How to use genomic tests in early breast cancer?

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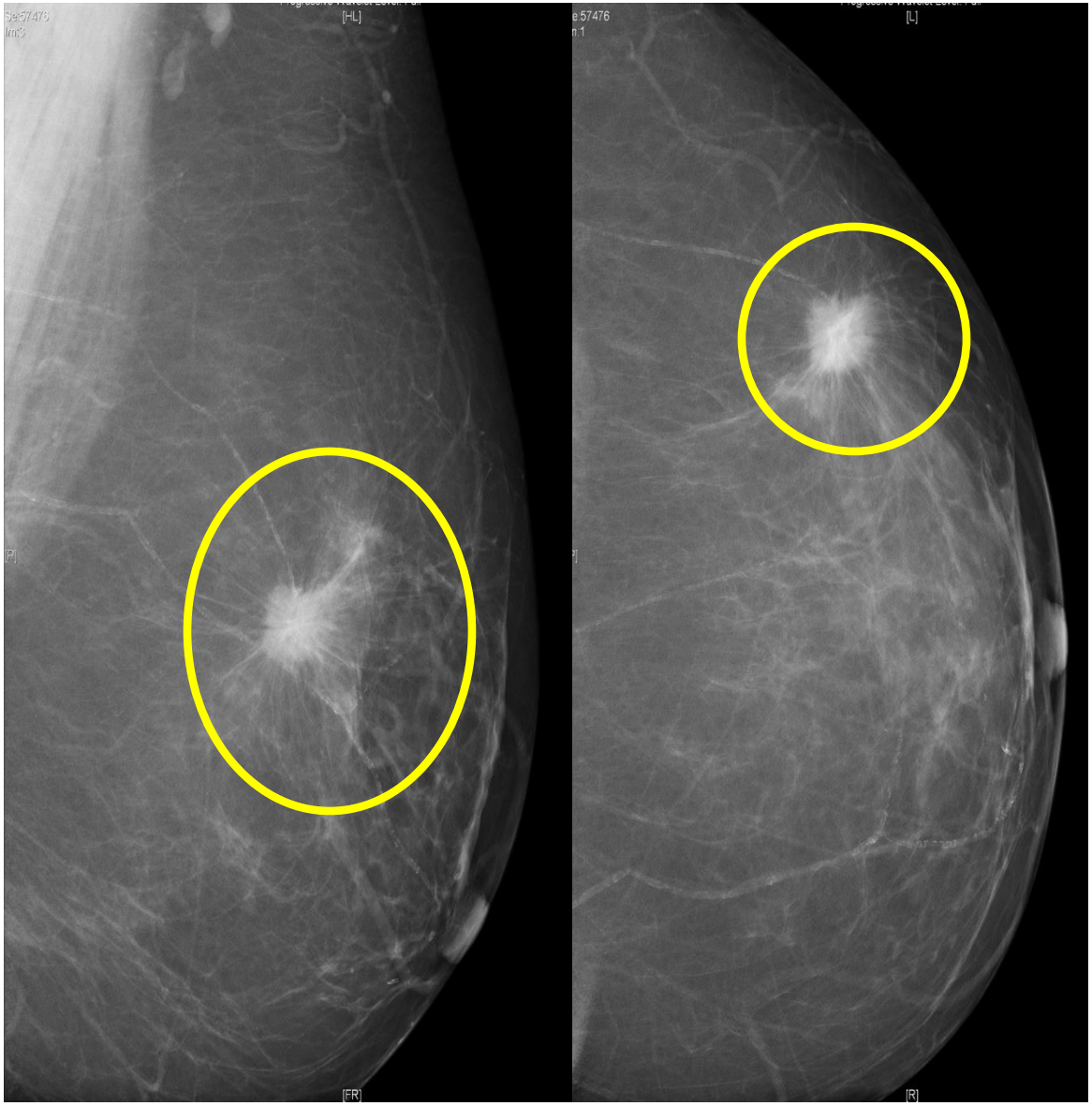
Tata Memorial Centre

Mumbai, India

Case 1

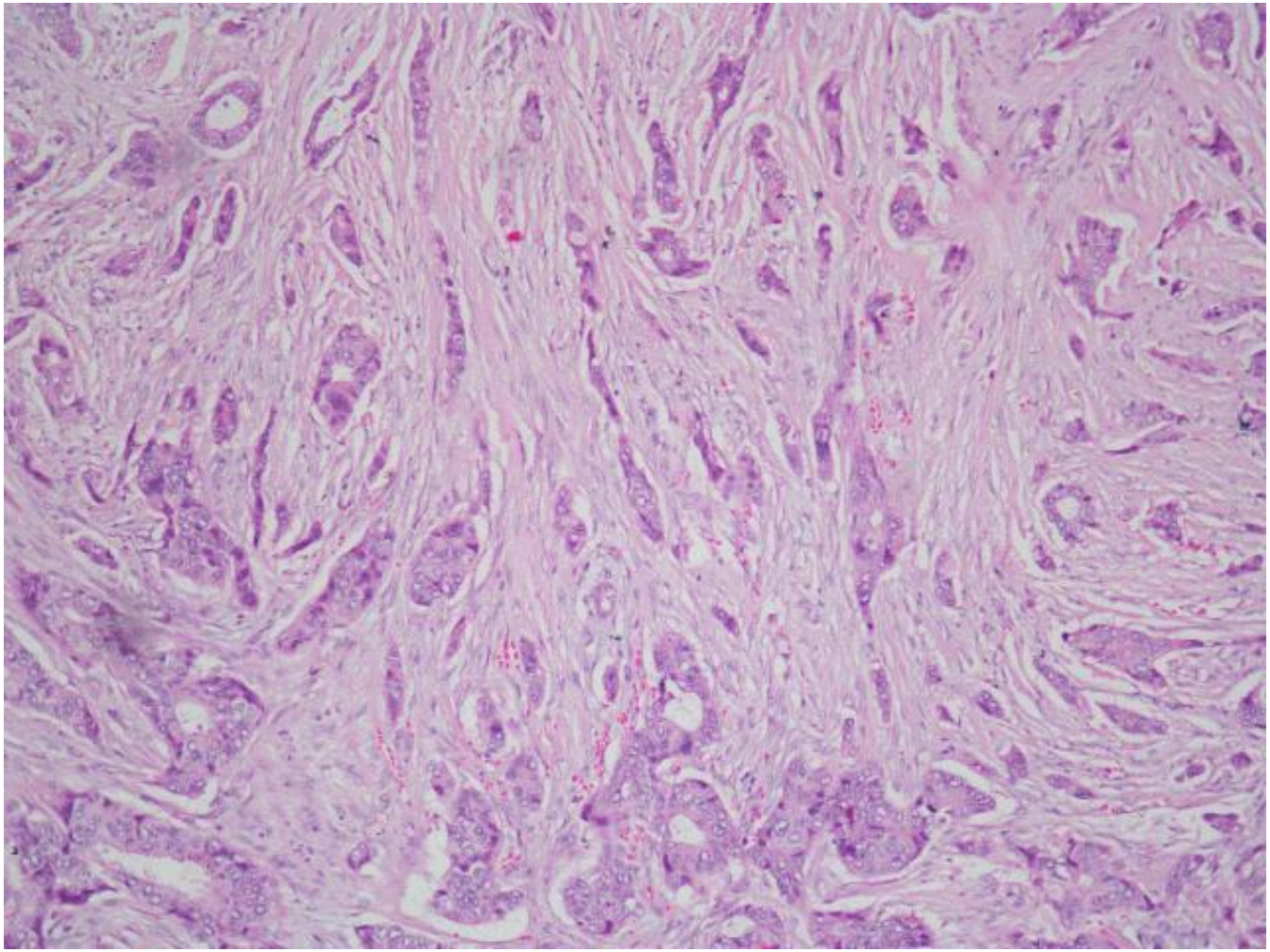
- **A 64 years old woman with well controlled hypertension, presents with lump in the left breast**
- **There is no other comorbidity and no family history of breast cancer**
- **General examination is normal**
  - **breast examination shows a 1.9 cm mobile lump in upper outer quadrant**
  - **Bilateral axillae and supraclavicular fossae shows no palpable LN**



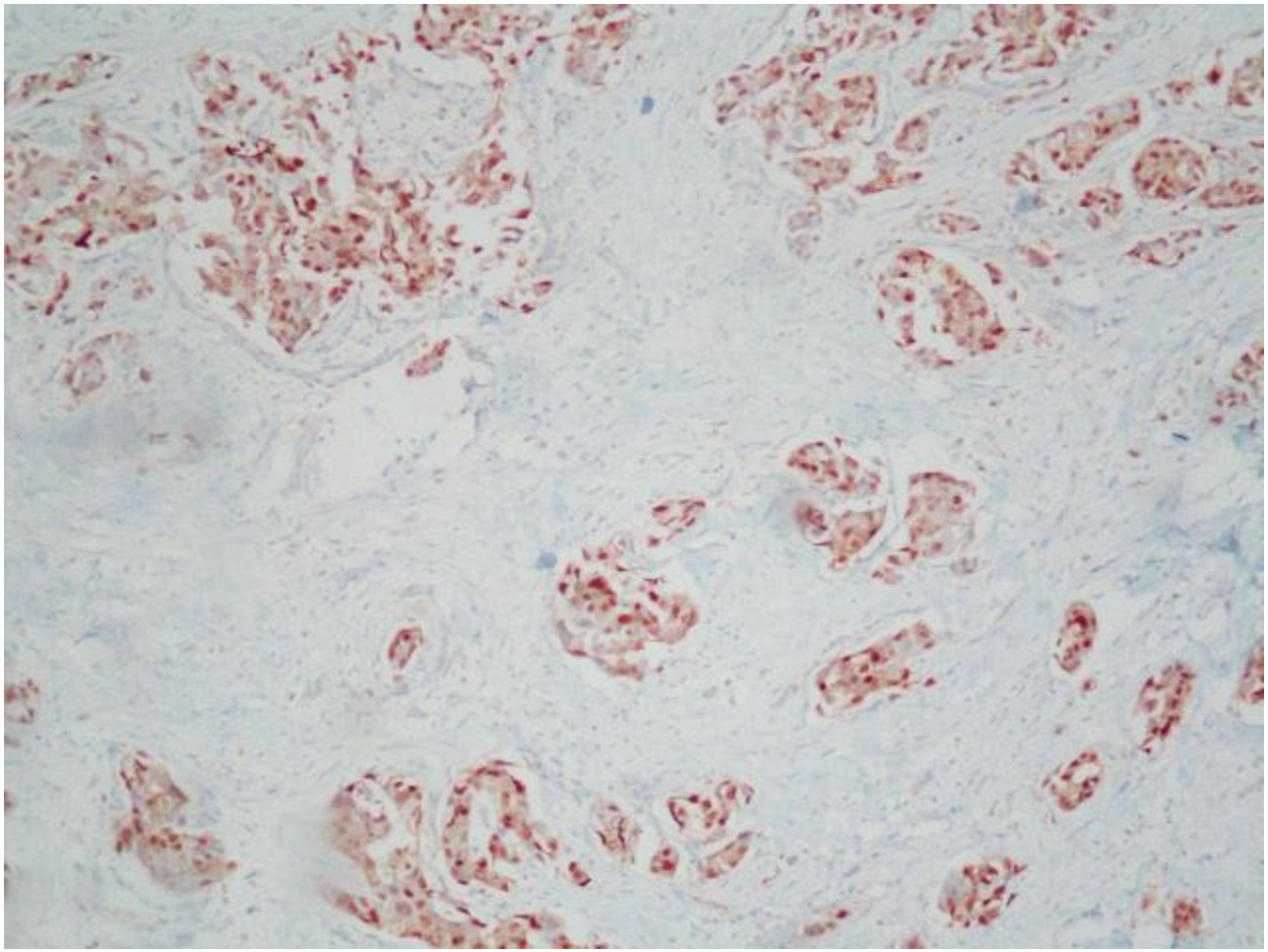
A small, less than 2 cm sized, spiculated mass is seen in the upper outer quadrant of the left breast.

Case 1

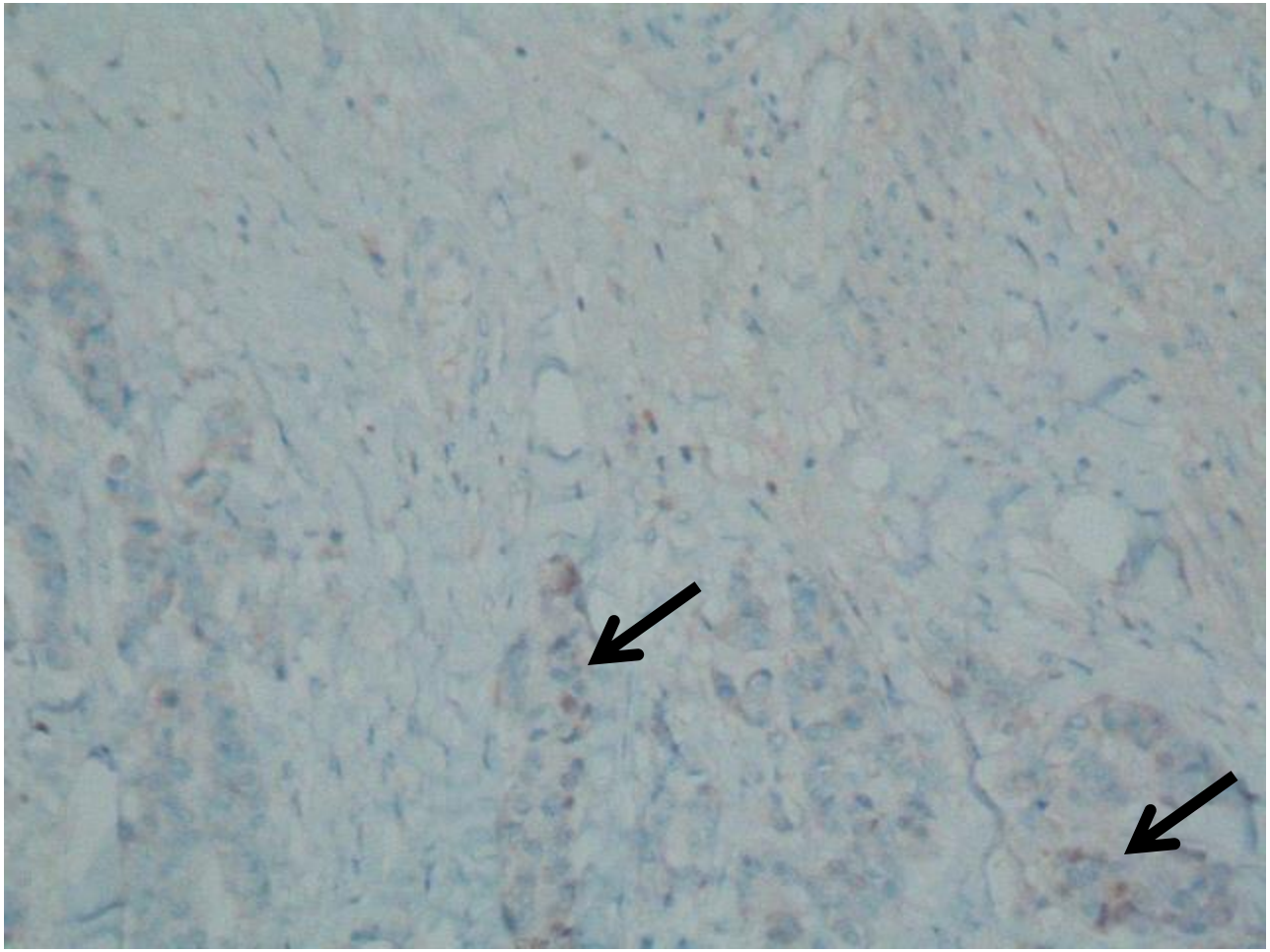
- **She undergoes breast conserving surgery with sentinel lymph node (blue and hot):**



