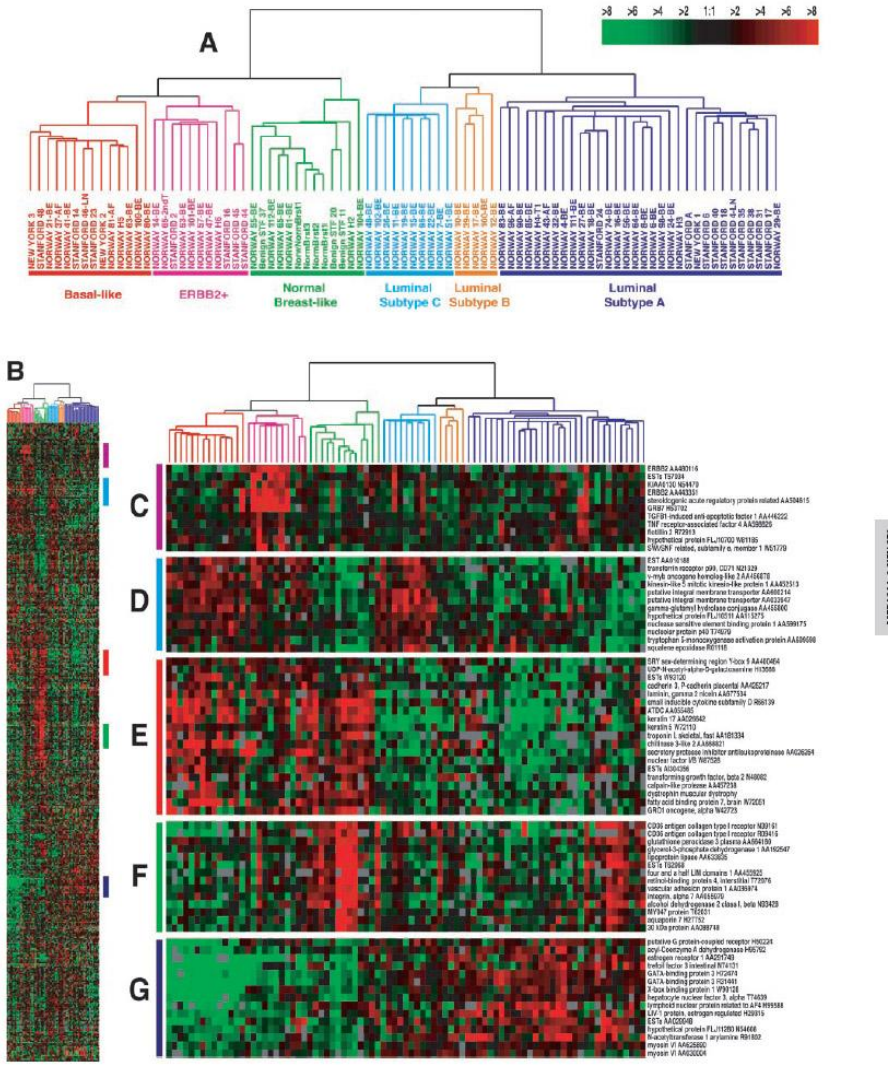


Fig. 1. Gene expression patterns of 85 experimental samples representing 78 carcinomas, three benign tumors, and four normal tissues, analyzed by hierarchical clustering using the 476 cDNA intrinsic clone set. (*A*) The tumor specimens were divided into five (or six) subtypes based on differences in gene expression. The cluster dendrogram showing the five (six) subtypes of tumors are colored as: luminal subtype A, dark blue; luminal subtype B, yellow; luminal subtype C, light blue; normal breast-like, green; basal-like, red; and ERBB2+, pink. (*B*) The full cluster diagram scaled down (the complete 456-clone cluster diagram is available as Fig. 4). The colored bars on the right represent the inserts presented in *C–G*. (*C*) *ERBB2* amplicon cluster. (*D*) Novel unknown cluster. (*E*) Basal epithelial cell-enriched cluster. (*F*) Normal breast-like cluster. (*G*) Luminal epithelial gene cluster containing *ER*.

↓

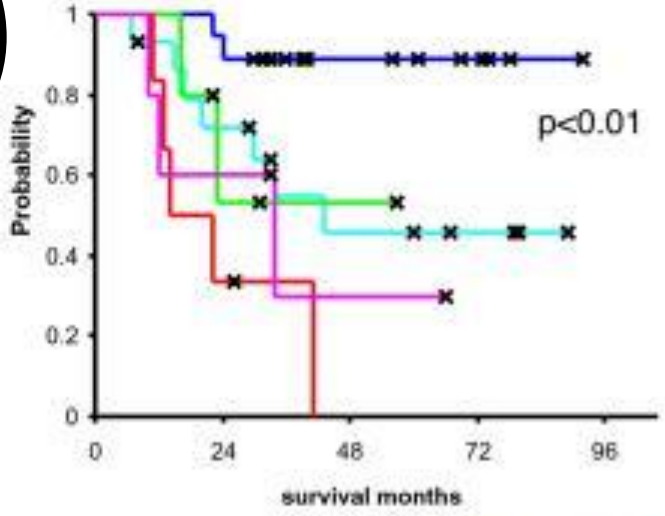
? sub-type specific therapies

Solie et al , Proc Natl Acad Sci U S A. 2001

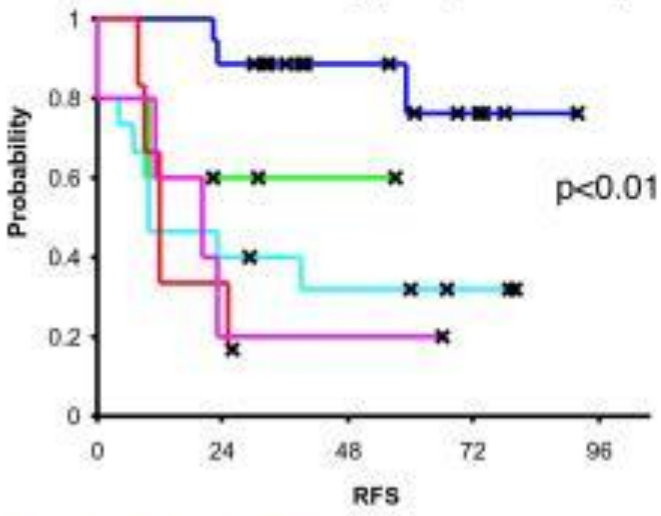
Subtype	Characteristics
Luminal A	**- High expression of ERa gene, GATA 3, XBP 1, LIV-1, HNF3A** **- Low expression of proliferative genes**
Luminal B	**- High expression of CCH, LAPTMB4, NSEP1 and CCNE1** **- Low expression of luminal specific genes including ER cluster comparing with luminal type A**
Normal breast like type	**- Fat tissue, nonepithelial mesenchymal tissue related genes** **- High expression of basal type related genes** **- Low expression of luminal type related genes**
HER2 positive	**- ERBB-2, GRB7**
Basal-like type	**- High expression of CK5/6, CK17, Her-1, c-kit, laminin, fatty acid binding pretein** **- Her-2(-), ER(-)**

OS

A 5 tumor subtypes (based upon Fig 1)



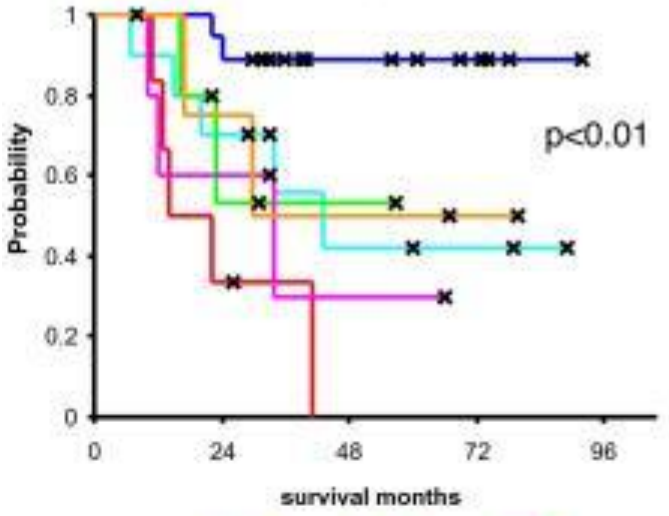
B 5 tumor subtypes (based upon Fig 1)



RFS

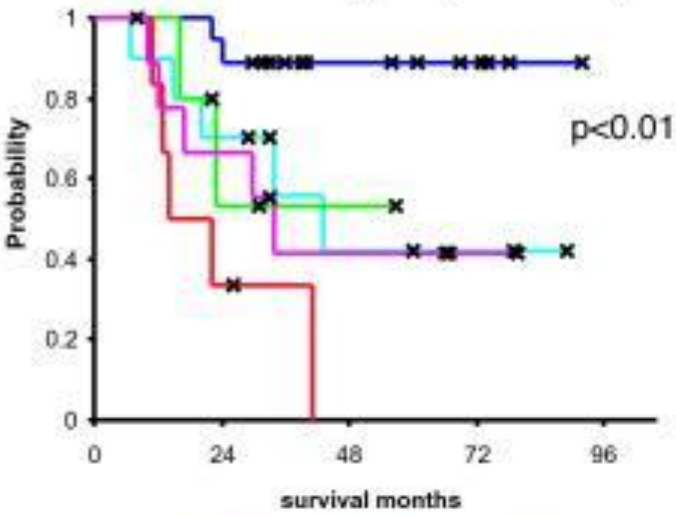
X Censored, Lum A, Lum B+C, NorB-like, Basal, ERBB2+

