5 Minute JournalClub

Key SABCS Presentations

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CME Information

LEARNING OBJECTIVES

- Recognize the strengths and weaknesses of the novel RSPC relative to the standard Onco*type* DX RS as a prognostic and/or predictive breast cancer biomarker.
- Effectively integrate the Onco*type* DX RS into risk-stratified adjuvant breast cancer treatment decision-making.
- Compare and contrast the accuracy with which pre- and postneoadjuvant RS predicts patient risk for disease recurrence.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Harold J Burstein, MD, PhD
Associate Professor of Medicine
Harvard Medical School
Breast Oncology Center
Dana-Farber Cancer Institute
Boston, Massachusetts

No real or apparent conflicts of interest to disclose.

Clifford Hudis, MD
Chief, Breast Cancer Medicine Service
Solid Tumor Division
Department of Medicine
Memorial Sloan-Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical College
New York, New York

Paid Research: Merck and Company Inc, Onyx Pharmaceuticals Inc.

Comparing the Prediction of Chemotherapy Benefit in Node-Negative, ER-Positive Breast Cancer Using the Recurrence Score and RSPC, a New Measure Integrating Clinical and Pathologic Data with the Recurrence Score

Tang G et al.

Proc SABCS 2010;Abstract S4-9.

Objective

- To compare the value of a new clinical tool called the Recurrence Score-Pathology-Clinical (RSPC) risk assessment vs the Onco*type* DX® Recurrence Score® (RS) in predicting chemotherapy benefit.
  - The RSPC was developed to assess risk of distant recurrence by integrating:
    - RS
    - Tumor grade
    - Pathologic tumor size
    - Patient age at surgery
    - Hormonal therapy (tamoxifen or anastrozole)

Tang G et al. *Proc SABCS* 2010;Abstract S4-9.

Methods

- Retrospective analysis of data from the NSABP-B-20 trial
- Eligibility
  - Participated in the NSABP-B-20 trial (ie, node-negative, ER-positive) of tamoxifen (TAM) or TAM plus chemotherapy (TAM/chemo).
  - Successful Onco*type* DX RS
  - ER score ≥6.5
- The chemotherapy benefit associated with each risk assessment tool was determined using a Cox proportional hazards regression model to determine RS or RSPC risk benefit x treatment interaction.

Tang G et al. *Proc SABCS* 2010;Abstract S4-9.

Patient Characteristics

	TAM alone	TAM/chemo	All
Clinically eligible with evaluable tumor block, n	227	424	651
Onco*type* DX and ER ≥6.5, n (%)	225 (99.1%)	400 (94.3%)	**625 (96%)**
Distant recurrence events, n	31	29	60

Tang G et al. *Proc SABCS* 2010;Abstract S4-9.

Patient Characteristics by Treatment Group (N = 625)

	TAM alone	TAM/chemo
RS, mean	20	21
Tumor grade*		
Low	25%	24%
Intermediate	41%	51%
High	34%	25%
Tumor size, mean	2.1 cm	2.1 cm
Age at surgery, mean	52 years	52 years
RSPC, mean	-2.05	-2.05

*p = *0.037 for TAM vs TAM/chemo*

Tang G et al. *Proc SABCS* 2010;Abstract S4-9.