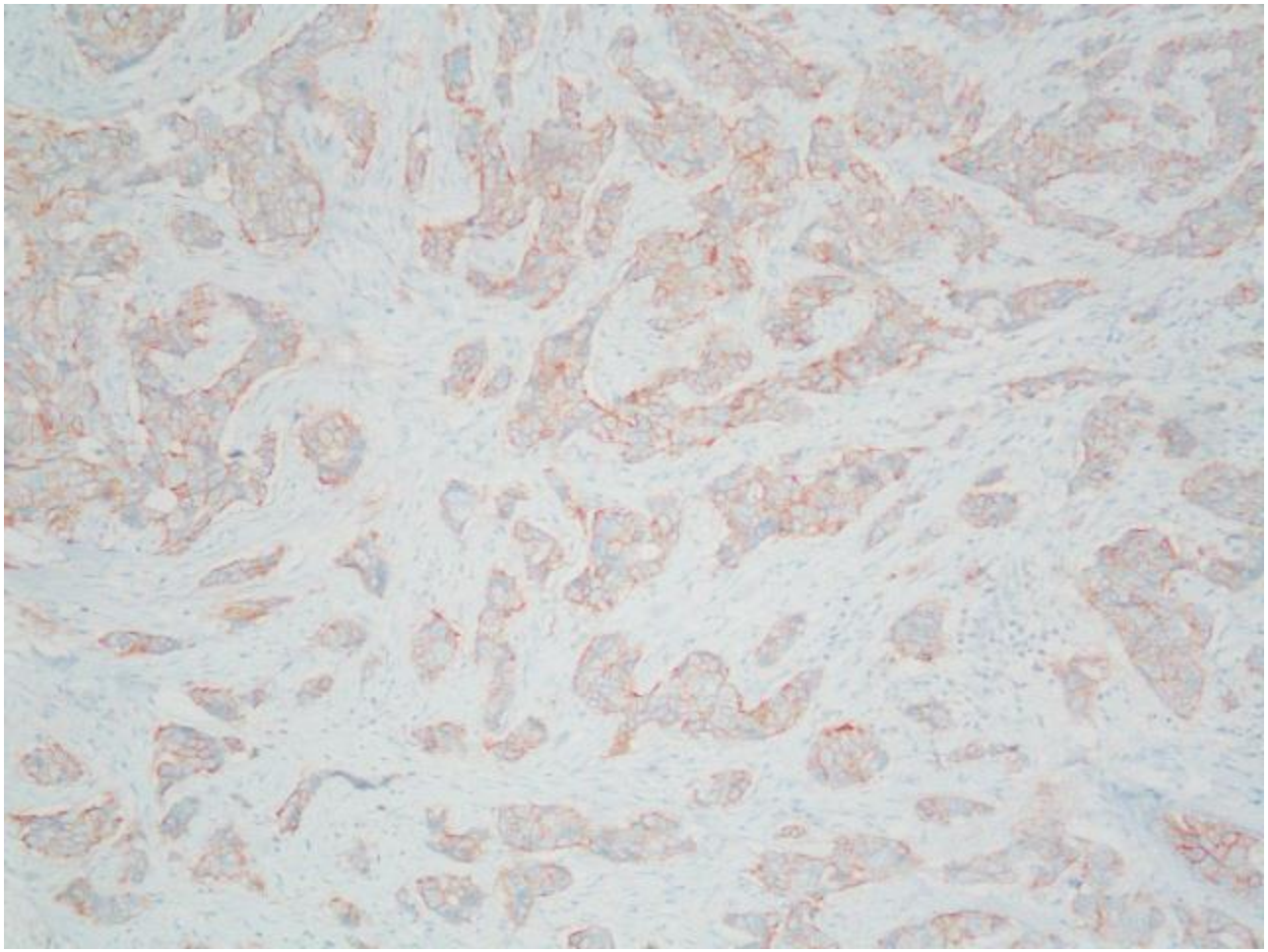
IDC grade 2



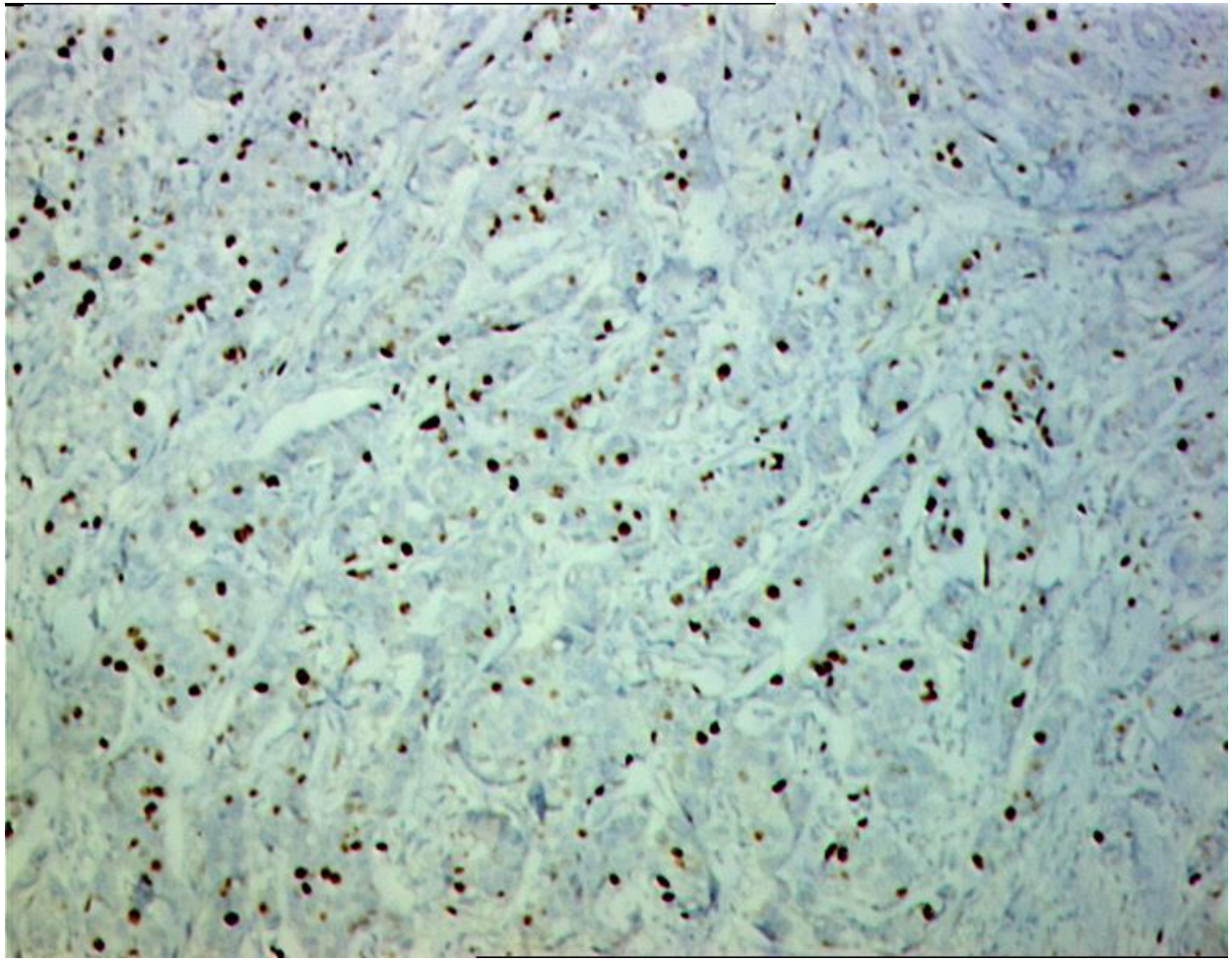
ER positive - Allred score 7/8



PR weak positive 2% nuclei weak stained – Allred score 3/8



HER2 was 1+ (negative)



MIB1 20 %

Case 1

- **She undergoes breast conserving surgery with sentinel lymph node (blue and hot):**
  - **pT 2.4 cm,**
  - **IDC grade 2**
  - **N 0/4,**
  - **ER 7/8, PR 3/8, HER2 negative.**
  - **MIB1 – 20%**
  - **No LVI**

Question 1

- Would you advise her to take adjuvant chemo?
  - Yes
  - No chemo, only endocrine therapy
  - Advise additional multigene testing to decide

Using clinical-pathological features to decide treatment

predict

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Information for professionals

Welcome to PREDICT, an online prognostication and treatment benefit tool designed to help clinicians and patients make informed decisions about treatment following breast cancer surgery. The survival estimates, presented both with and without adjuvant therapy (hormone therapy, chemotherapy and trastuzumab), are provided for 5 and 10 years following surgery. Development of the model was a collaborative project between the Cambridge Breast Unit, University of Cambridge Department of Oncology and the Eastern Cancer Information and Registration Centre (ECRIC) and was supported by an unrestricted educational grant from Pfizer Limited.

We welcome any feedback you may have about PREDICT. If you have questions about its development or there are features you would like to have added to the model please let us know by emailing us at info@predict.nhs.uk

Using PREDICT

Model development

Model validation

Model extension: HER2 status

Model extension: KI67 status

PREDICT and Oncotype DX™

Using PREDICT

Use the interactive PREDICT tool to estimate breast cancer survival and the benefits of hormone therapy, chemotherapy and trastuzumab.

The model is easy to use following data entry for an individual patient including patient age, tumour size, tumour grade, number of positive nodes, ER status, HER2 status, KI67 status and mode of detection. Survival estimates, with and without adjuvant therapy, are presented in visual and text formats. Treatment benefits for hormone therapy and chemotherapy are calculated by applying relative risk reductions from the Oxford overview to the breast cancer specific mortality. Predicted mortality reductions are available for both second generation (anthracycline-containing, >4 cycles or equivalent) and third generation (taxane-containing) chemotherapy regimens.

The Cambridge Breast Unit (UK) uses the absolute 10-year survival benefit from chemotherapy to guide decision making for adjuvant

http://www.predict.nhs.uk/predict.html

Using clinical-pathological features to decide treatment- Scenario 1

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PREDICT Tool: Breast Cancer Survival; Input

Age at diagnosis:	64			
Mode of detection:	○ Screen-detected	◉ Symptomatic	○ Unknown	
Tumour size in mm:	24	(blank if unknown)		
Tumour Grade:	○ 1	◉ 2	○ 3	○ Unknown
Number of positive nodes:	0	(blank if unknown)		
ER status:	◉ Positive	○ Negative		
HER2 status:	○ Positive	◉ Negative	○ Unknown	
KI67 status:	◉ Positive	○ Negative	○ Unknown	
Gen chemo regimen:	○ No chemo	◉ Second	○ Third	

Predict Survival | Clear All Fields | Print Results

http://www.predict.nhs.uk/predict.html

ACTREC

PREDICT Tool: Breast Cancer Survival; Results

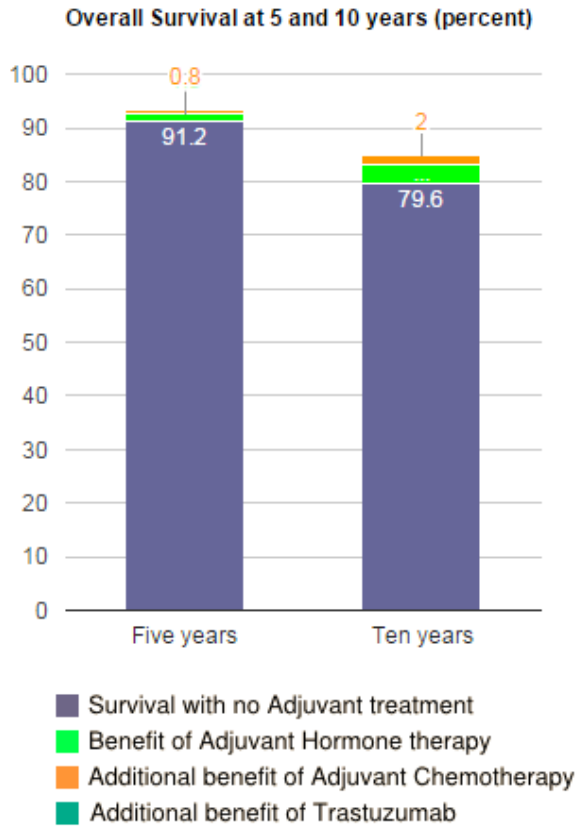
Five year survival

91 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 1 out of 100 women treated are alive because of hormone therapy
An extra 2 out of 100 women treated are alive because of hormone therapy & chemotherapy

Ten year survival

80 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 3 out of 100 women treated are alive because of hormone therapy
An extra 5 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
(Or tap segment if using a mobile device)



*Disclaimer: **PREDICT** can only provide a general guide to possible outcomes in any individual case. As we are all different, for the more complete picture in your case, you should speak to your own specialist. You may wish to print this page out and share it with your specialist.*

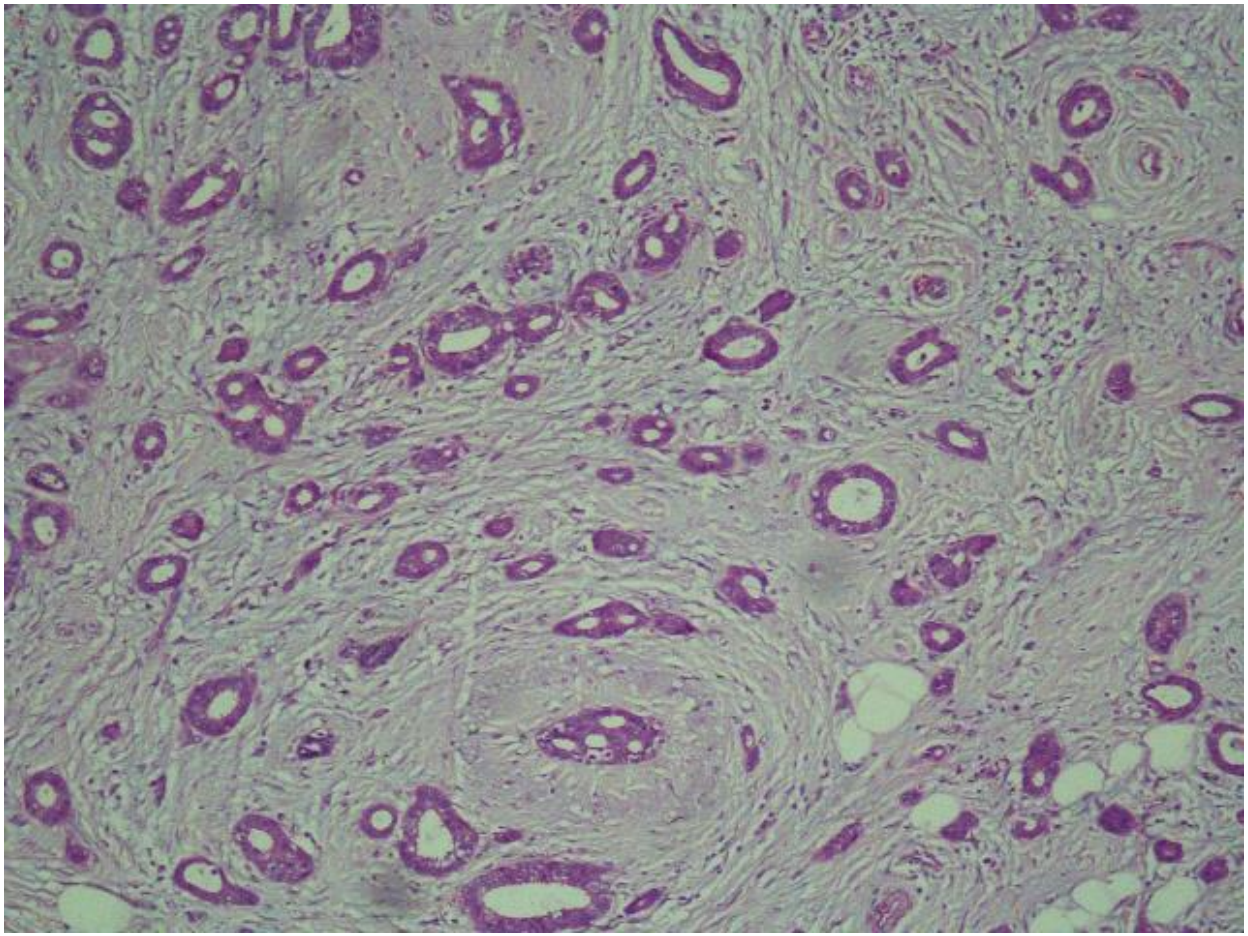
Question 1

- **Would you advise her to take adjuvant chemo?**
  - **Yes**
  - **No chemo, only endocrine therapy**
  - ***Advise additional multigene testing to decide***

Question 1

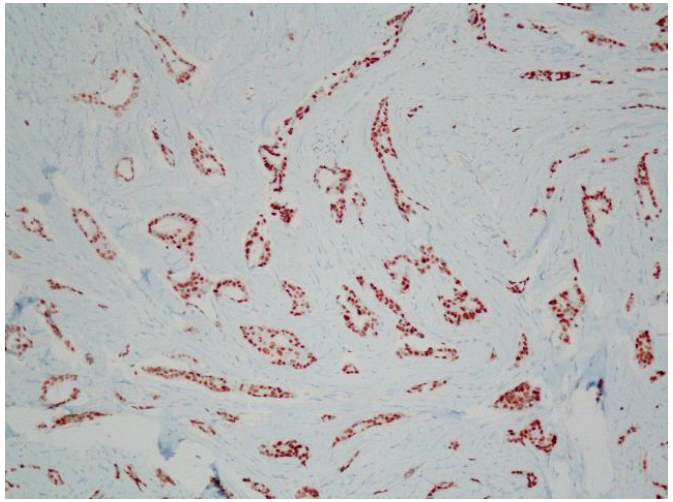
- **Would you advise her to take adjuvant chemo?**
  - ***Yes***
  - **No chemo, only endocrine therapy**
  - ***Advise additional multigene testing to decide***

Would your decision change if she had the following histology?