C 6 tumor subtypes (based upon Fig 1)



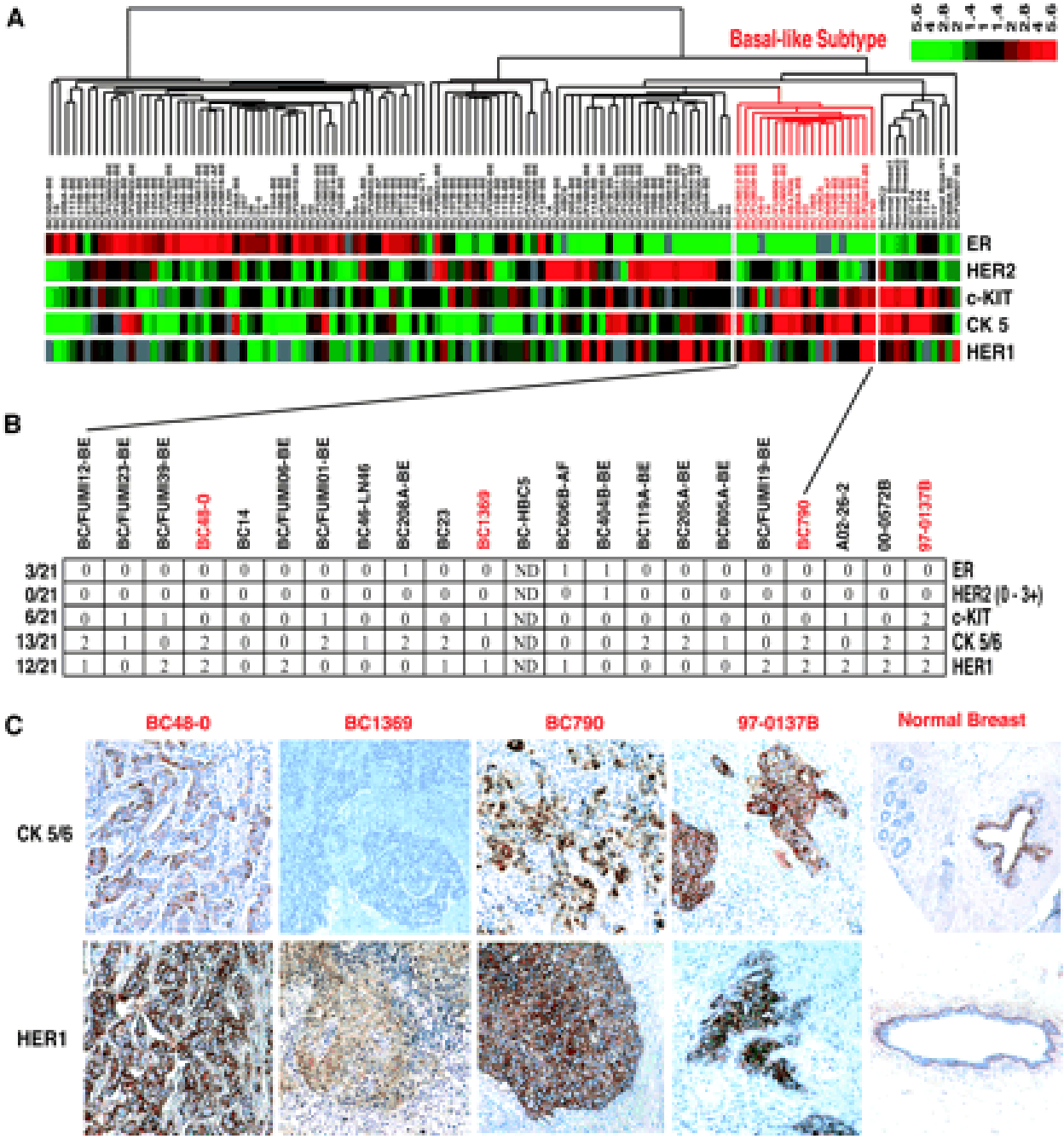
X Censored, Lum A, Lum C, NorB-like, Basal, ERBB2+, Lum B

D 5 tumor subtypes (based upon Fig 5)

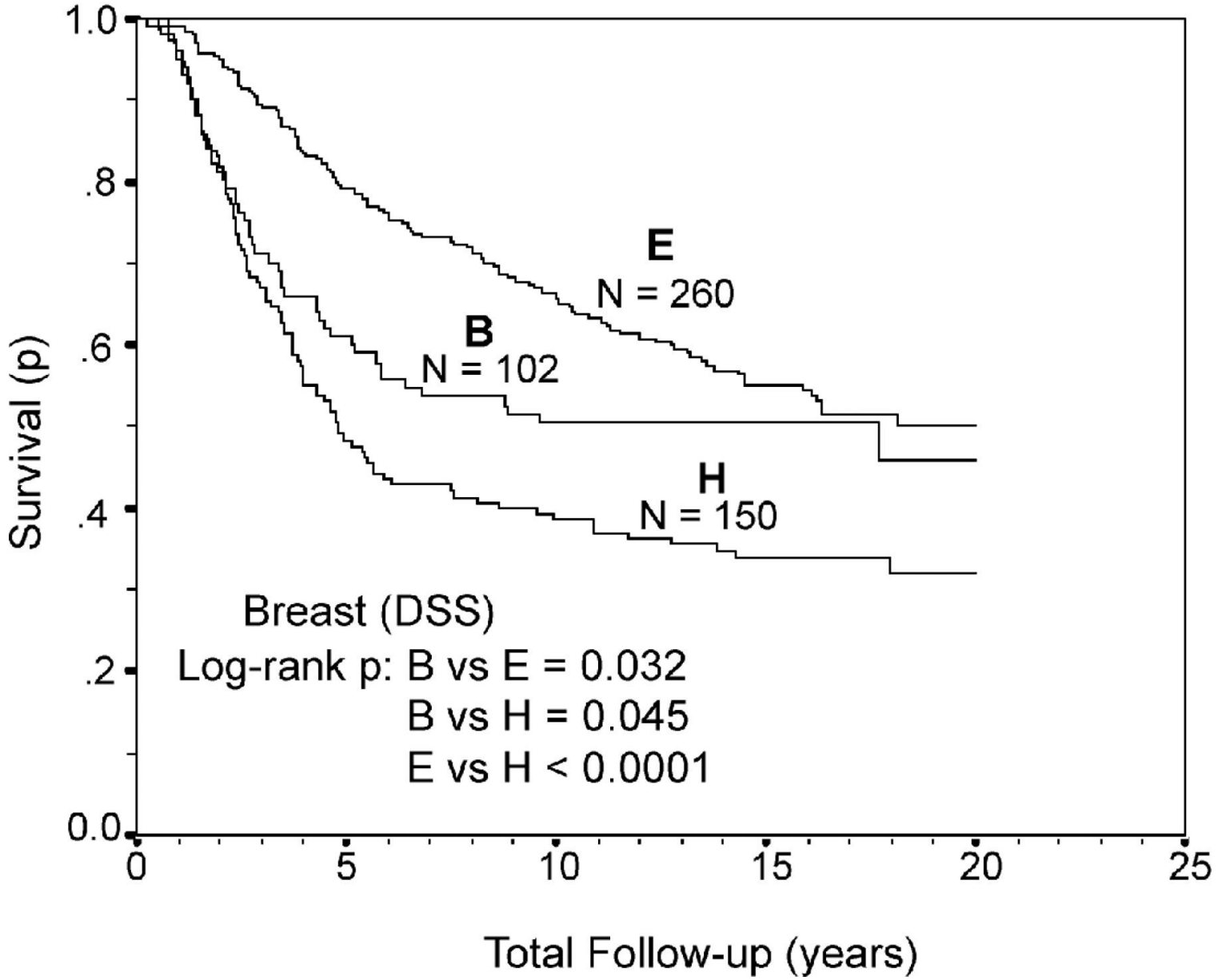


X Censored, Lum A, Lum C, NorB-like, Basal, ERBB2+ and Lum B

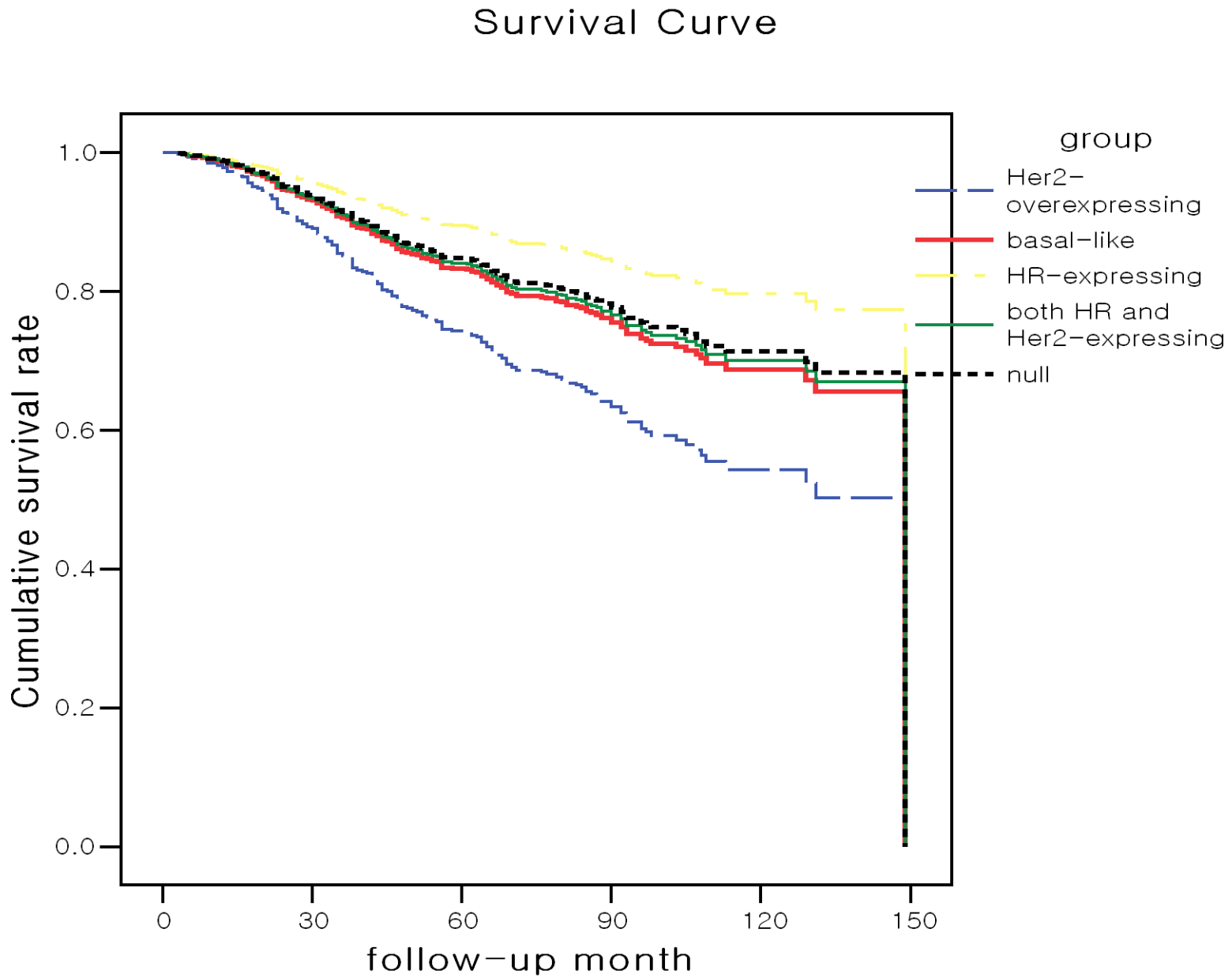
Solie et al , Proc Natl Acad Sci U S A. 2001



Nielsen TO et al, Clin Cancer Res. 2004



Nielsen TO et al, Clin Cancer Res. 2004



Kim MJ et al, Human pathology ,2008

Immunophenotyping to Approximate Molecular Subtype Using Three Markers

Brenton 2005

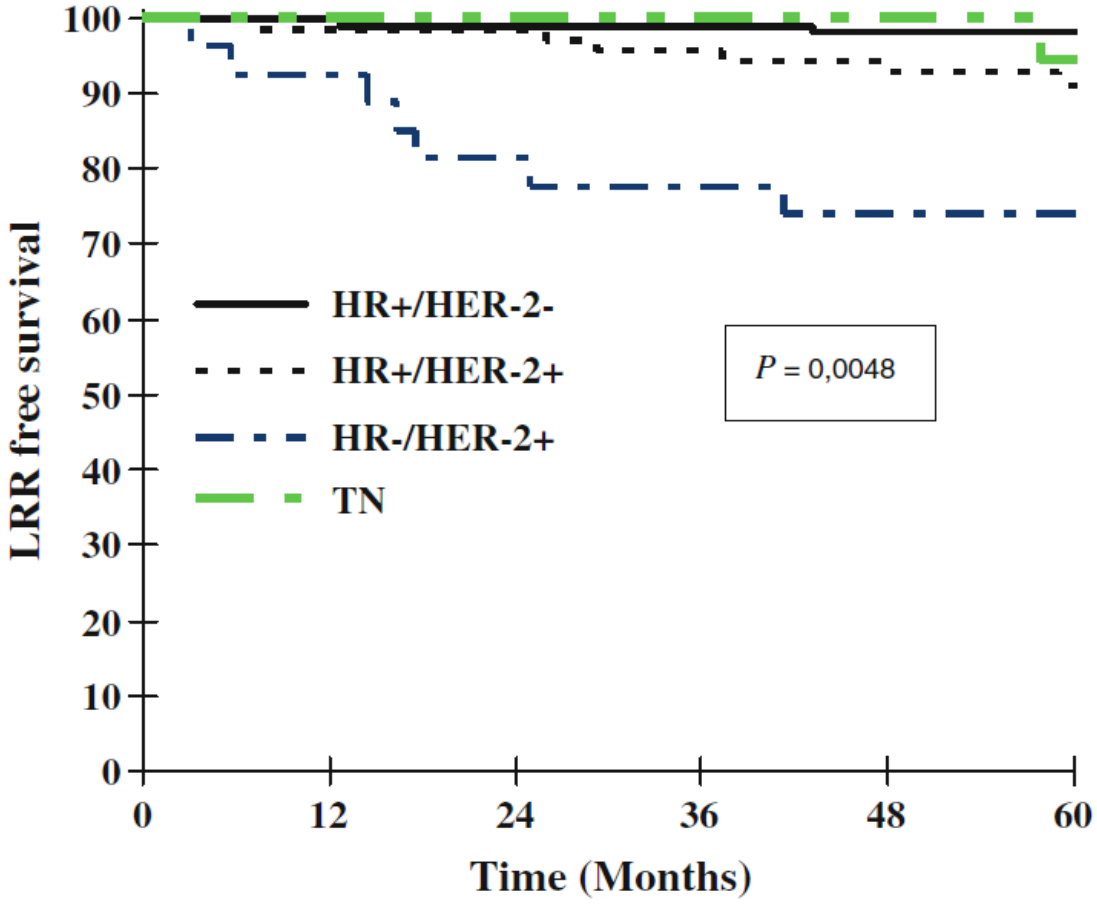
	Luminal A	Luminal B	HER2	Basal-like
ER	+	+	-	-
PR	+	+	-	-
HER2	-	+	+	-

Characteristics of breast cancer subtypes defined by gene expression profiles

	Luminal A	Luminal B	HER2-overexpressing	Basal-like	Normal-like
Approximate distribution:	55-65%	7-12%	6-10%	10-15%	5-10%
Tumor biology/ appearance:					
Presumed cellular origin	Luminal epithelial	Luminal epithelial	Basoluminal	Basal epithelial	Non-epithelial
Predominant tumor marker expression pattern:	ER+ and/or PR +, HER2-	ER+ and/or PR+, HER2+	ER-, PR-, HER2+	ER-, PR-, HER2-, CK 5/6+ and/or EGFR +	ER-, PR-, HER2-, CK5/6-, EGFR-
Stage at diagnosis:					
I	44%	39%	28%	24%	48%
II	47%	54%	53%	62%	39%
III-IV	9%	6%	19%	13%	13%
Grade:					
Poorly differentiated	58%	56%	70%	82%	81%
Mod./well-differentiated	42%	44%	30%	18%	19%
Clinical characteristics:					
A verage 5-year survival:	75-90%	45-90%	20-75%	30-80%	50-87%
Targeted therapies:	Tamoxifen	Tamoxifen, possibly trastuzumab	Trastuzumab	None available	None available

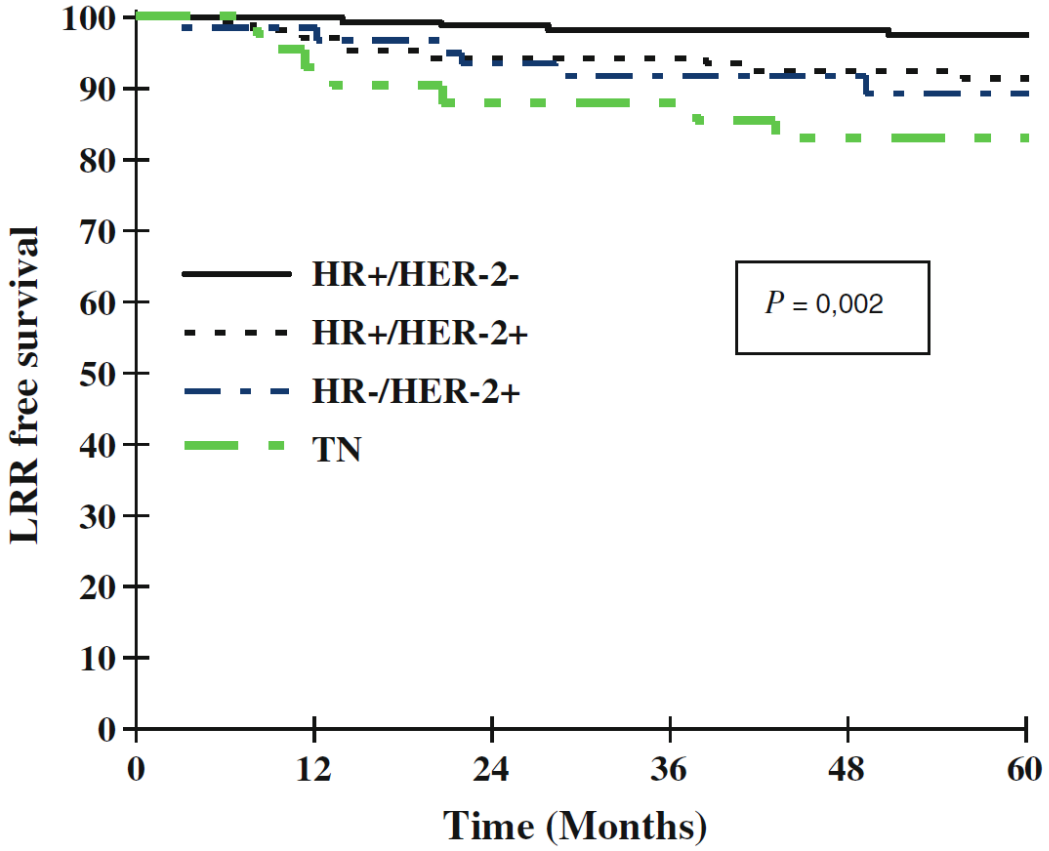
Phipps AI et al, Breast Cancer Epidemiology, LLC 2010