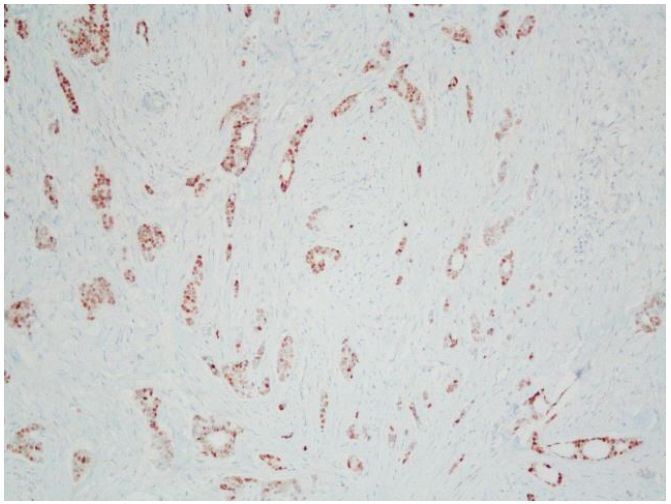


IDC grade 1

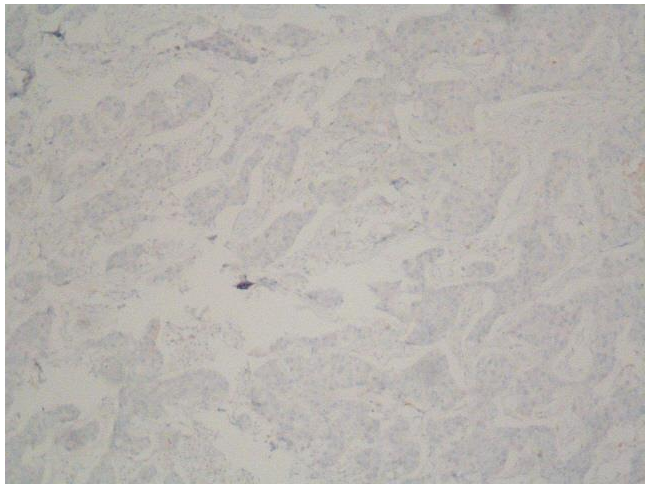
Would your decision change if she had the following histology?



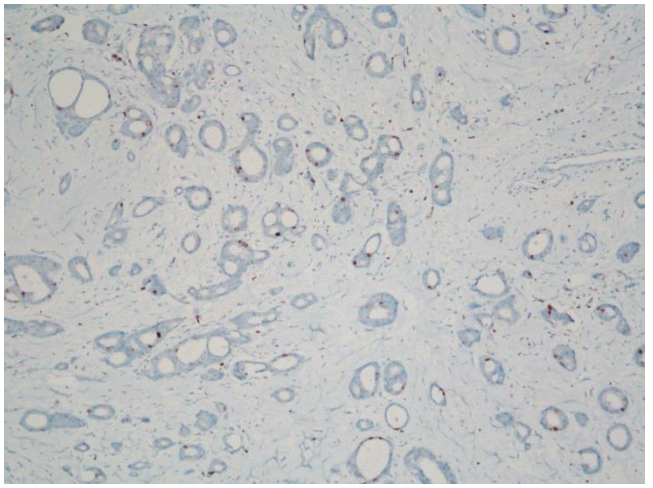
ER 8/8



PR 8/8



HER2 - 0 (neg)



MIB1: 5 to 8%

Question 2

- **Would you advise her to take adjuvant chemo?**
  - **Yes**
  - **No chemo, only endocrine therapy**
  - **Advise additional testing to decide**

Question 2

- **Would you advise her to take adjuvant chemo?**
  - **Yes**
  - ***No chemo, only endocrine therapy***
  - **Advise additional testing to decide**

Using clinical-pathological features to decide treatment- Scenario 2

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KI67 status:	○ Positive	● Negative	○ Unknown	
Gen chemo regimen:	○ No chemo	● Second	○ Third	

Predict Survival | Clear All Fields | Print Results

http://www.predict.nhs.uk/predict.html

ACTREC

PREDICT Tool: Breast Cancer Survival; Results

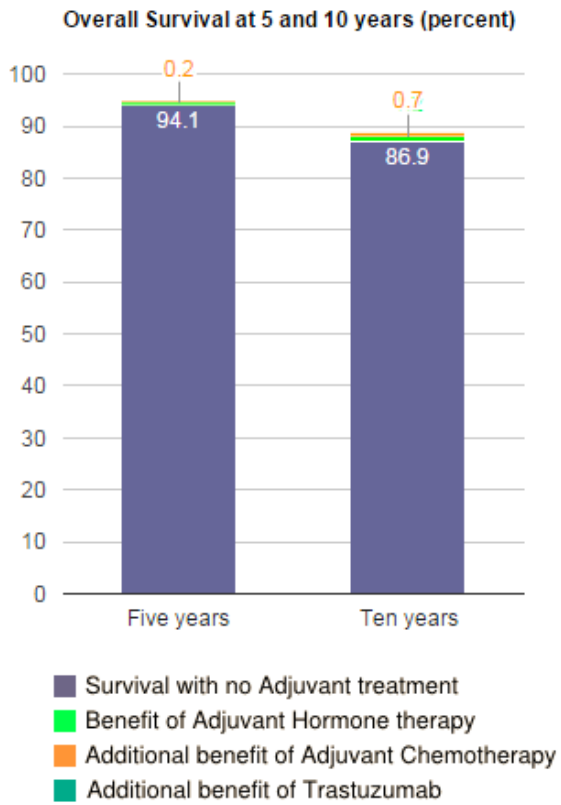
Five year survival

94 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 0 out of 100 women treated are alive because of hormone therapy
An extra 1 out of 100 women treated are alive because of hormone therapy & chemotherapy

Ten year survival

87 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 1 out of 100 women treated are alive because of hormone therapy
An extra 2 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
(Or tap segment if using a mobile device)



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the Journal of Cancer Surgery
ELSEVIER
EJSO 37 (2011) 411–417
www.ejso.com

A population-based validation of the prognostic model PREDICT for early breast cancer

G.C. Wishart [a,g], C.D. Bajdik [e], E.M. Azzato [b,c], E. Dicks [b], D.C. Greenberg [d], J. Rashbass [d], C. Caldas [a,b,f,g], P.D.P. Pharoah [b,*]

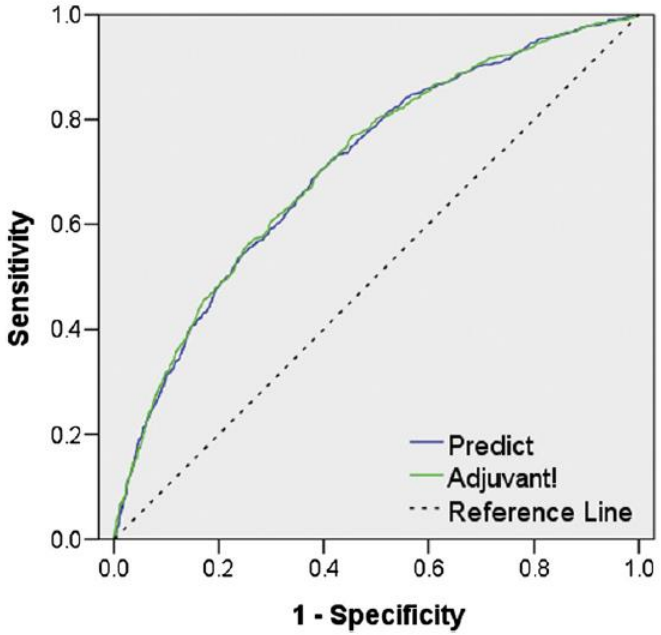


Figure 1. Receiver-operator characteristic (ROC) curves for overall survival in 3140 patients based on Predict and Adjuvant! breast cancer prognostic models.

OS

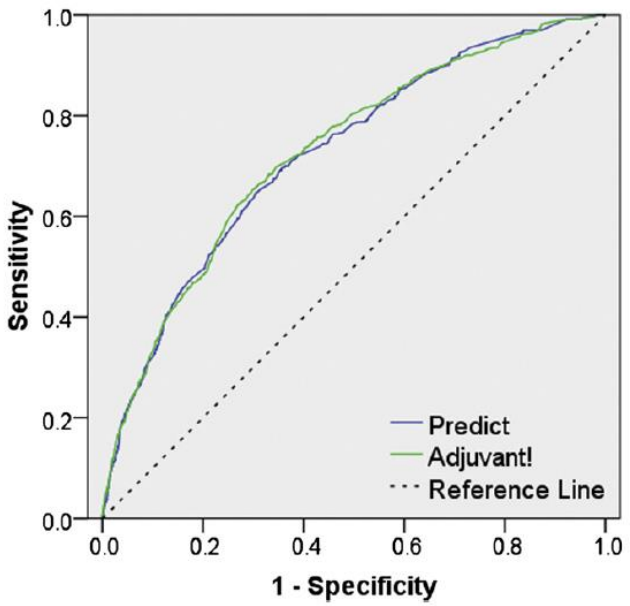


Figure 2. Receiver-operator characteristic (ROC) curves for breast cancer specific survival in 3122 patients based on Predict and Adjuvant! breast cancer prognostic models.

BCSS

Table 3
Classification of 3140 patients according to estimated absolute survival benefit from Predict and Adjuvant!

Adjuvant!	Predict			
	<3%	3–5%	>5%	Total
<3%	1911	43	6	1960
3–5%	138	219	107	464
>5%	3	89	624	716
Total	2052	351	737	3140

Concordance in estimating benefit of chemo = 87.7%

Prognostic Significance of Progesterone Receptor–Positive Tumor Cells Within Immunohistochemically Defined Luminal A Breast Cancer

Aleix Prat, Maggie Chon U. Cheang, Miguel Martín, Joel S. Parker, Eva Carrasco, Rosalía Caballero, Scott Tyldesley, Karen Gelmon, Philip S. Bernard, Torsten O. Nielsen, and Charles M. Perou

Samples for pathology and gene expression from 5 Independent cohorts

Conclusion

Semiquantitative IHC expression of PR adds prognostic value within the current IHC-based luminal A definition by improving the identification of good outcome breast cancers. The new proposed IHC-based definition of luminal A tumors is HR positive/HER2 negative/Ki-67 less than 14%, and PR more than 20%.

J Clin Oncol 31:203-209. © 2012

[S1-08] High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: Results from DBCG77B randomized trial

Nielsen TO, Jensen M-B, Gao D, Leung S, Burugu S, Liu S, Tykjær Jørgensen CL, Balslev E, Ejlertsen B.

Methods: We performed a full intrinsic subtype analysis on the 709 breast cancers available from DBCG77B on tissue microarrays using previously published, locked-down immunohistochemical (IHC) methods and intrinsic subtype definitions based on ER, PR, HER2, Ki67 and basal markers (Prat et al. JCO 2014). Biomarker scoring was performed in Vancouver by researchers with no access to the clinical database. A full statistical plan was

- **N=165/709 (23%) had luminal A**
- **HR for chemo Vs not = 1.07, p=0.86**

Conclusions: In a formal prospective-retrospective analysis of the DBCG 77B study randomizing women to adjuvant cyclophosphamide-based chemotherapy vs. no chemotherapy arms, patients with non-luminal A breast tumors (defined by IHC), but not luminal A tumors, benefit from adjuvant chemotherapy.

Clinical-Pathological Scores for Adjuvant Treatment

Scheme/Variable	Age	Mode of Detection	Comorbidity	Menopausal Status	T Size	Node status	Grade	ER	PR	HER2	Ki-67	Rx details
PREDICT Plus	✓	✓			✓	✓	✓	✓		✓	✓	✓
Adjuvant !	✓		✓	✓	✓	✓		✓				✓
IHC4-Clinical	✓				✓	✓	✓	✓	✓	✓	✓	✓
IHC Intrinsic subtype								✓	✓	✓	✓	

British Journal of Cancer (2012) 107, 800–807

Journal of Clinical Oncology, Vol 19, No 4 (February 15), 2001: pp 980-991

J Clin Oncol 29:4273-4278. © 2011

J Clin Oncol 31:203-209. © 2012

Clinical-Pathological Scores for Adjuvant Treatment

- Need ***high quality pathology***
- Need ***quantitative or semi-quantitative estimation*** of some pathological characteristics such as receptors
- Each score gives ***a quantitative output*** of the estimate of prognosis without chemotherapy
- Patients with ‘excellent’ prognosis, after due discussion, can be spared chemotherapy

Common multigene tests

Oncotype Dx Recurrence Score	RS	Twenty-one-gene–based expression profile score using qRT-PCR (16 cancer genes, five housekeeping genes). FFPE blocks used to extract RNA.	Paik et al: N Engl J Med 351: 2817-2826, 2004
Prosigna Risk of Recurrence Score	ROR	Fifty gene–based expression profile score using qRT-PCR. FFPE blocks used to extract RNA to perform analysis on nCounter system.	Dowsett et al[12]
Breast Cancer Index	BCI	Multigene assay using qRT-PCR. Combination of two biomarkers: HOXB13/IL17BR and molecular grade index.	Zhang et al,[7] Sgroi et al[8]
EndoPredict	EPClin	Twelve gene–based expression profile score using qRT-PCR (eight cancer genes, four housekeeping genes). FFPE blocks used to extract RNA to perform analysis.	Dubsky et al[9]

Abbreviations: ER, estrogen receptor; FFPE, formalin-fixed paraffin-embedded; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PgR, progesterone receptor; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; TransATAC, translational research cohort within the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial.

+ Mammaprint

J Clin Oncol 33:916-922. © 2014

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

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS =
+ 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

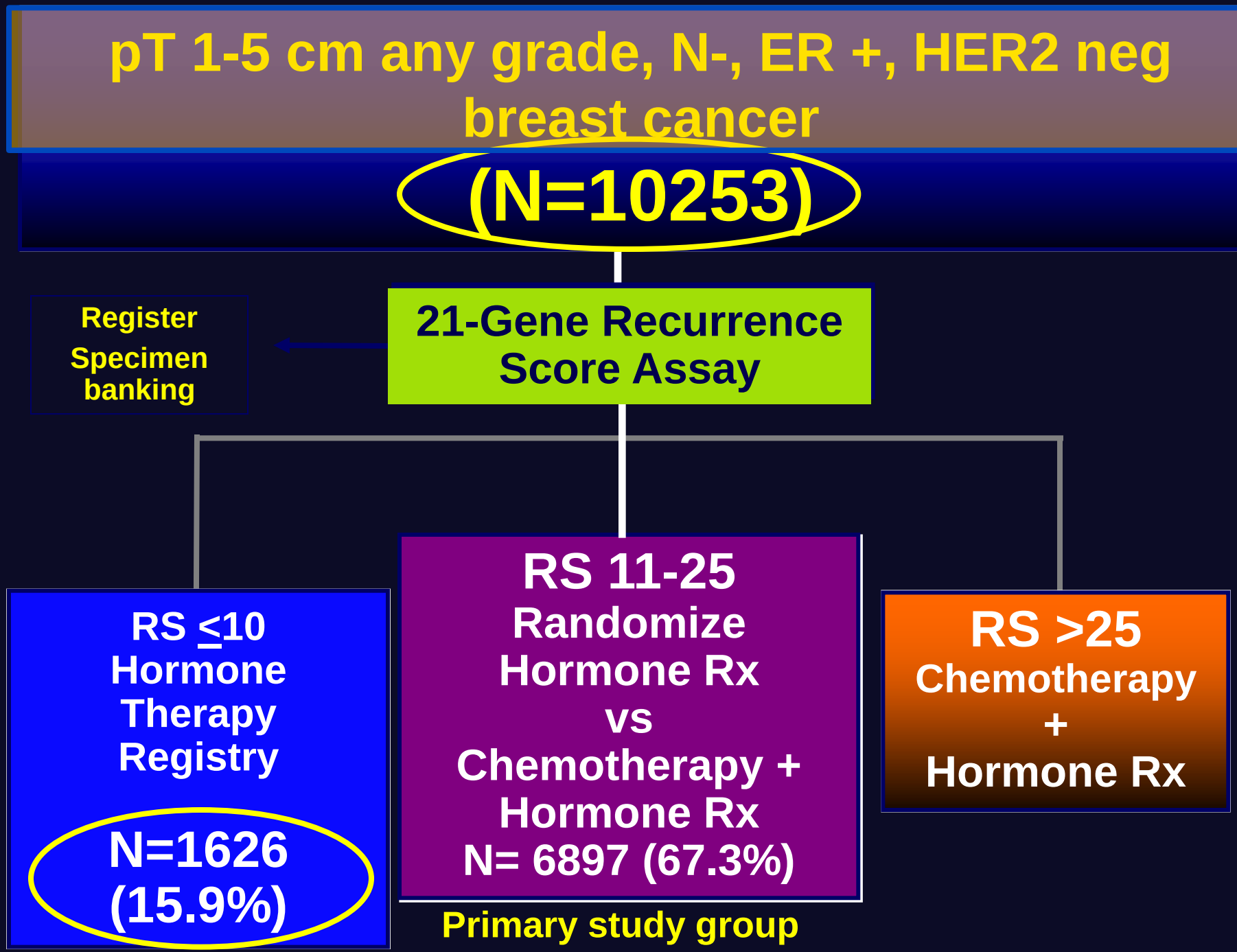
Category	RS (0 -100)
Low risk	RS <18
Int risk	RS 18 - 30
High risk	RS ≥ 31

Paik et al. *N Engl J Med.* 2004;351:2817-2826

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

N Engl J Med 2015;373:2005-14.

- **The principal question was this:**
  - **Can adjuvant chemotherapy be safely avoided in a subgroup of patients while preserving outcomes?**
  - **This question is direct result of a liberal policy of giving adjuvant chemotherapy for minor benefits in breast cancer for the past two decades.**


pT 1-5 cm any grade, N-, ER +, HER2 neg breast cancer
(N=10253)
Register
Specimen banking
21-Gene Recurrence Score Assay
RS ≤10
Hormone Therapy Registry
N=1626 (15.9%)
RS 11-25
Randomize
Hormone Rx
vs
Chemotherapy + Hormone Rx
N= 6897 (67.3%)
Primary study group
RS >25
Chemotherapy
+
Hormone Rx

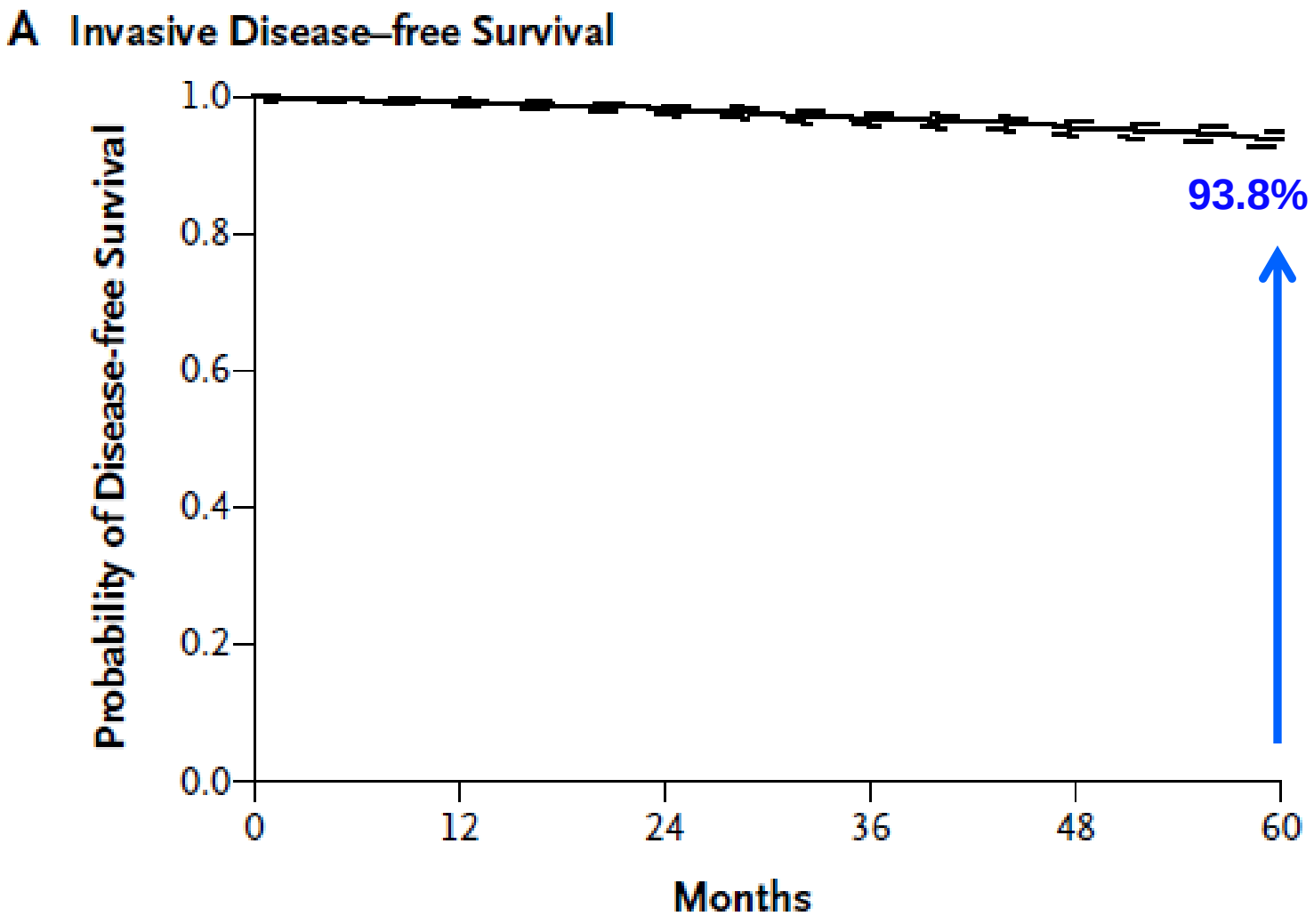

A Invasive Disease–free Survival
Probability of Disease-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
93.8%
0
12
24
36
48
60
Months

Table 1. Characteristics of the Patients at Baseline, According to Recurrence-Score Cohort.*

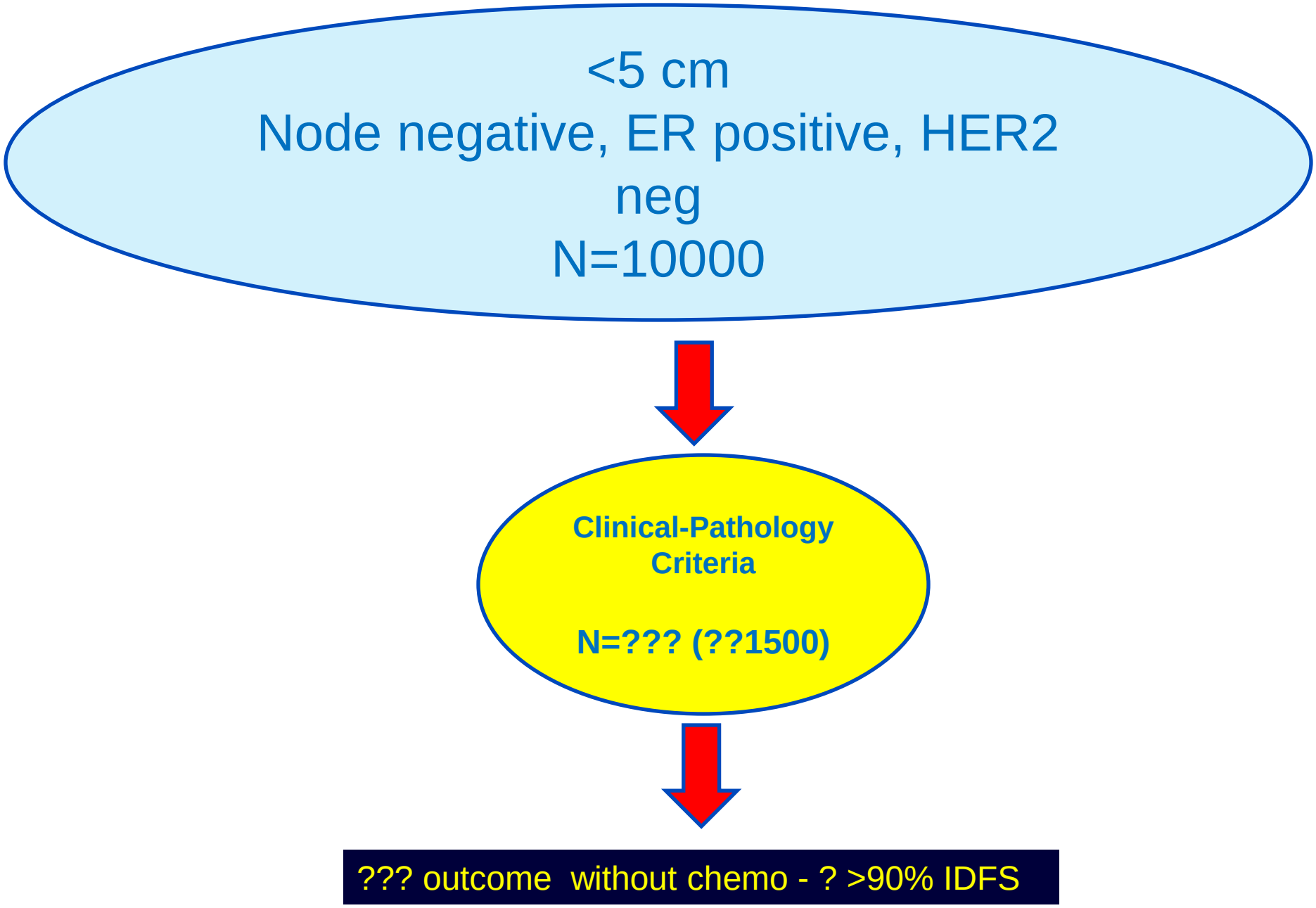
Characteristic	Recurrence Score, 0–10 (N = 1626)
Percent of all enrolled patients	15.9
Age	
Median (interquartile range) — yr	58 (50–64)
Mean — yr	57±9
Distribution — no. (%)	
≤40 yr	58 (4)
41–50 yr	372 (23)
51–60 yr	566 (35)
61–70 yr	519 (32)
>70 yr	111 (7)
Menopausal status — no./total no. (%)	
Postmenopausal	1143/1623 (70)
Premenopausal	480/1623 (30)
Tumor size in the greatest dimension	
Median (interquartile range) — cm	1.5 (1.2–2.0)
Mean — cm	1.74±0.77
Distribution — no./total no. (%)	
<1.0 cm	128/1626 (8)
1.0–1.9 cm	993/1626 (61)
2.0–2.9 cm	366/1626 (23)
3.0–3.9 cm	104/1626 (6)
≥4.0 cm	35/1626 (2)

Histologic grade of tumor — no./total no. (%)	
Low	530/1578 (34)
Intermediate	937/1578 (59)
High	111/1578 (7)
Estrogen-receptor expression — no./total no. (%)	
Negative	5/1626 (<1)
Positive	1621/1626 (>99)
Progesterone-receptor expression — no./total no. (%)	
Negative	28/1590 (2)
Positive	1562/1590 (98)
Primary surgery — no./total no. (%)	
Lumpectomy	1106/1626 (68)
Mastectomy	520/1626 (32)

- **Oncotype </=10 among ER pos/HER2 neg/node neg is able to cull out a subgroup (15.9%) with exceptionally good prognosis**

- **This is largely comprised of small, low-int grade, PR positive, older post-menopausal women.**

- **Could one use conventional criteria to avoid chemo?**


<5 cm
Node negative, ER positive, HER2 neg
N=10000
Clinical-Pathology Criteria
N=??? (??1500)
??? outcome without chemo - ? >90% IDFS

ATAC Data: Dowsett M, et al.