Locoregional recurrence free survival in patients treated with breast-conserving surgery



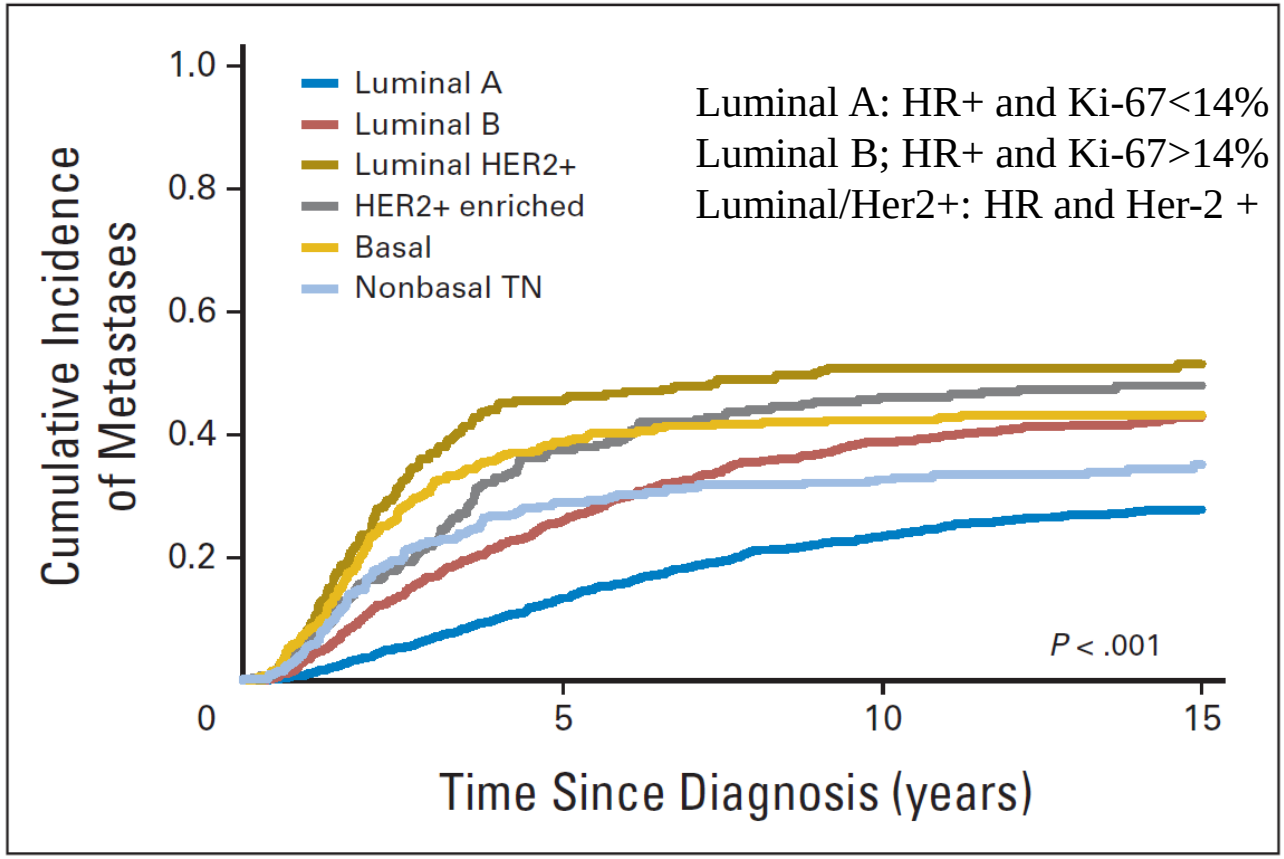
Gabos Z, et al. Breast Cancer Res Treat 2010

Locoregional recurrence free survival in patients treated with modified radical mastectomy



Gabos Z, et al. Breast Cancer Res Treat 2010

Cumulative incidence curves of first distant metastasis by breast cancer subtype.



Kennecke H, et al. J Clin Oncol 2 010

Frequency of Site-Specific Metastasis Among Patients Who Developed Distant Disease

Subtype	No. of Patients	Brain		Liver		Lung		Bone		Distant Nodal		Pleural/ Peritoneal		Other		Unknown	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Luminal A	458	35	7.6	131	28.6	109	23.8	305	66.6	73	15.9	129	28.2	62	13.5	36	7.9
Luminal B	378	41	10.8	121	32.0	115	30.4	270	71.4	88	23.3	133	35.2	73	19.3	13	3.4
HER2 +, ER/PR +	117	18	15.4	52	44.4	43	36.8	76	65.0	26	22.2	40	34.2	16	13.7	6	5.1
HER2 +, ER/PR -	136	39	28.7	62	45.6	64	47.1	81	59.6	34	25.0	43	31.6	23	16.9	6	4.4
Basal-like	159	40	25.2	34	21.4	68	42.8	62	39.0	63	39.6	47	29.6	38	23.9	11	6.9
TN nonbasal	109	24	22.0	35	32.1	39	35.8	47	43.1	39	35.8	31	28.4	28	25.7	6	5.5
P		< .001		< .001		< .001		< .001		< .001		.3214		.0056		.1338	

NOTE. *P* values were obtained using Pearson's X2 test.
Abbreviations: HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; TN, triple negative.

Kennecke H, et al. J Clin Oncol 2010

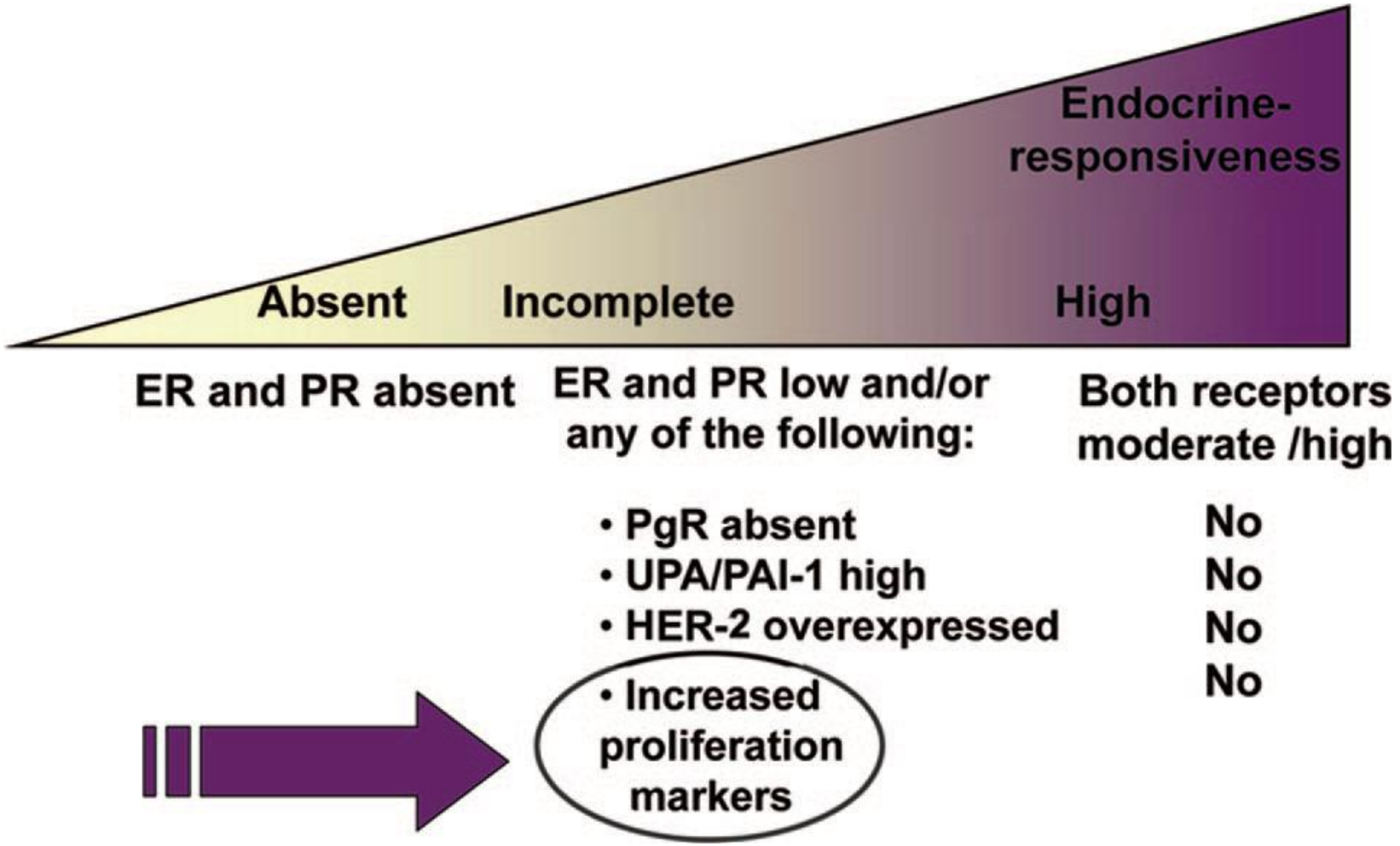
Multivariate Analysis of Metastatic Site Among Patients With Distant Relapse