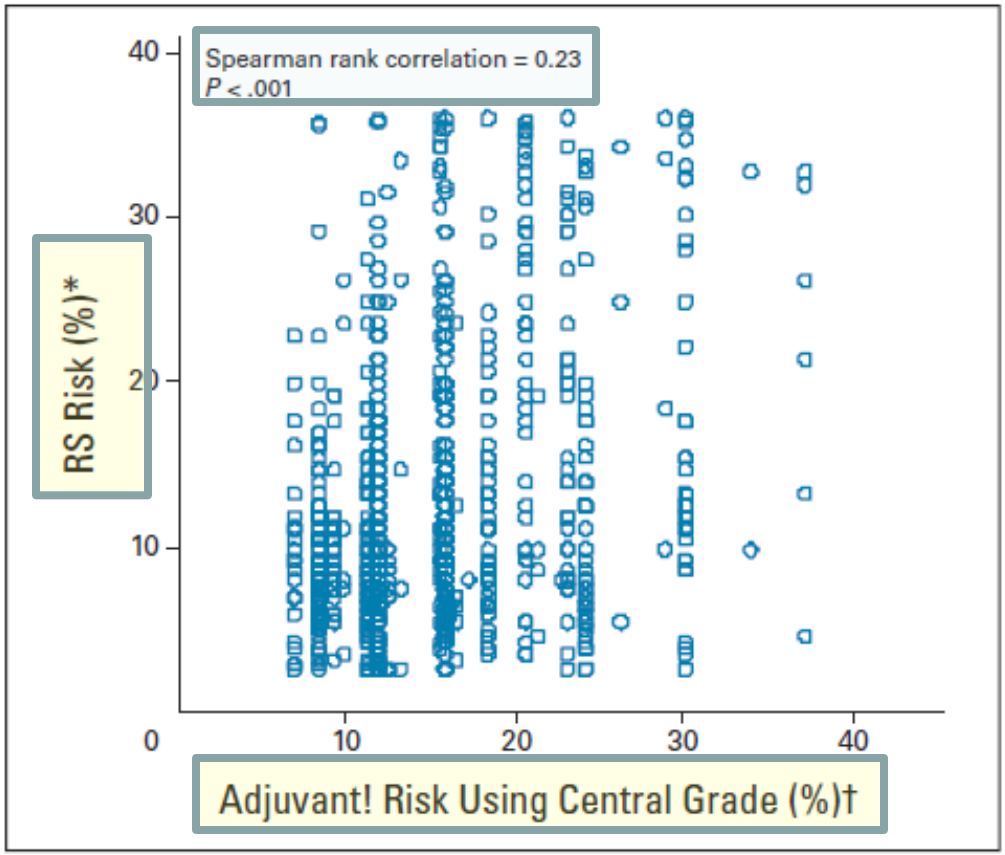
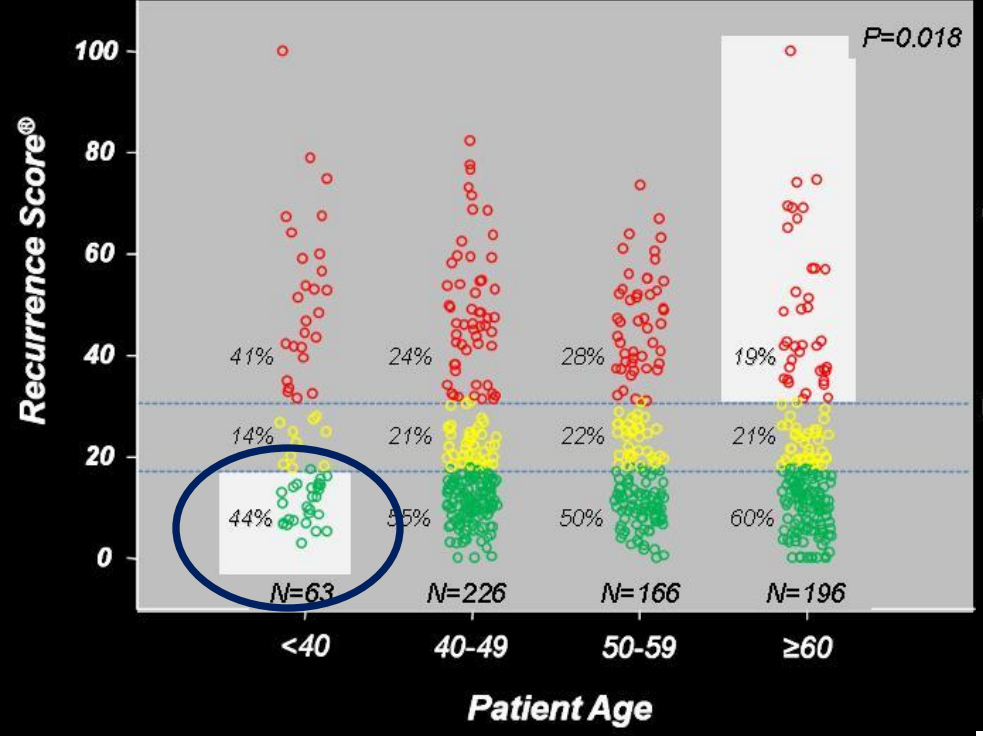
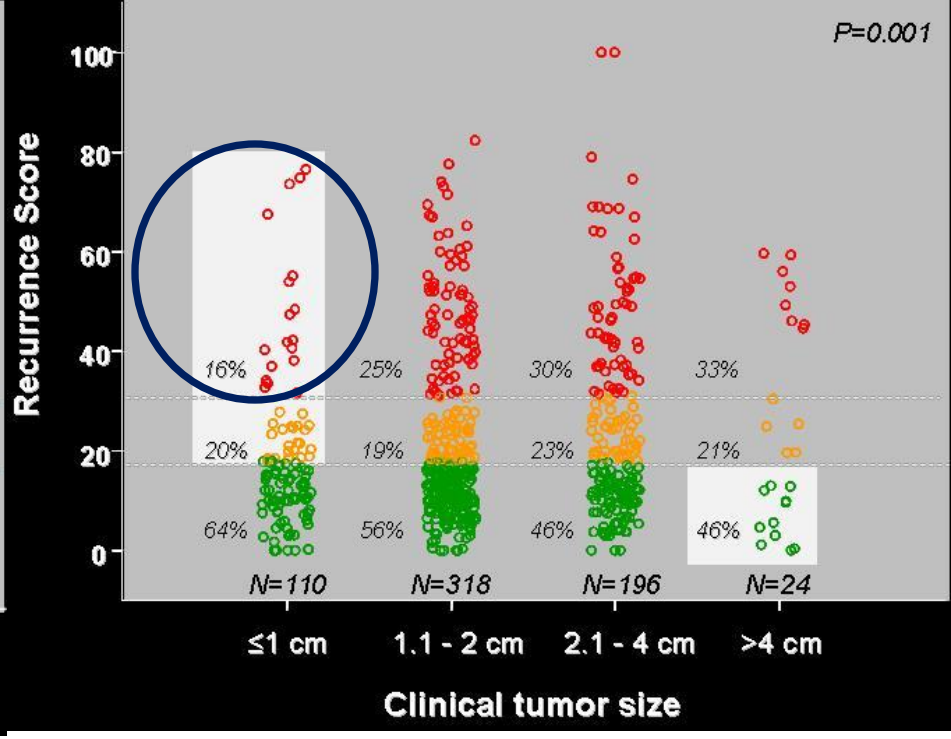


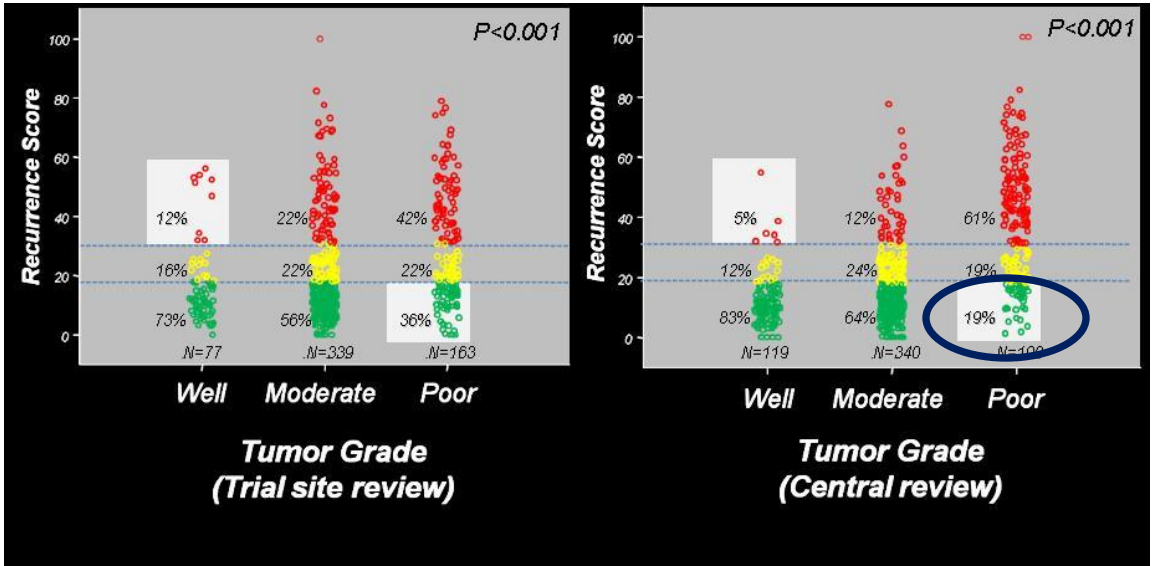
Fig 4. Predicted risk of recurrence by recurrence score (RS) and Adjuvant! N0 patients (n = 872). (*) Predicted risk of distant recurrence at 10 years from RS. (†) Predicted risk of recurrence at 10 years from Adjuvant!

J Clin Oncol 28:1829-1834. © 2010





NSABP B-20: Young patients may have low recurrence scores



NSABP B-20: Small tumors can have intermediate to high recurrence scores

NSABP B-20: High-grade tumors can have low recurrence scores

Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.

How well (or otherwise) have conventional criteria served to prognosticate/predict?

Are treatment decisions based on criteria such as tumor size and nodal status *reasonably* accurate?

Prognostic Value of a Combined ER, PgR, Ki67, HER2 Immunohistochemical (IHC4) Score and Comparison with the GHI Recurrence Score – Results from TransATAC (Abstract 74)

SABCS 2009

Cuzick J, Dowsett M, Wale C, Salter J, Quinn E, Zabaglo L, Howell A, Buzdar A, Forbes JF

J Clin Oncol 29:4273-4278. © 2011

Clinical & IHC4 Scores

Based on Distant Recurrence & All Patients

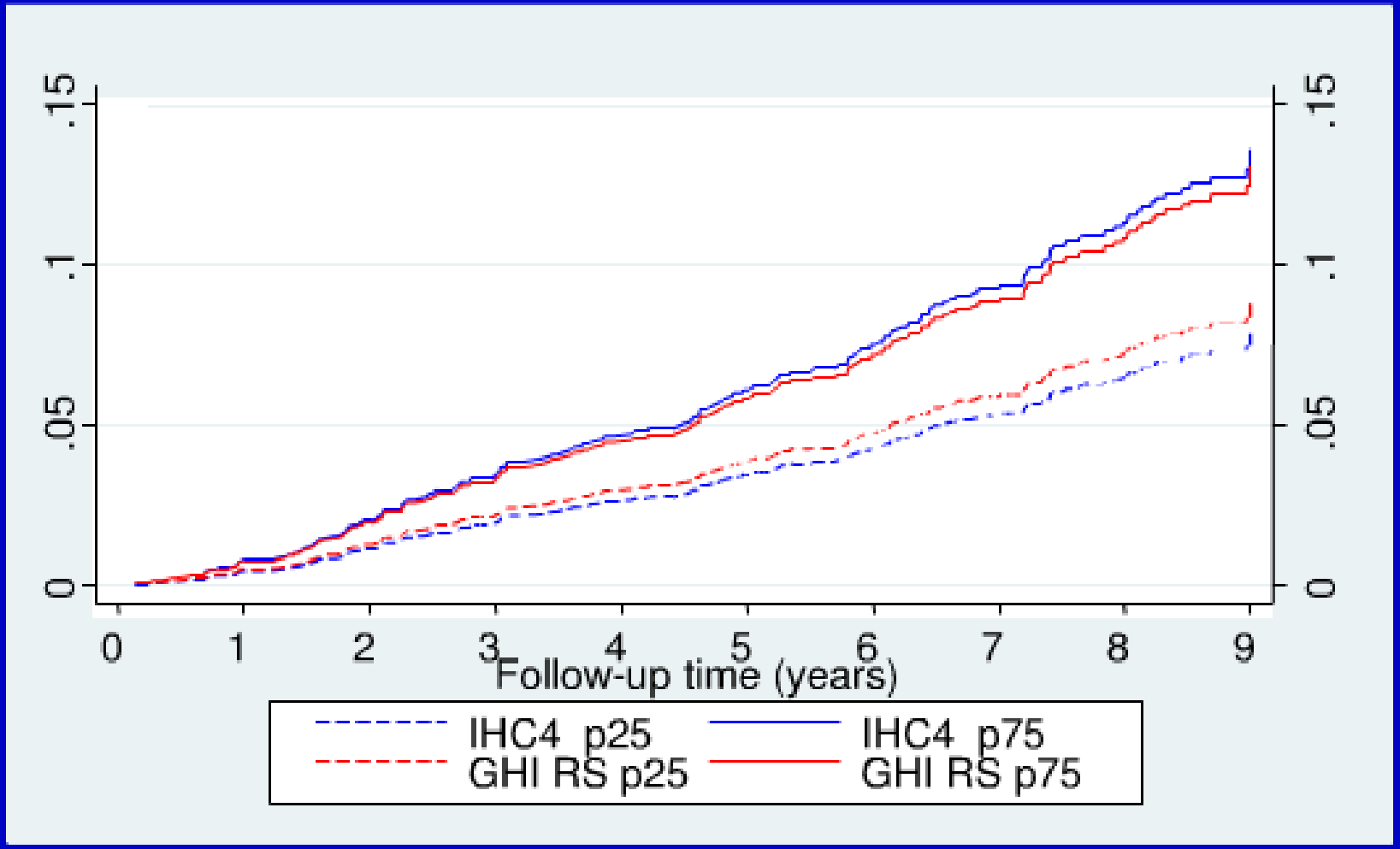
Clinical score = $100 \times \{0.473N_{1-3} + 1.728N_{4+}$
$+ 0.707\ T_{2-5} + 1.190T_{>5}$
$+ 0.598\ Gr_2 + 0.990\ Gr_3$
$+ 0.220$ Age (≥65y) – 0.153 Ana$\}$

IHC4 score = $100 \times \{-0.105\ ER_{10} –$
$0.0760\ PgR_{10} + 0.528$ HER2
$+0.214$ ln $(1 + 10 \times$ Ki-67$)\}$

Cuzick J, et al. *Cancer Res.* 2009;69(Suppl): Abstract 74.