Variable	Brain		Liver		Lung		Bone		Distant Nodal		Pleural/ Peritoneal		Other	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Luminal A (reference)	1		1		1		1		1		1		1	
Luminal B	1.4	0.8 to 2.3	1.1	0.8 to 1.5	1.4	1.0 to 1.9	1.2	0.9 to 1.7	1.4	0.9 to 2.0	1.3	0.9 to 1.8	1.3	0.8 to 1.9
HER2 +, ER/PR +	2.1	1.1 to 4.1	2.3	1.4 to 3.7	2.0	1.3 to 3.3	0.9	0.6 to 1.5	1.1	0.6 to 1.9	1.3	0.8 to 2.0	0.8	0.4 to 1.5
HER2 +, ER/PR +	5.3	3.0 to 9.2	1.7	1.1 to 2.6	3.2	2.1 to 5.0	0.9	0.6 to 1.3	1.5	0.9 to 2.5	1.1	0.7 to 1.7	1.1	0.6 to 2.0
Basal-like	3.6	2.1 to 6.4	0.5	0.3 to 0.9	2.5	1.6 to 3.9	0.4	0.2 to 0.6	2.9	1.8 to 4.5	1.0	0.6 to 1.6	2.0	1.2 to 3.3
TN nonbasal	3.6	1.9 to 6.9	1.0	0.6 to 1.7	2.1	1.3 to 3.5	0.4	0.2 to 0.6	2.9	1.7 to 4.9	0.9	0.5 to 1.5	1.8	1.0 to 3.2
T3/4	0.2	0.1 to 0.4	0.5	0.3 to 0.8	—	—	—	—	—	—	—	—	—	—
LVI, yes	—	—	1.4	1.1 to 1.9	0.7	0.6 to 1.0	—	—	—	—	—	—	—	—
Chemotherapy, yes	—	—	2.3	1.8 to 3.1	—	—	—	—	2.1	1.6 to 2.9	1.5	1.2 to 2.0	2.2	1.6 to 3.1
Hormones, yes	—	—	—	—	—	—	2.2	1.6 to 3.0	—	—	—	—	1.5	1.0 to 2.3
Age > 50 years	0.5	0.4 to 0.7	—	—	—	—	0.6	0.5 to 0.8	—	—	—	—	—	—

NOTE. Variables included were T stage, N stage, LVI, age, chemotherapy, and hormone therapy. Nodal stage was not significant in any of the univariate analyses and thus not included in the multivariate model. A blank (—) field indicates that the variable was not significant in the univariate analysis and not included in the multivariate analysis. Boldface indicates statistical significance. Abbreviations: OR, odds ratio; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; TN, triple negative; LVI, lymphovascular invasion.

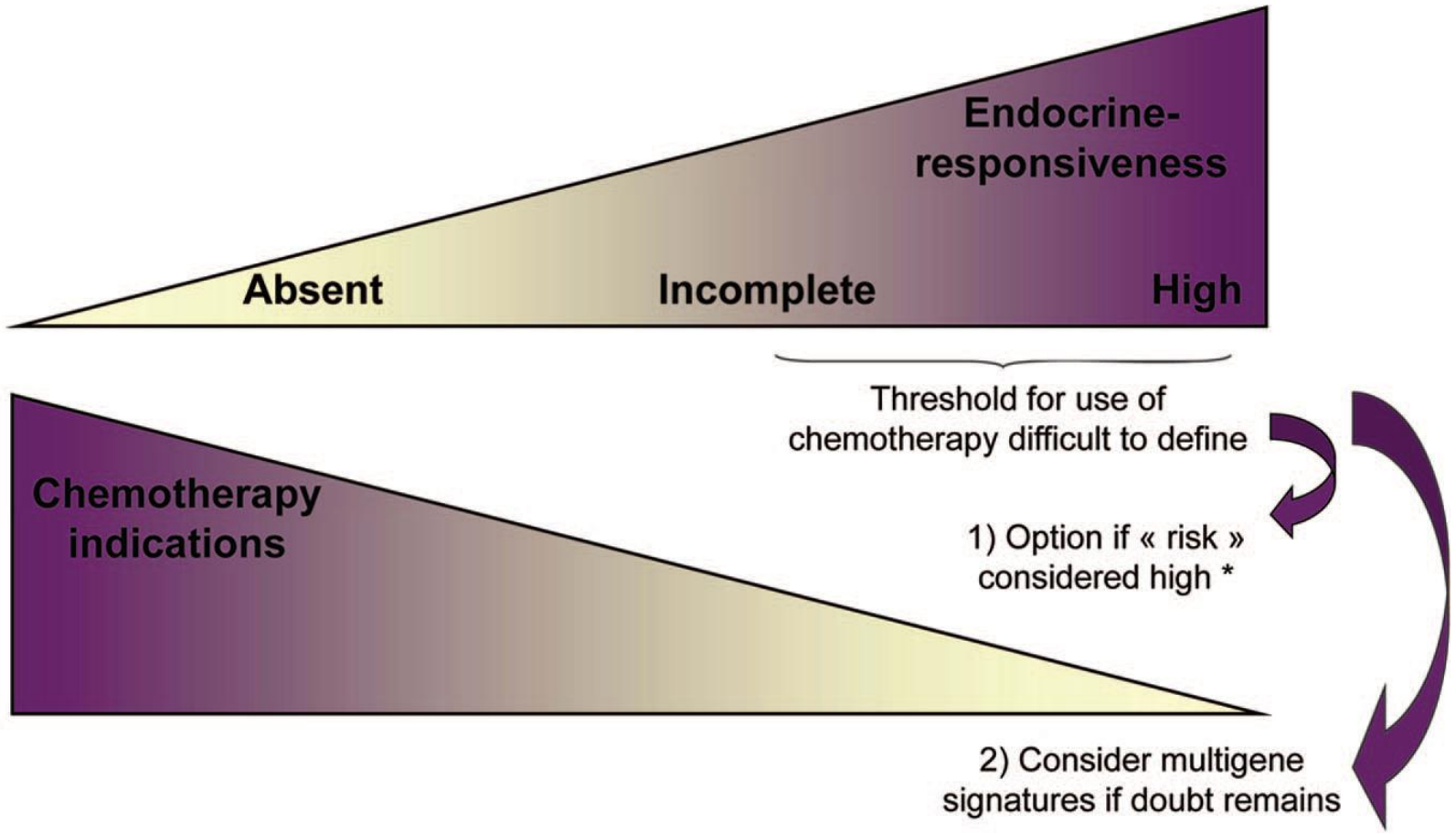
Kennecke H, et al. J Clin Oncol 2010

St. Gallen 2007: Endocrine responsiveness. From a biological continuum to “practical” subgroups



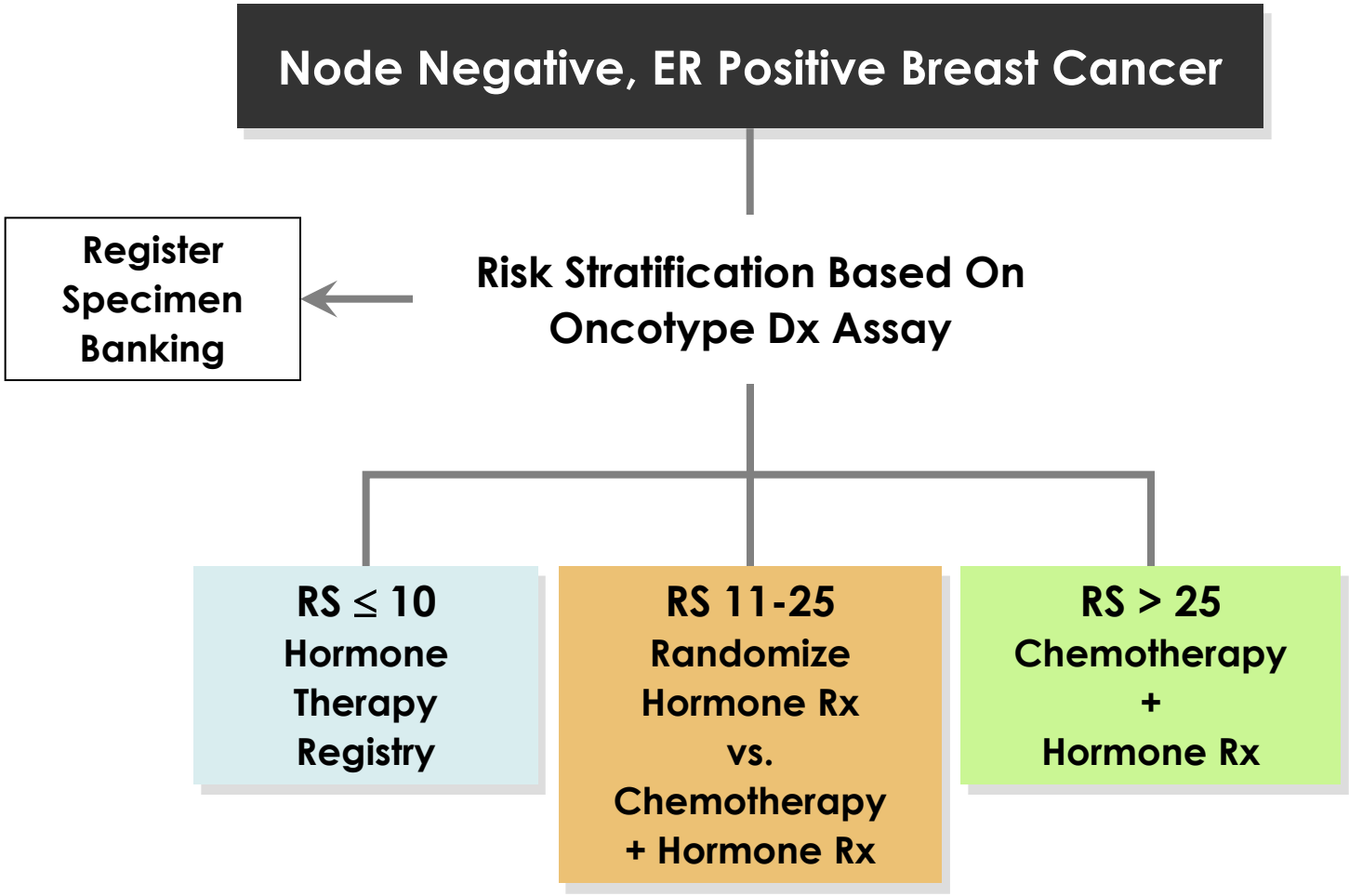
Piccart MJ . The Oncologist, 2011

St. Gallen 2009: Threshold for chemoendocrine therapy

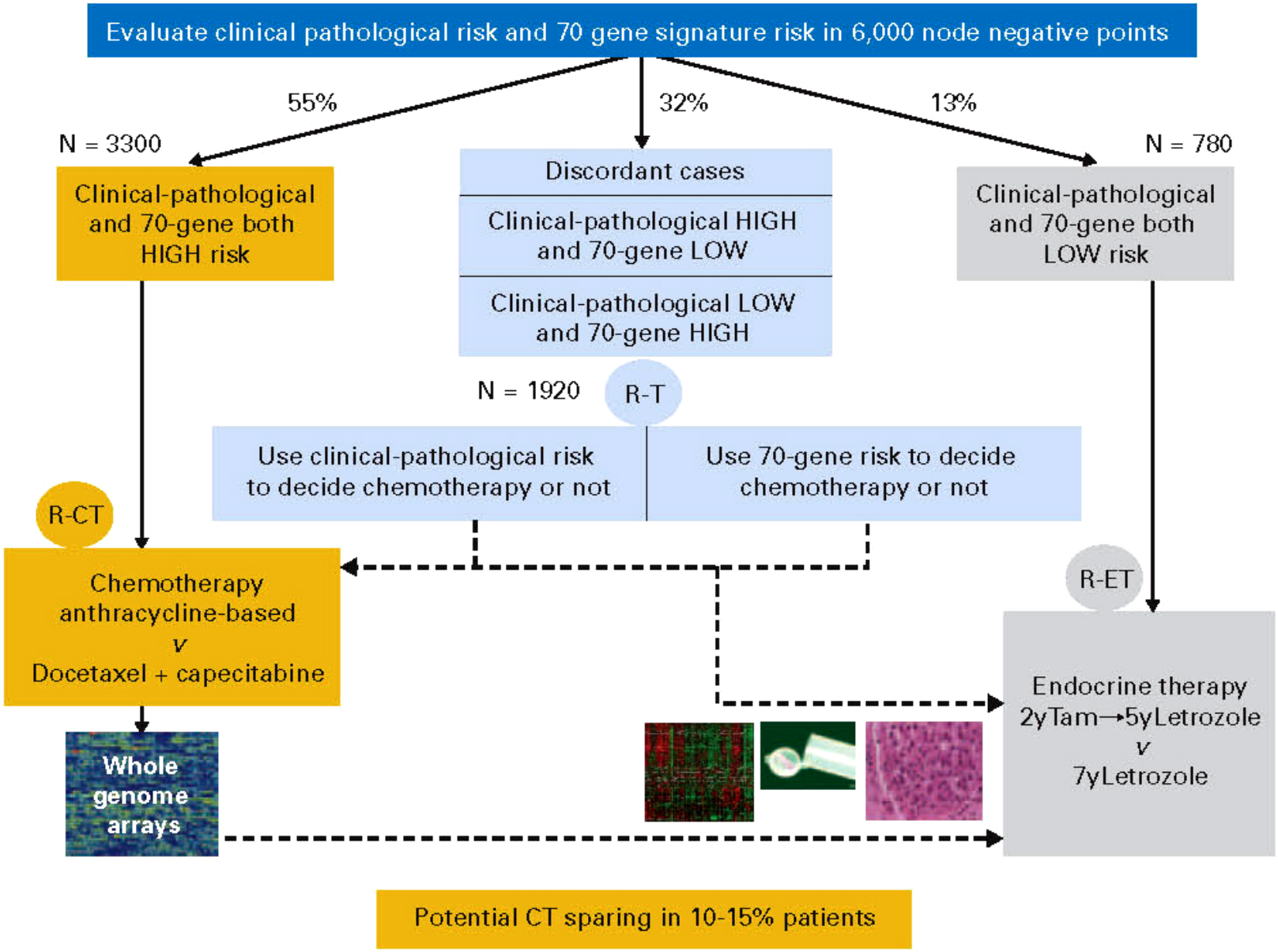


* pT > 5cm, extensive peritumoral vascular invasion, ≥ 4 positive nodes

Piccart MJ , The Oncologist 2011

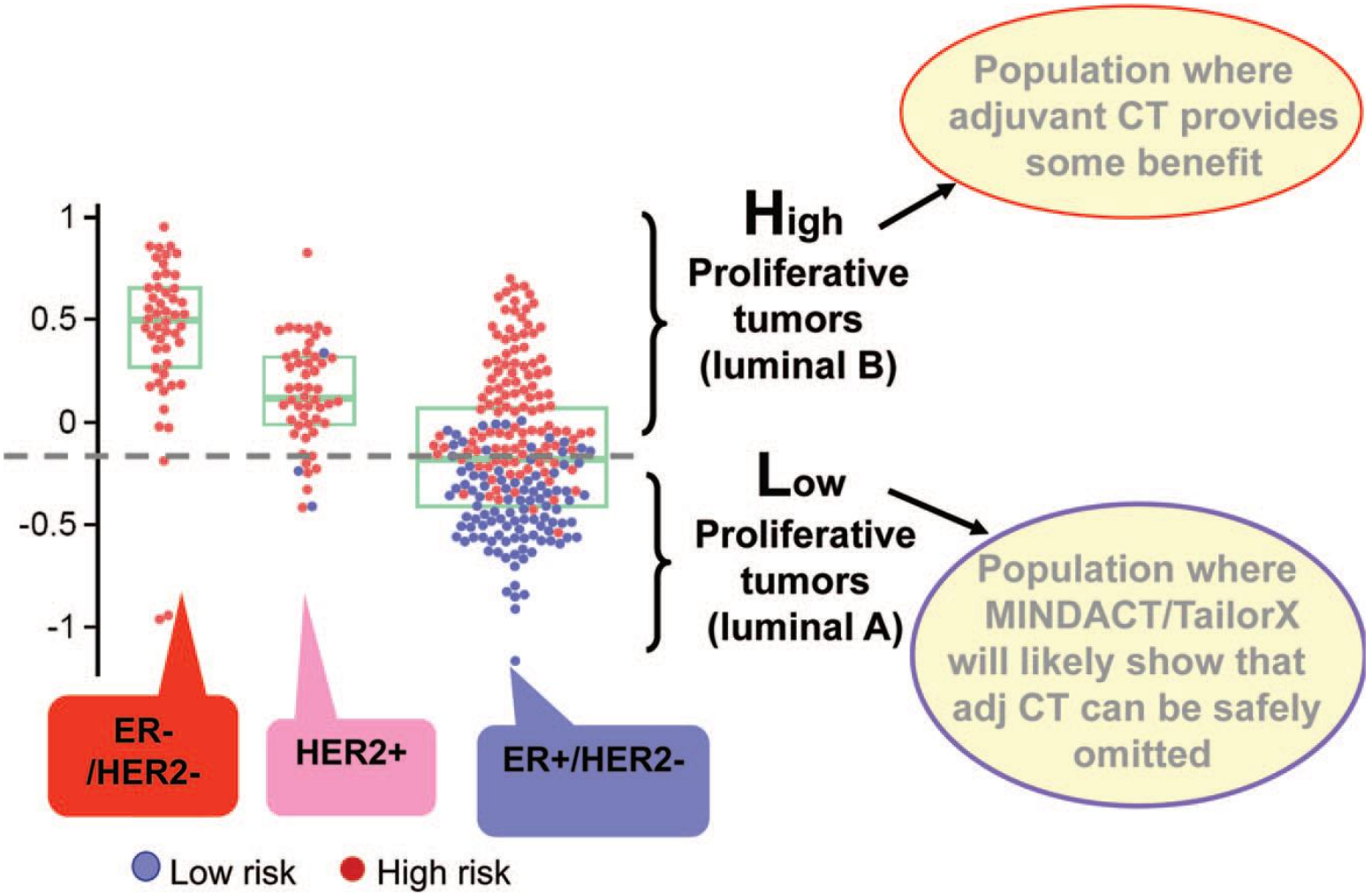


The schema for the TAILORx trial. Stratification of patients into prognostic risk scores (RS) determines the individualized treatment arm.