Distant recurrence - predicted values

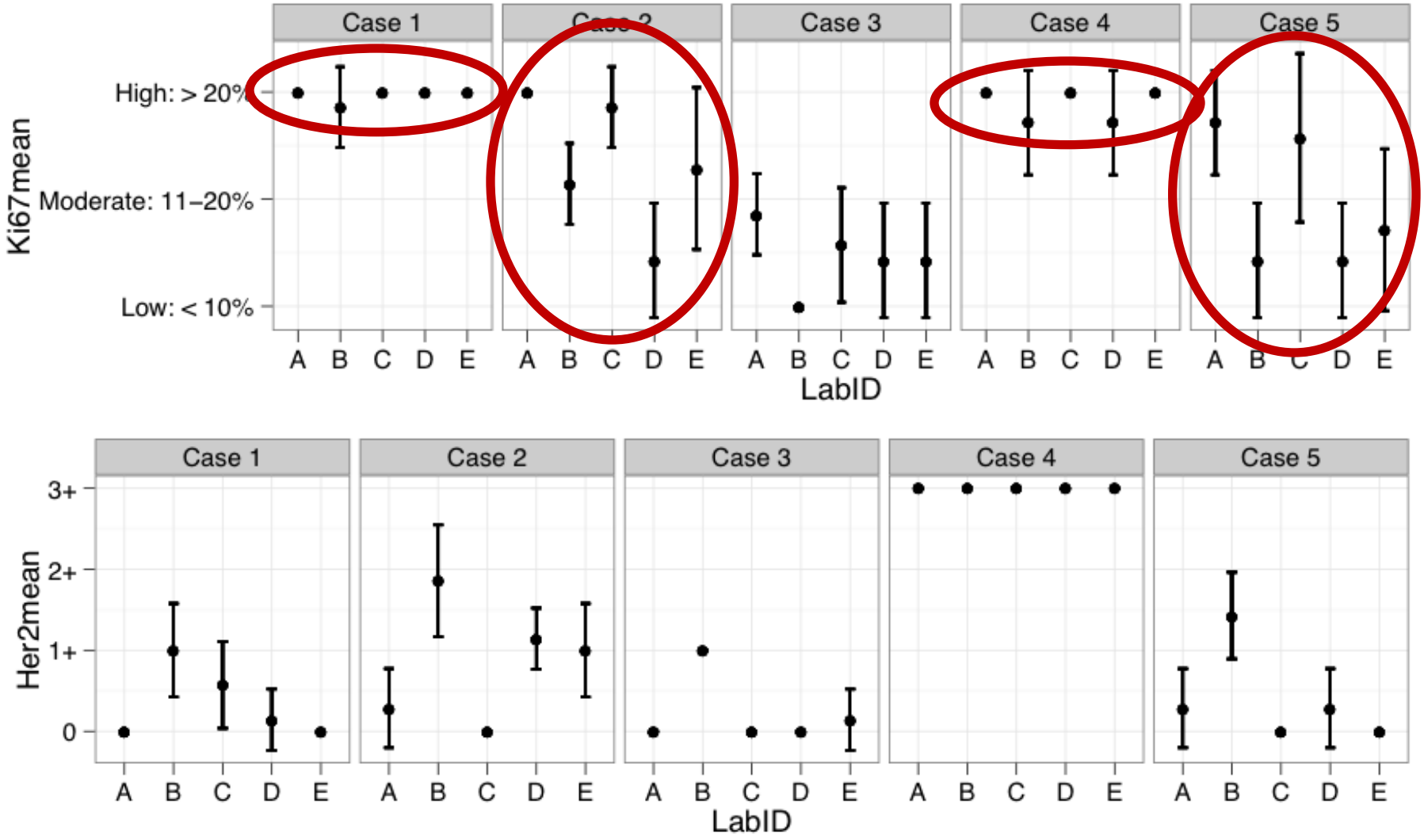
KM curves to 9 yrs with shrinkage adjustment for IHC4 (6.8%) and inflation of GHI-RS (12.2%)



Node neg, Poor/undifferentiated, Size ≤2cm, Age ≥65y , anastrozole

- Nodal status remains the strong prognostic factor for recurrence and distant recurrence.
- The IHC4 score provided substantial prognostic information which was independent of nodal status, tumour size, grade, age and treatment in both node positive and node negative women.
  - Done in single expert lab and may not reflect routine use
- In this study the prognostic information in the IHC4 score was quantitatively similar to that provided by the GHI recurrence score.
  - minimal extra information in the Recurrence Score.
  - Strong correlation between the score (p~0.70)

Ki67 and Her2 Results



Reader and technical variance: Athena Harmonization Project, Borowsky et al

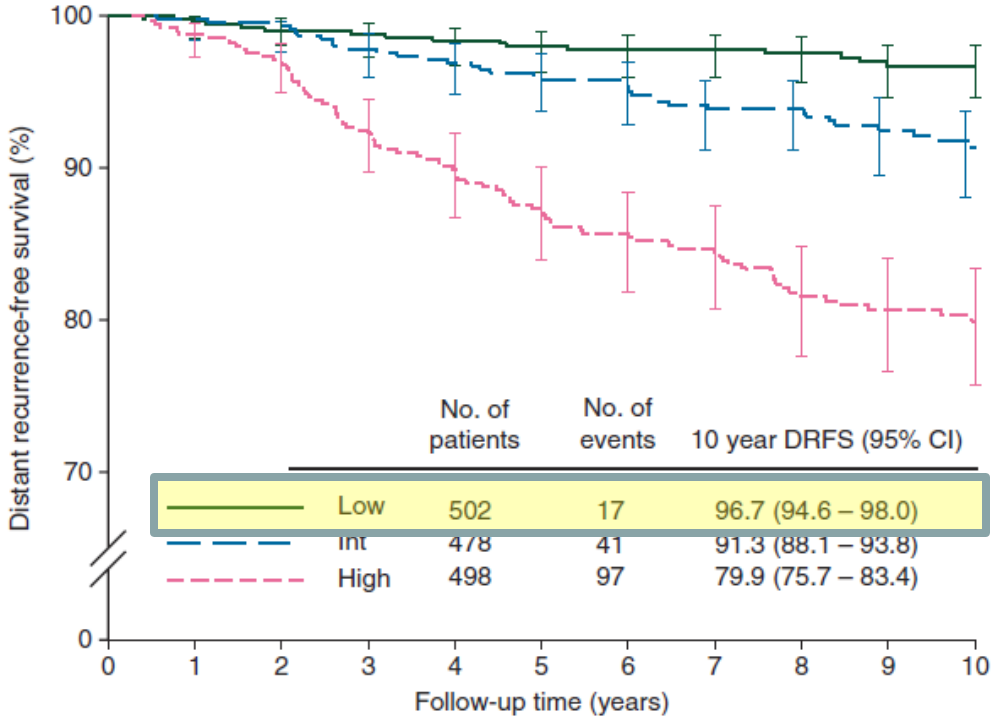
Summary of the Recurrence Score International Decision Impact Studies

Study	Patient Population	Pre-Oncotype DX Recommendation (HT; CHT)	Post-Oncotype DX Recommendation (HT; CHT)	Percent Change
Lo (US)	89 N0	52%; 47%	67%; 26%	32%
Klang (Israel)	313 N0	44%; 56%	72%; 28%	40%
Rezai (Germany)	366 N0/N+	42%; 57%	54%; 46%	33%
Albanell (Spain)	107 N0	64%; 36%	73%; 27%	32%
Holt (UK)	142 N0/N+(mic)	56%; 44%	70; 30%	33%
Yamauchi (Japan)	90 N0/N+	41%; 59%	74%; 26%	38%
de Boer (Australia)	151 N0/N+	56%; 44%	64%; 36%	24%
Hornberger (Meta-Analysis)	1154 N0/N+	42%; 58%	66%; 39%	35%

PAM50

- **ROR score calculation**
- Each patient's ROR score was calculated using the test variables that include Pearson correlations with prototypical gene expression profiles for the ***four intrinsic subtypes*** (based on a 46 gene subset of the 50 genes), a ***proliferation score*** (mean expression of an 18 gene subset of the 50 genes), and ***pathological tumor size*** (coded as 0 if ≤ 2 cm or 1 if > 2 cm). The test variables are multiplied by pre-defined weights, obtained originally during algorithm training from a Cox Proportional Hazards model, and summed to produce the ROR score according to the formula:
-
- ROR=54.7690*(-0.0067*A+0.4317*B-0.3172*C+0.4894*D+0.1981*E+0.1133*F+0.8826)
-
- where A = basal-like Pearson's correlation, B = Her2-enriched Pearson's correlation, C = luminal A Pearson's correlation, D = luminal B Pearson's correlation, E = proliferation score, and F = tumor size

PAM50 ROR score prognostication of outcome in ABCSG-8: N=3901 (ana f/b tam Vs tam) of which N=1478 used in this retrospective study

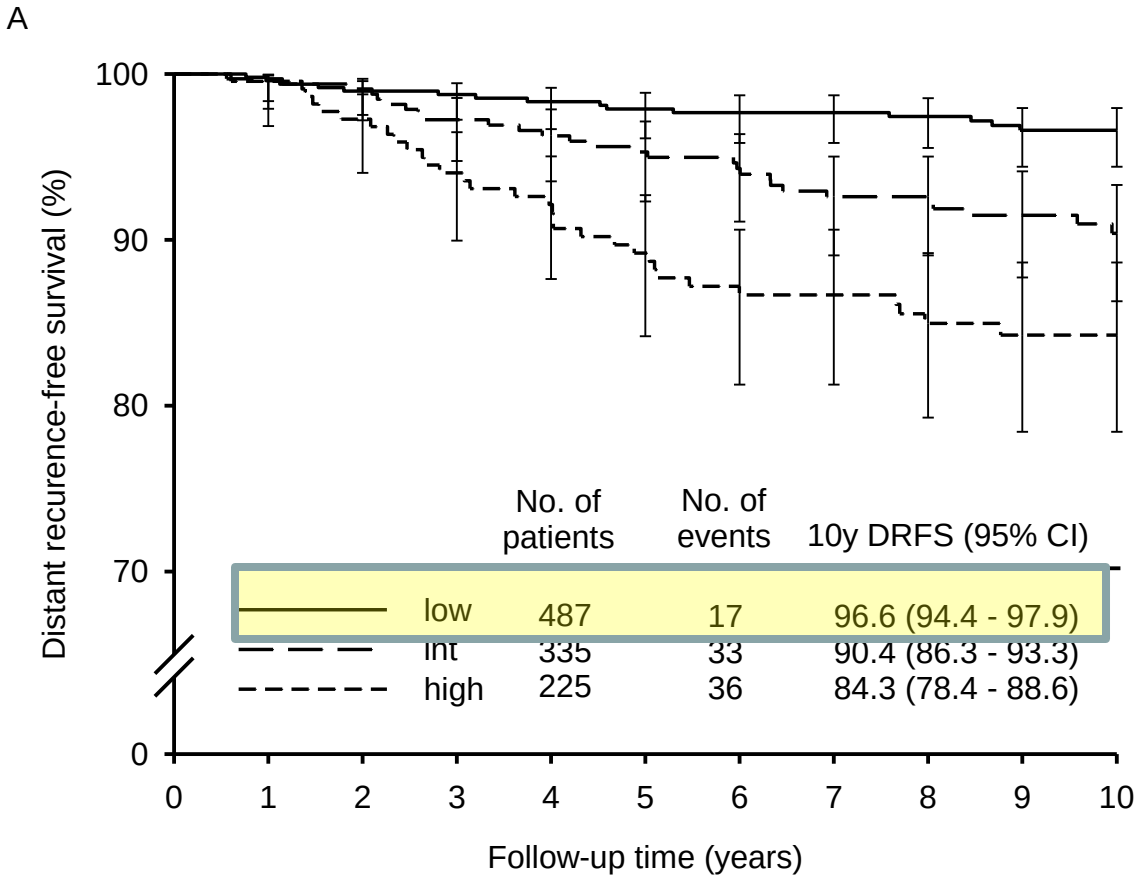


No. at risk:

Low	502	497	488	479	469	460	447	439	412	331	250
Int	478	466	454	437	423	416	400	387	370	289	220
High	498	484	465	428	399	370	347	330	301	238	198

Annals of Oncology 25: 339–345, 2014

ABCSG-8: PAM 50 ROR SCORE IN NODE NEGATIVE PATIENTS



No. at risk:

low	487	482	474	466	457	448	435	427	400	323	245
int	335	330	322	308	296	292	280	269	257	204	156
high	225	221	213	200	191	179	165	160	146	112	94

Annals of Oncology 25: 339–345, 2014

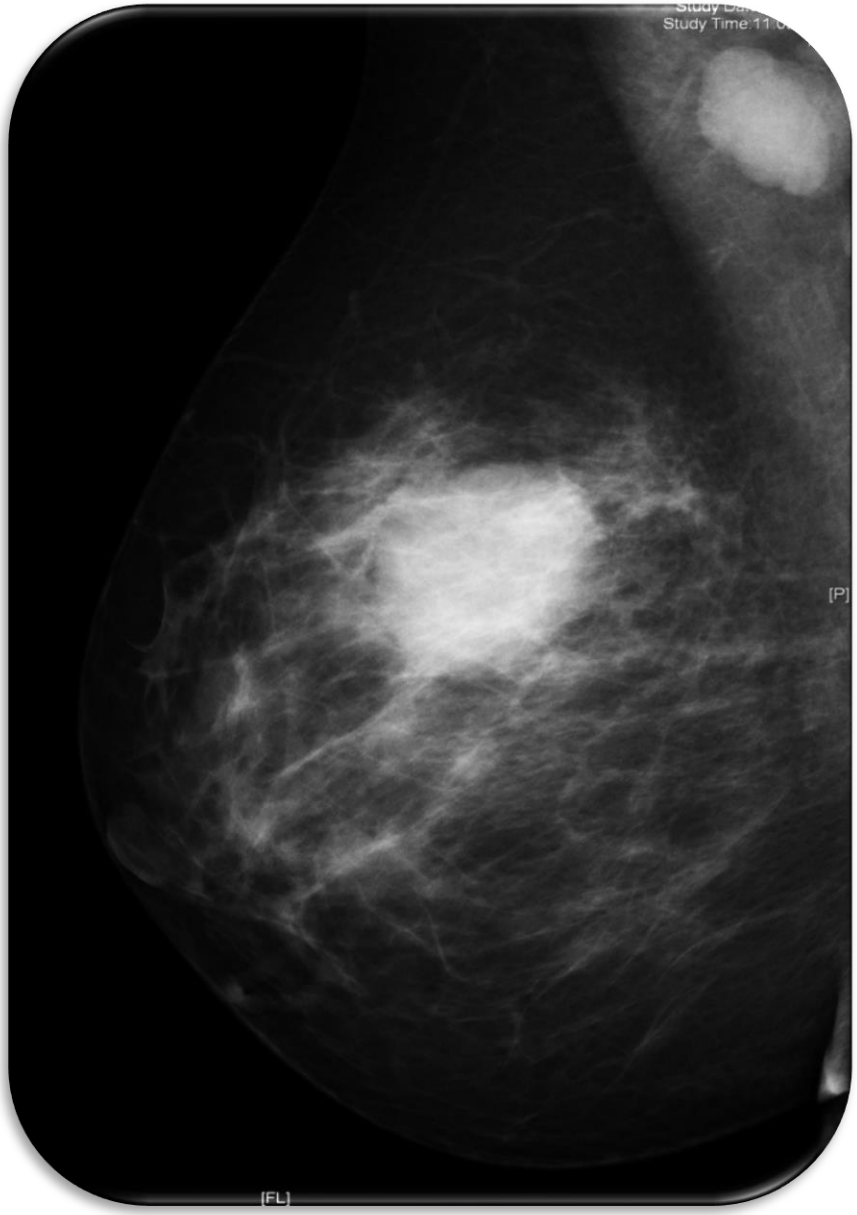
Use of multigene tests

- ***Careful and meticulous pathology evaluation*** **probably captures most of the information provided by 1st generation multi-gene tests.**
- **They *may be useful in a fraction* of patients with equivocal clinical-pathology features**

- **However such tests, especially Recurrence Score, have become popular in deciding about chemotherapy in ER pos, node negative women.**

Case 2

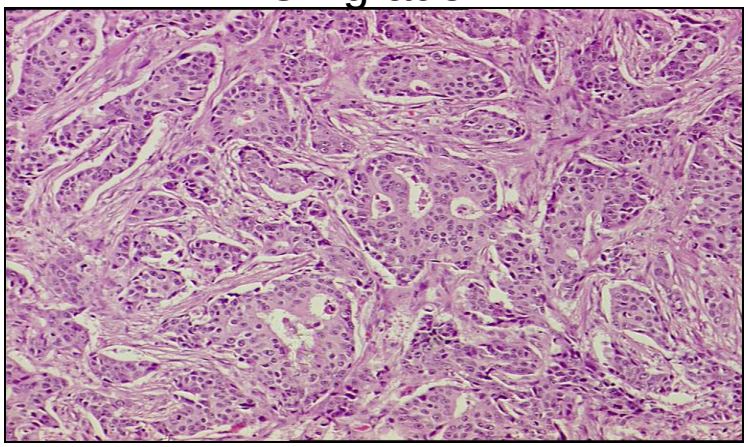
- 59 yrs old, postmenopausal woman with no comorbidities,
- Right breast lump of 13 months duration.
- Examination – 3.5 cm lump with single, palpable, mobile axillary LN of 2 cm
- CT scan of lungs and liver normal and bone scan shows no mets.