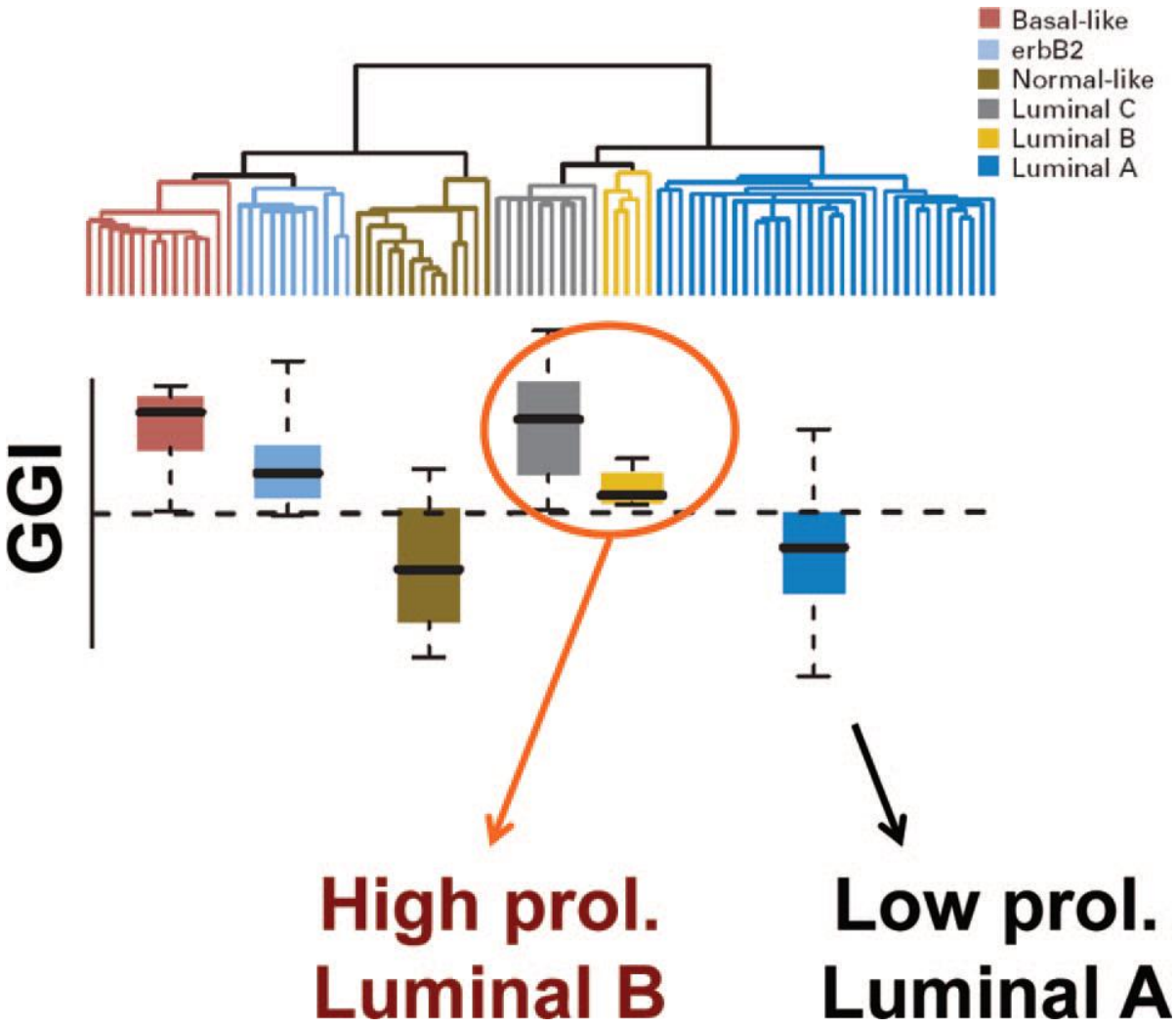
J Clin Oncol 2008;26:733

Segregation of breast cancer subtypes using a gene expression proliferation module

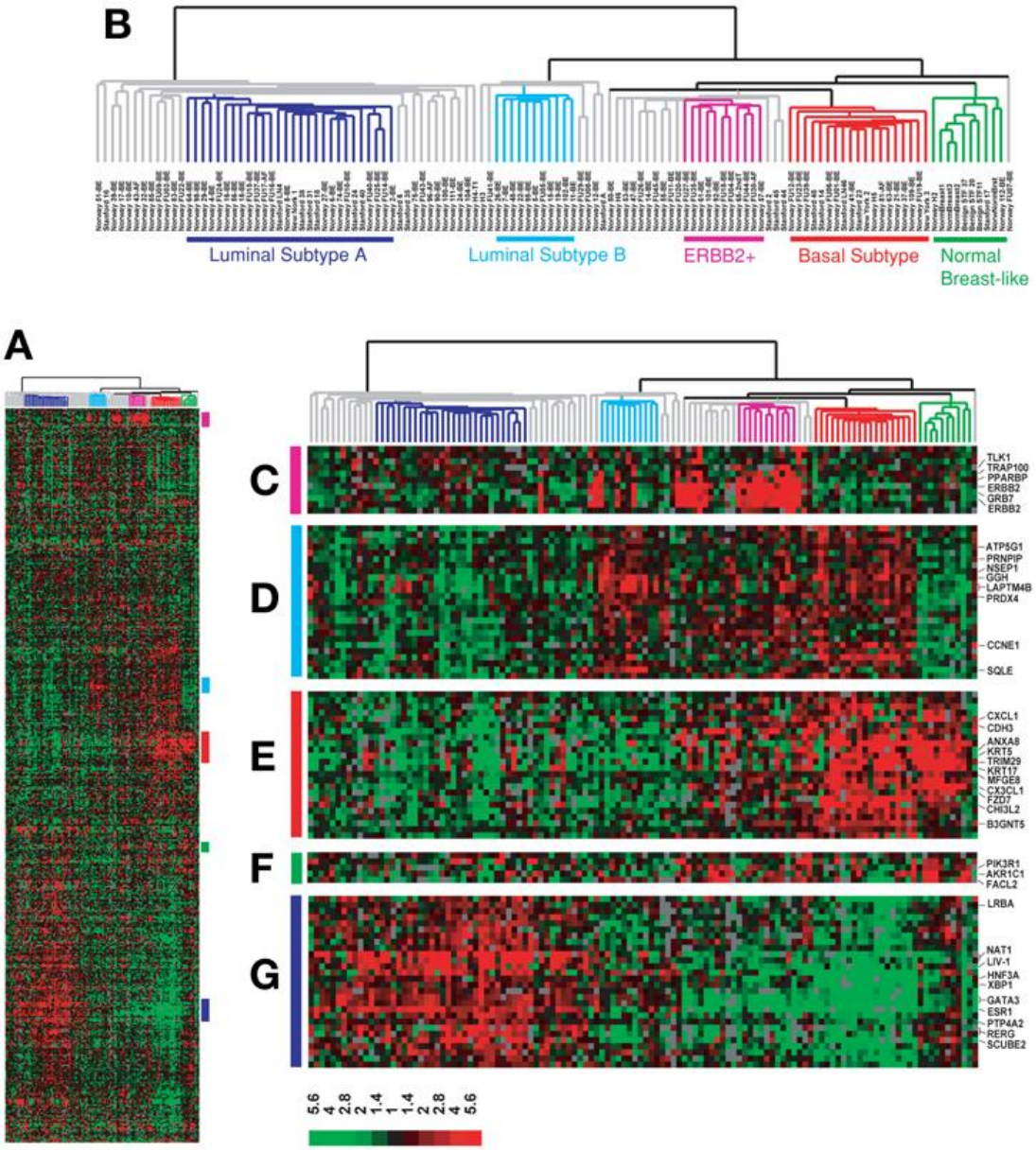


Piccart MJ . The Oncologist, 2011

Genomic Grading Index



Loi S et al, JCO, 2007


B
Luminal Subtype A
Luminal Subtype B
ERBB2+
Basal Subtype
Normal Breast-like
A
C
D
E
F
G
TLK1
TRAP100
PPARBP
ERBB2
GRB7
ERBB2
ATP5G1
PRNPIP
NSEP1
GSH
LAPTM4B
PRDX4
CCNE1
SQLE
CXCL1
CDH3
ANXA8
KRT5
TRIM29
KRT17
MFGE8
CX3CL1
FZD7
CHI3L2
B3GNT5
PIK3R1
AKR1C1
FACL2
LRBA
NAT1
LIV-1
HNF3A
XBP1
GATA3
ESR1
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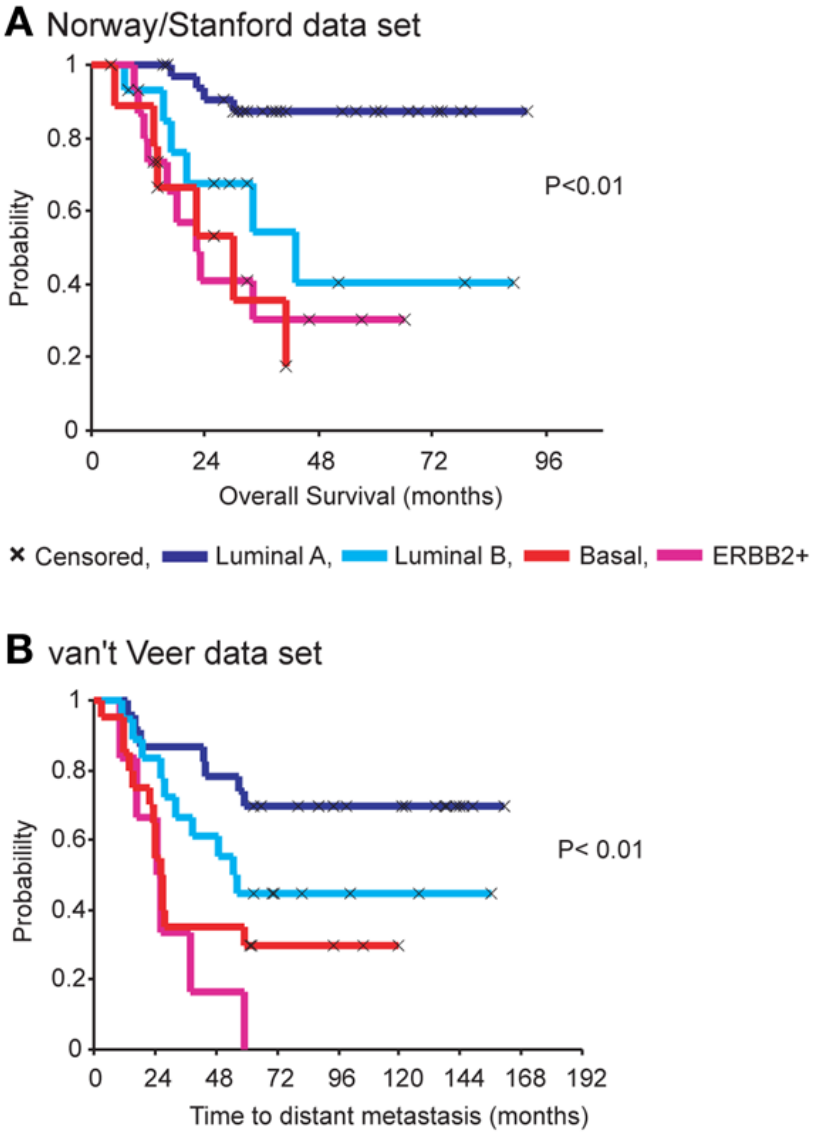
2.8
4
5.6


A Norway/Stanford data set
Probability
1
0.8
0.6
0.4
0.2
0
0
24
48
72
96
Overall Survival (months)
P<0.01
× Censored, Luminal A, Luminal B, Basal, ERBB2+
B van't Veer data set
Probability
1
0.8
0.6
0.4
0.2
0
0
24
48
72
96
120
144
168
192
Time to distant metastasis (months)
P< 0.01

Surrogate definitions of intrinsic subtypes of breast cancer

Intrinsic Subtype (1)	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** **ER and/or PgR positive** **HER2 negative** **Ki-67 low (<14%)**	**This cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping .** **Local quality control of Ki-67 staining is important.**
Luminal B**	**'Luminal B (HER2 negative)'** **ER and/or PgR positive** **HER2 negative** **Ki-67 high**	**Genes indicative of higher proliferation are markers of poor prognosis in multiple genetic assays . If reliable Ki-67 measurement is not available, some alternative assessment of tumor proliferation such as grade may be used to distinguish between 'Luminal A' and 'Luminal B (HER2 negative)'.**
	'Luminal B (HER2 positive)' **ER and/or PgR positive** **Any Ki-67** **HER2 over-expressed or amplified**	**Both endocrine and anti-HER2 therapy may be indicated.**
Erb-B2 Overexpression	**'HER2 positive (non luminal)'** **HER2 over-expressed or amplified** **ER and PgR absent**	**Approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype but 'triple negative' also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence.**
'Basal-like'	**'Triple negative (ductal)'** **ER and PgR absent** **HER2 negative**	**Staining for basal keratins although shown to aid selection of true** **basal-like tumors, is considered insufficiently reproducible for general use.**

Goldhirsch A, et al. Ann Oncol. 2011

Systemic treatment recommendations for subtypes

'Subtype'	Type of therapy	Notes on therapy
'Luminal A'	**Endocrine therapy alone**	**Few require cytotoxics (e.g. high nodal status or other indicator of risk: see text).**
'Luminal B (HER2 negative)'	**Endocrine +/-cytotoxic therapy**	**Inclusion and type of cytotoxics may depend on level of endocrine receptor expression, perceived risk and patient preference.**
'Luminal B (HER2 positive)'	**Cytotoxics + anti-HER2 + endocrine therapy**	**No data are available to support the omission of cytotoxics in this group.**
'HER2 positive (non luminal)'	**Cytotoxics + anti-HER2**	**Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.**
'Triple negative (ductal)'	**Cytotoxics**	
'Special histological types'*		
A. Endocrine responsive	**Endocrine therapy**	
B. Endocrine nonresponsive	**Cytotoxics**	**Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).**

***Special histological types: Endocrine responsive (cribriform, tubular, and mucinous); Endocrine nonresponsive (apocrine, medullary, metaplastic).adenoid cystic and metaplastic).**

Goldhirsch A, et al. Ann Oncol. 2011

Ki67 Index, HER2 Status, and Prognosis of Patients With Luminal B Breast Cancer

Table 2. Association of patient and tumor characteristics with relapse-free survival and breast cancer–specific survival among 883 patients with lymph node–negative, hormone receptor–positive breast cancer with complete data for covariates and who did not receive any adjuvant systemic therapy*

	Relapse-free survival (n = 883)		Breast cancer–specific survival (n = 879)	
Characteristic and comparison	**HR (95% CI)**	***P* value†**	**HR (95% CI)**	***P* value†**
Age at diagnosis‡	1.00 (0.99 to 1.01)	.43	1.01 (0.99 to 1.02)	.30
Grade (3 vs 2 or 1)	1.10 (0.84 to 1.44)	.50	1.24 (0.88 to 1.75)	.22
Tumor size (>2 cm vs ≤2 cm)	1.43 (1.09 to 1.86)	.010	1.59 (1.14 to 2.23)	.007
LVI (positive vs negative)	1.49 (1.04 to 2.13)	.031	1.72 (1.11 to 2.66)	.015
Breast cancer subtypes				
Luminal B vs luminal A	1.43 (1.08 to 1.90)	.013	1.84 (1.28 to 2.63)	.001
Luminal/HER2+ vs luminal A	1.57 (0.97 to 2.54)	.066	2.08 (1.15 to 3.76)	.016

* Multivariable Cox proportional hazards regression analyses were used to estimate the adjusted HRs for the breast cancer subtypes. HR = hazard ratio;

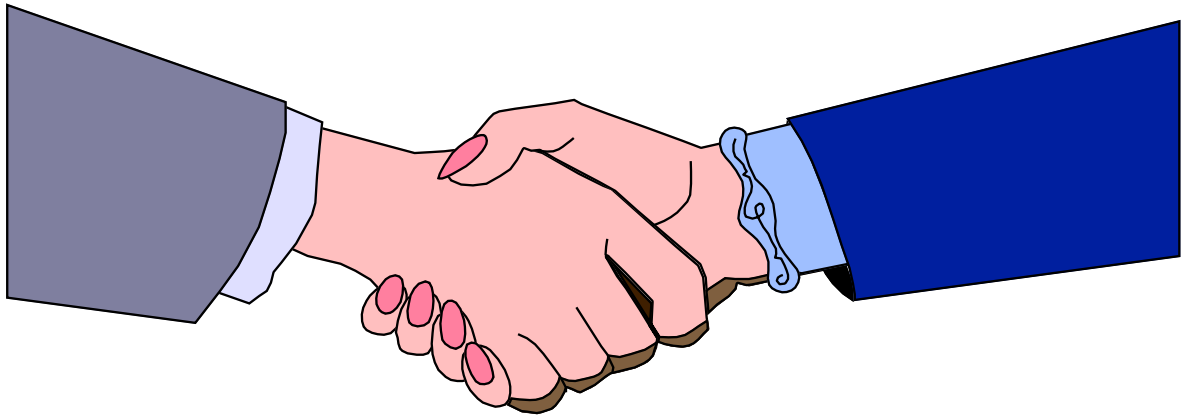
The best Ki67 index cut point to distinguish luminal B from luminal A tumors was 13.25%.

Cheang MCU et al, J Natl Cancer Inst 2009;101: 736 – 750

In St Gallen 2011 Recommendation;
This cut-point is derived from comparison with gene array data as a prognostic factor. Optimal cut-points in Ki-67 labelling index for prediction of efficacy of endocrine or cytotoxic therapy may vary.

Summary

- Luminal subtype must be subclassified
  into luminal A and B (Her-2 positive and negative),
  and managed differently.
- Luminal A and B breast cancers appear to be distinguished by the expression of estrogen receptor, progesterone receptor, HER2, and Ki67 proteins.
- In the analysis of the biomarkers , careful approach is essential to decide optimal cut-points in local laboratory.



Thank You !