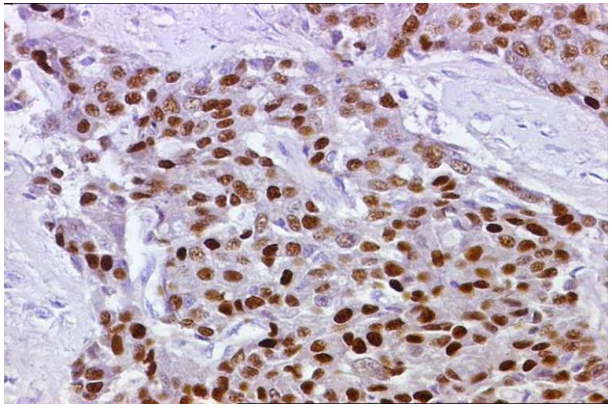
This MLO view shows a large mass in the upper aspect of the breast with enlarged nodes in the right axilla.

- **Undergoes right MRM with axillary clearance**
  - **IDC, grade 2, T size 3.1 cm, N 2/16**
  - **ER – 8/8, PR – 6/8, HER2 negative, Ki-67 – 10%**

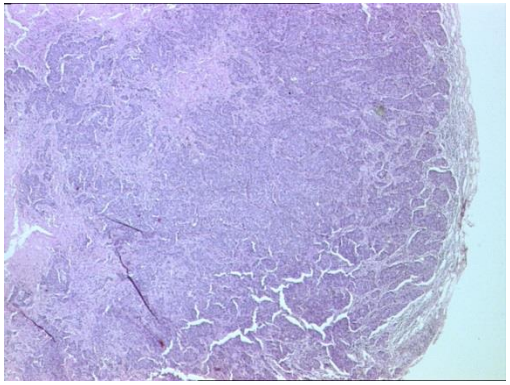
IDC - grade 2



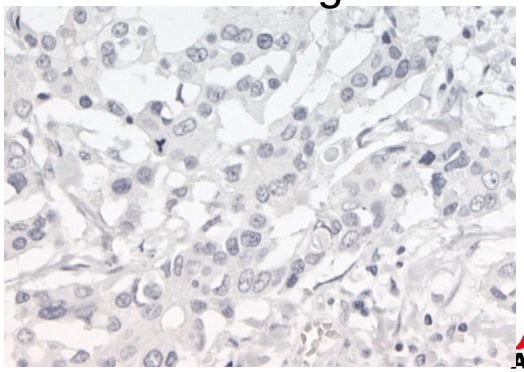
ER – strong +



LN shows mets



HER2 negative



Patient comes for post-operative counseling and adjuvant decision-making to you. She is somewhat reluctant for chemotherapy.

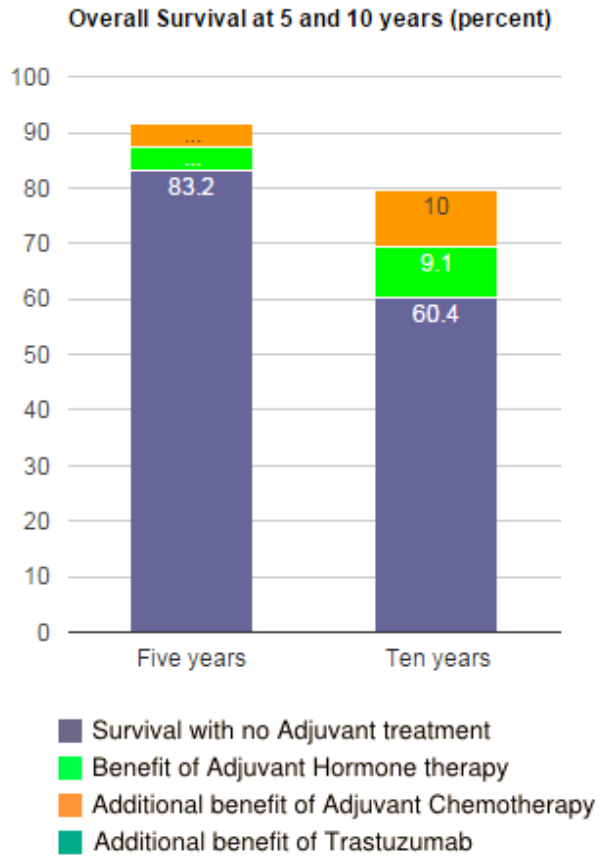
- **What would you do?**
  - ***Convince her about the likely benefit*** **of chemotherapy and its relative safety**
  - **Tell her that it is *okay to omit chemotherapy* and Rx with endocrine therapy only**
  - **Tell her *you are not sure* about the benefit of chemotherapy and would like additional multigene testing**

PREDICT Tool: Breast Cancer Survival; Results

Five year survival
83 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
An extra 4 out of 100 women treated are alive because of hormone therapy
An extra 8 out of 100 women treated are alive because of hormone therapy & chemotherapy

Ten year survival
60 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
An extra 9 out of 100 women treated are alive because of hormone therapy
An extra 19 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
(Or tap segment if using a mobile device)



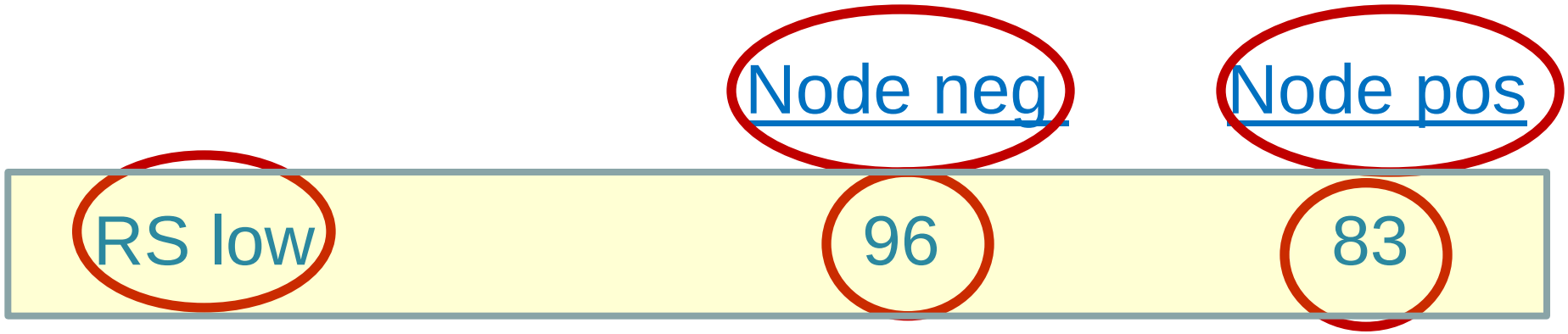
Use of Oncotype DX in Women with Node-Positive Breast Cancer

SWOG 8814 – Tam alone (Albain KS, et al). Lancet Oncol 2010

ATAC – Anastrazole Vs Tam (Dowsett M, et al). JCO 2010

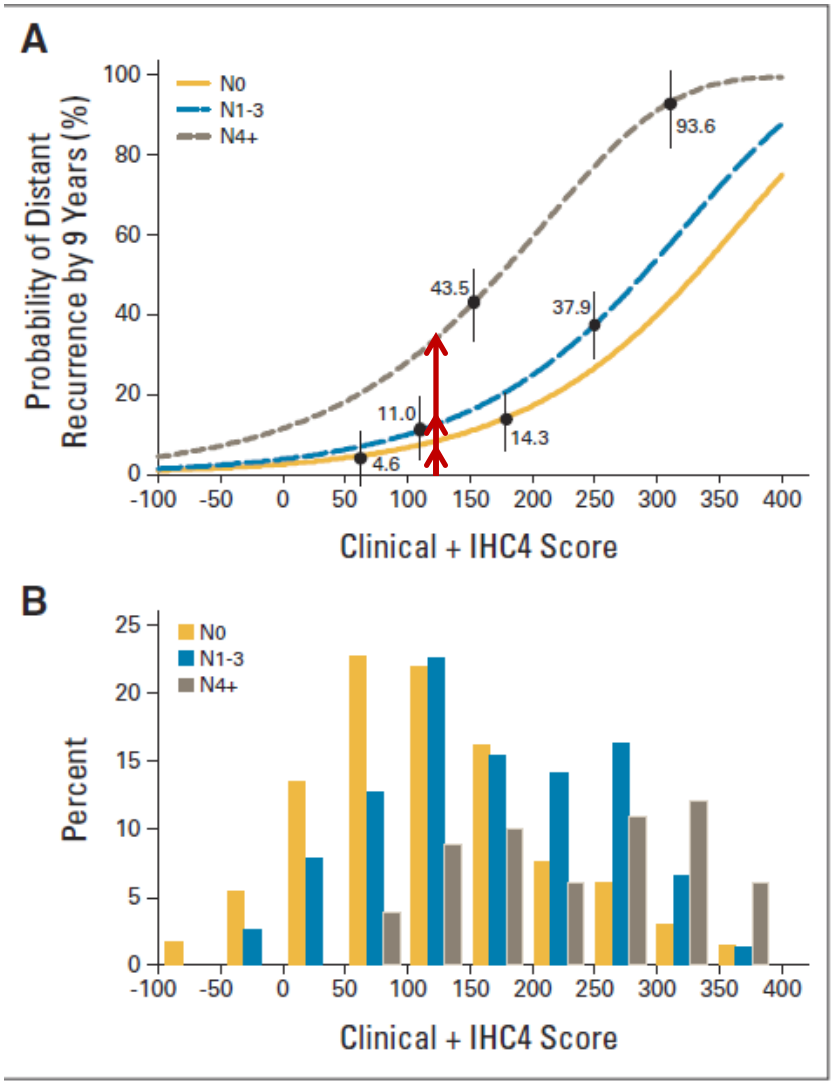
Effect of nodal status on 9-year distant RFS in RS categories: ATAC

9-year distant recurrence-free survival (%)



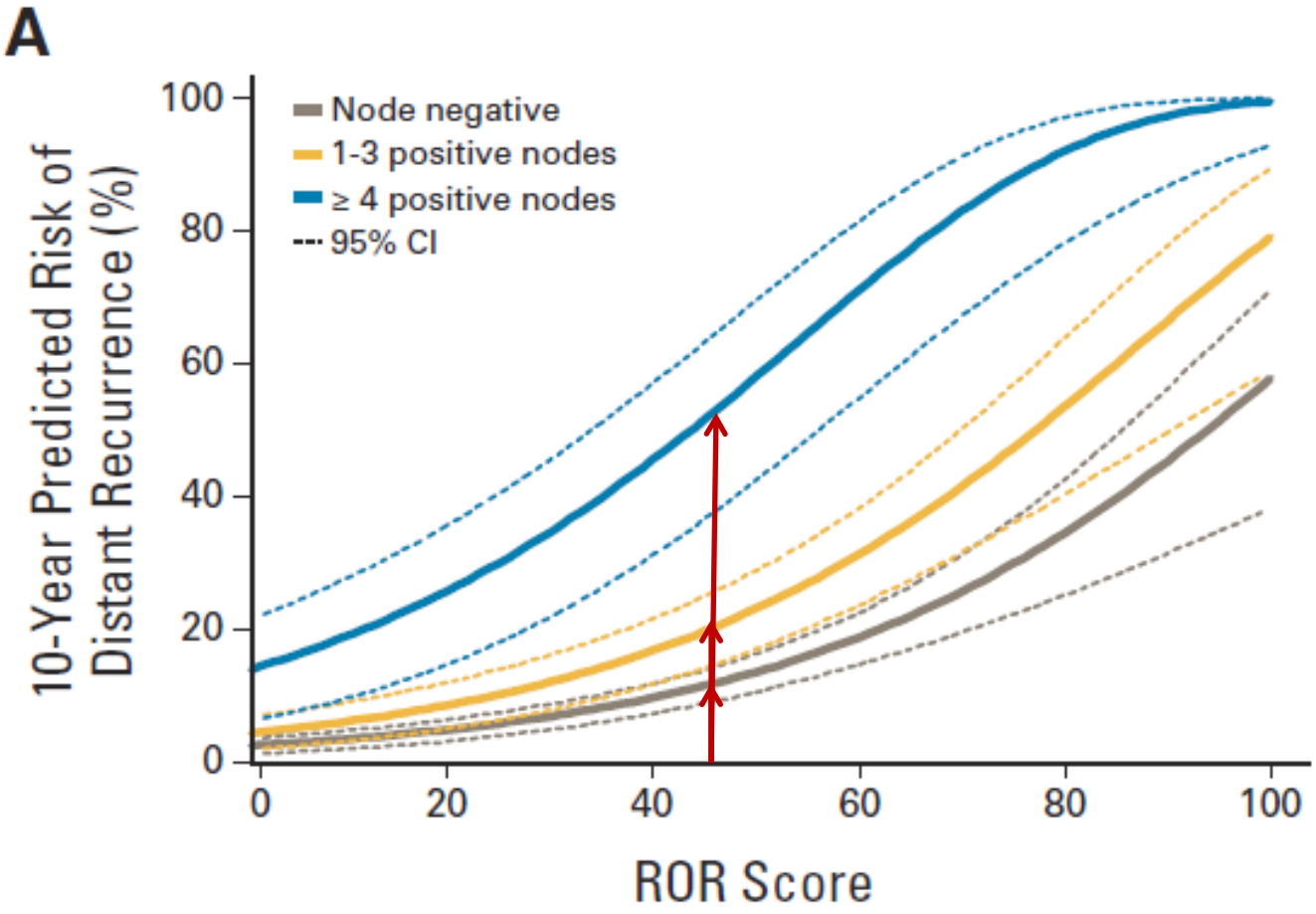
Dowsett M, et al. JCO 2010;28:1829-34

Impact of Nodal Status on risk of distant recurrence by IHC4-Clinical score ATAC data: Cuzick J, et al.



J Clin Oncol 29:4273-4278. © 2011

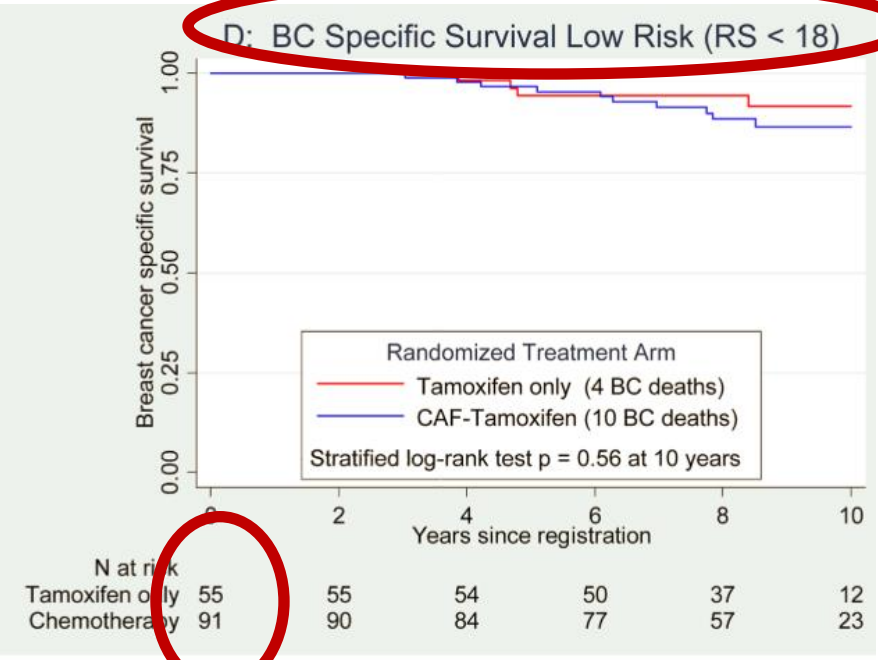
Impact of nodal status on risk of distant recurrence by PAM50 score. ATAC data, Dowsett et al.

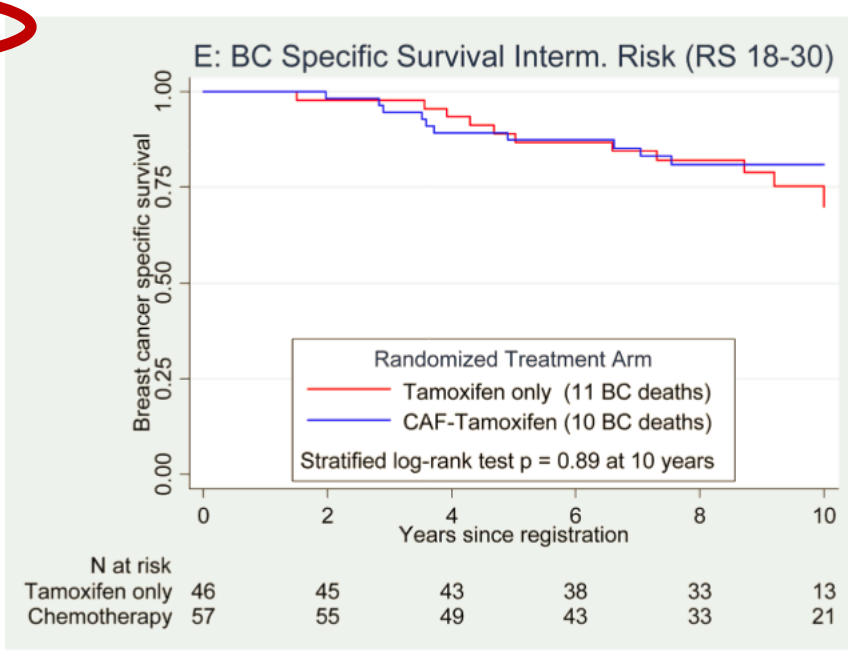


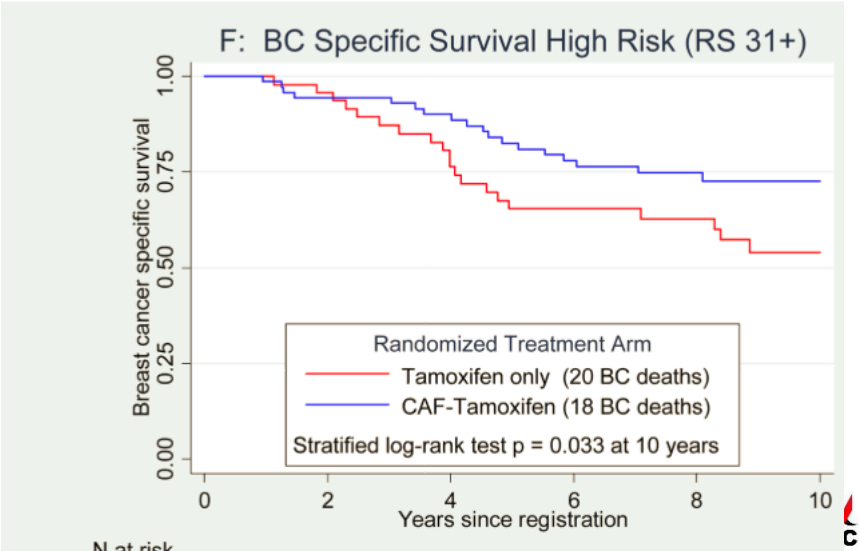
J Clin Oncol 31:2783-2790. © 2013

- ***Nodal status continues to exert a significant prognostic impact within multigene defined subgroups!***

Benefit of anthracycline chemotherapy by RS in node positive patients: SWOG-8814







Lancet Oncol. 2010 January ; 11(1): 55–65.

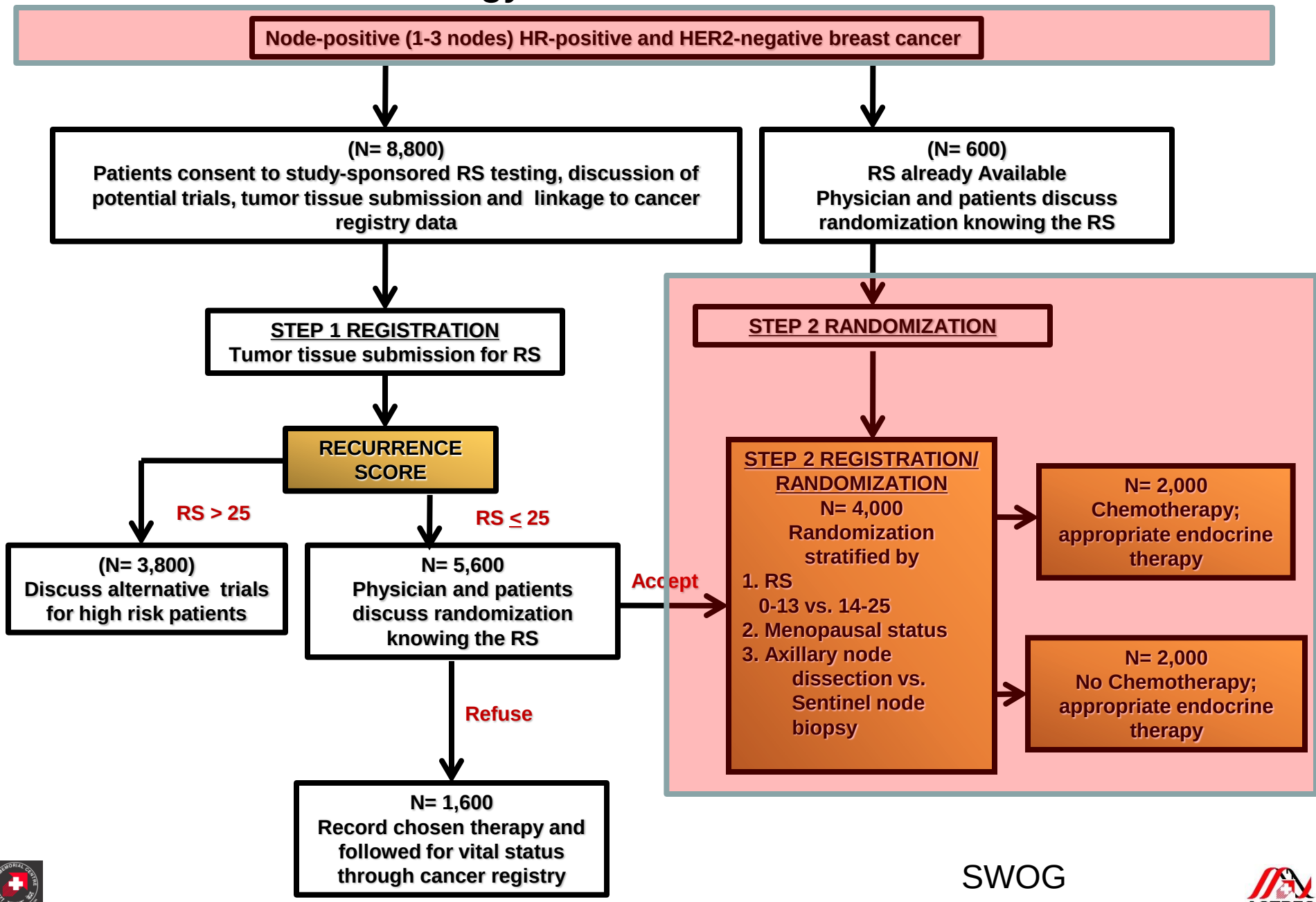
Targeting Adjuvant Chemotherapy: A Good Idea That Needs to Be Proven!

Daniel F. Hayes, *Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

Journal of Clinical Oncology, Vol 30, 2012

level evidence. I, and many of my colleagues, remain in equipoise, and I would urge caution to those who believe they are not. I completely support the RxPonder study. Until results from this landmark trial are available, I strongly recommend routine administration of adjuvant chemotherapy to women with positive axillary lymph nodes, regardless of their tumor biology.

RxPONDER: Biology Driven Rx for Node Positive Disease



SWOG

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  - **Tell her *you are not sure* about the benefit of chemotherapy and would like additional genomic testing**

Extended Adjuvant Endocrine Therapy

>5 years better than 5 years

- **ATLAS (tamoxifen after tamoxifen)**
- **aTTom (tamoxifen after tamoxifen)**
- **MA-17 (letrozole after tamoxifen)**
- **NSABP B-33 (exemestane after tamoxifen)**

For all? For some? Which?

Association of Clinical-Pathological features with late recurrence (recurrence >5 yrs, conditional upon surviving disease-free from years 0-5)

Multivariate Cox Models

Study/Variable	Age	T Size	N status	Grade	ER	PR	HER2	Ki-67
ATAC	-	✓	✓	X	X	-	X	X
Netherlands	X	X	✓	X	-	-	-	-
Austrian	X	X	✓	X	-	-	-	X

Sestak and Cuzick *Breast Cancer Research* (2015) 17:10
DOI 10.1186/s13058-015-0516-0

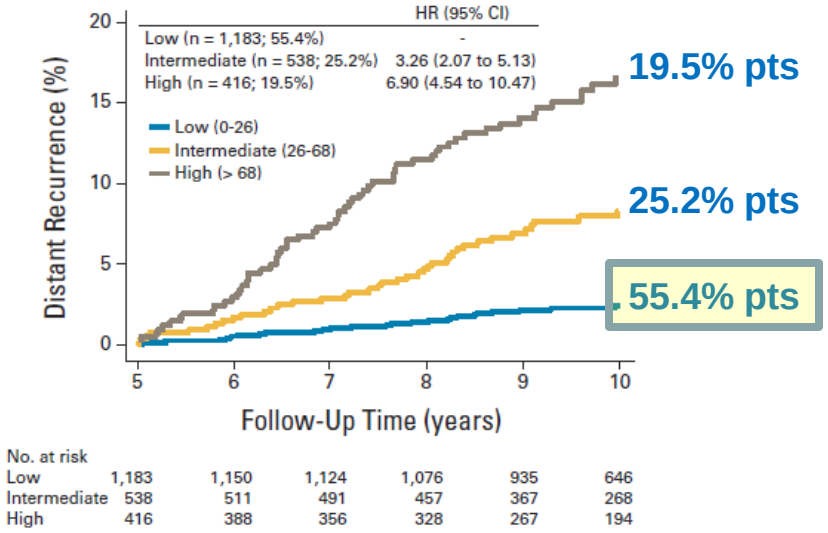
MOLECULAR ONCOLOGY 7 (2013) 987–999

British Journal of Cancer (2013) 109, 2959–2964

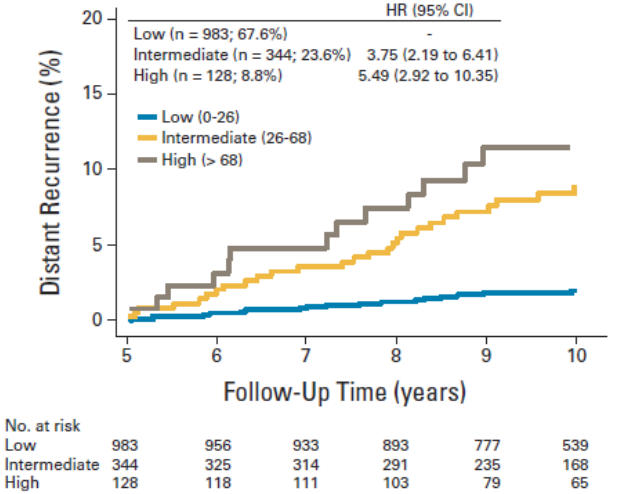
ACTREC

Prediction of Late Distant Recurrence After 5 Years of Endocrine Treatment: A Combined Analysis of Patients From the Austrian Breast and Colorectal Cancer Study Group 8 and Arimidex, Tamoxifen Alone or in Combination Randomized Trials Using the PAM50 Risk of Recurrence Score

Ivana Sestak, Jack Cuzick, Mitch Dowsett, Elena Lopez-Knowles, Martin Filipits, Peter Dubsky, John Wayne Cowens, Sean Ferree, Carl Schaper, Christian Fesl, and Michael Gnant



All patients



Node negative patients

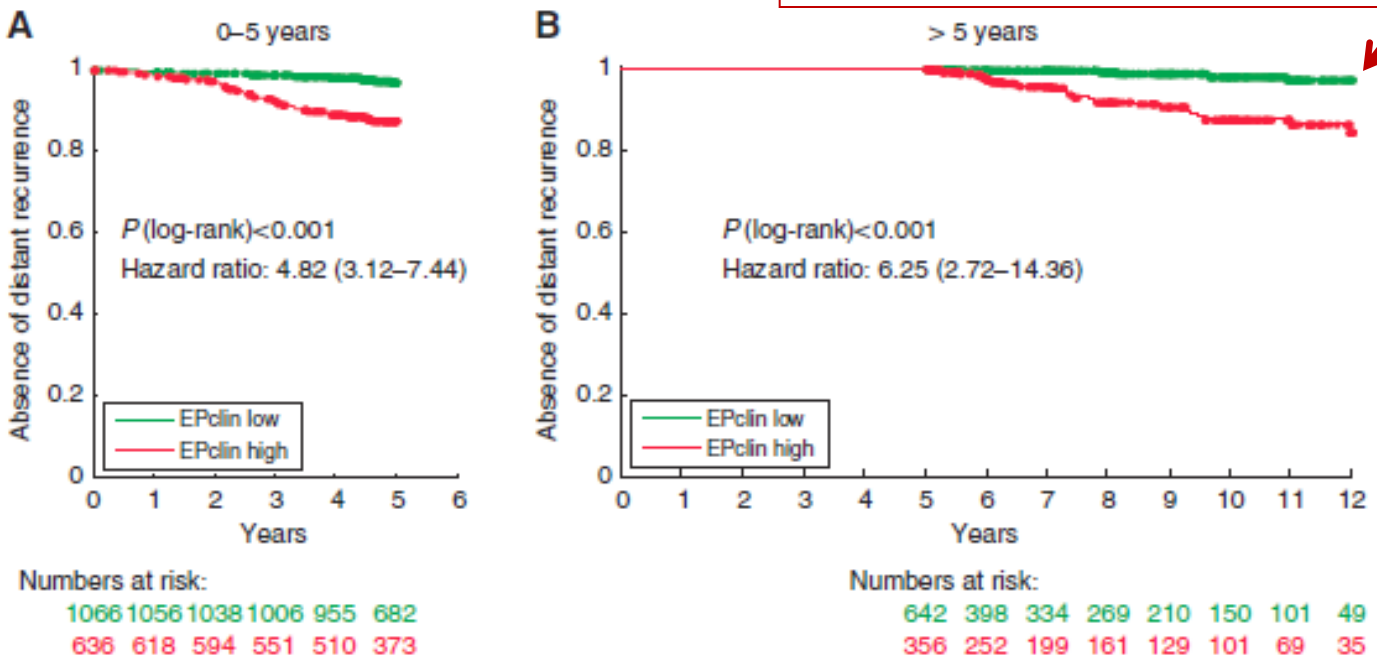
Among node positive patients, 24.6% were categorized as low-risk with 3.3% risk of relapse between yrs 5 to 10

J Clin Oncol 33:916-922. © 2014

The EndoPredict score provides prognostic information on late distant metastases in ER + /HER2 − breast cancer patients

P Dubsky*,[1], J C Brase[2], R Jakesz[1], M Rudas[3], C F Singer[4], R Greil[5], O Dietze[6], I Luisser[7], E Klug[8],

64% pts with distant met risk from yrs 5-10 of 1.8%



EndopredictClin = 3 proliferation + 5 ER + 4 housekeeping genes + Node + T size

British Journal of Cancer (2013) 109, 2959–2964 | doi: 10.1038/bjc.2013.671

FOLLIES AND FALLACIES IN MEDICINE

Third Edition

Petr Skrabanek
James McCormick

PLACEBOS

The physician's belief in his treatment and the patient's faith in his physician exert a mutually reinforcing effect; the result is a powerful remedy which is almost guaranteed to produce an improvement and sometimes a cure.

Char Chinar, Srinagar, Kashmir