Prediction of Chemotherapy Benefit

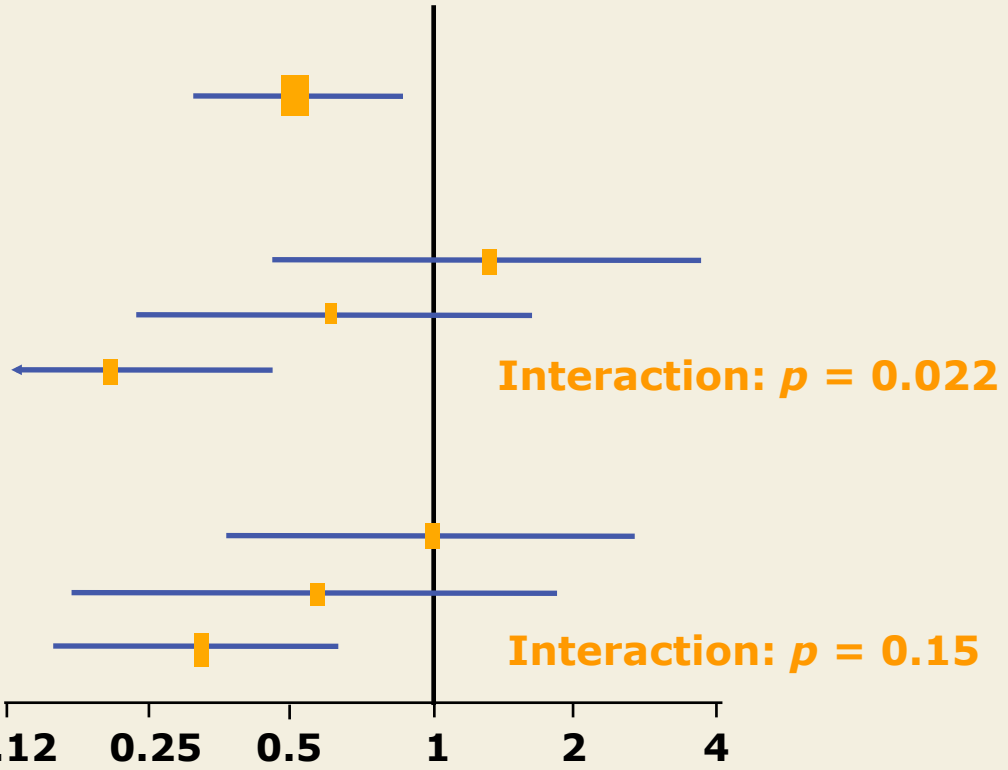
	Hazard ratio (95% CI)	*p*-value
RS*	2.22 (1.75-2.82)	<0.001
Treatment	0.63 (0.35-1.11)	0.11
RS* x treatment	0.65 (0.44-0.97)	0.034
RSPC*	2.43 (1.68-3.54)	<0.001
Treatment	0.64 (0.35-1.18)	0.156
RSPC* x treatment	0.65 (0.39-1.09)	0.1

*Standardized with standard deviation = 1.

Tang G et al. *Proc SABCS* 2010;Abstract S4-9.

Prediction of Chemotherapy Benefit by Risk Group

	TAM alone	TAM+ chemo
Included B-20 Patients	225	400
RS Risk Groups		
Low	135	217
Intermediate	45	90
High	45	93
RSPC Risk Groups		
Low	116	216
Intermediate	48	71
High	61	113



With permission from Tang G et al. *Proc SABCS* 2010;Abstract S4-9.

Conclusions

- The prediction of chemotherapy benefit was not improved with RSPC compared with RS.
  - Treatment interaction for RS x chemotherapy treatment was significant (p = 0.034) compared with that of RSPC (p = 0.10).
- The recommended method to predict chemotherapy benefit is RS alone.

Tang G et al. *Proc SABCS* 2010;Abstract S4-9.

Investigator Commentary: Prediction of Chemotherapy Benefit with the Recurrence Score with or without Clinical and Pathologic Factors

I believe the Recurrence Score-Pathology-Clinical (RSPC) risk assessment approach undermines the value of the Onco*type* DX assay, which is a gene-based assessment of chemotherapy sensitivity. In this study the investigators added in clinical and pathologic factors — with which, in multivariate analyses performed in the early days, the Recurrence Score was demonstrated to be superior.

The RSPC increased the number of patients who are deemed to have "low-risk" disease, but we lose the distinguishing feature of the Onco*type* DX assay, which is its ability to predict chemotherapy benefit. The predictive utility is key for me because it's always been what distinguished the Onco*type* DX assay from many other available prognostic tests. So, at the moment, it's difficult to see what advantage the RSPC offers compared to other prognostic tests. Currently, the Onco*type* DX assay is the only test that has any degree of validation for prediction of benefit from chemotherapy, and that goes away under this RSPC model.

Commentary by Clifford Hudis, MD, December 11, 2010

Meta-Analysis of the Decision Impact of the 21-Gene Breast Cancer Recurrence Score in Clinical Practice

Hornberger J, Chien R.

Proc SABCS 2010;Abstract P2-09-06.

Methods

- Meta-analysis performed on seven studies (n = 912)
  - Six retrospective chart reviews
  - One prospective analysis (Lo S et al. *J Clin Oncol* 2010)

- Studies were included that reported the following:
  - Number of patients who switched from treatment plan of chemotherapy plus hormone therapy (CT+HT) to hormone (HT) only based upon Onco*type* DX® Assay Recurrence Score® (RS) (CT+HT → HT)
  - Number of patients who switched from HT-only treatment plan to CT+HT (HT → CT+HT) based upon RS

Hornberger J, Chien R. *Proc SABCS* 2010;Abstract P2-09-06.

Study Summaries

Before RS	CT + HT		HT	
After RS	**CT + HT**	**HT**	**CT + HT**	**HT**
Asad J et al. *Am J Surg* 2008 (n = 81)	24	36	8	13
Henry L et al. *J Surg Oncol* 2009 (n = 29)	6	7	2	14
Klang S et al. *Value in Health* 2010 (n = 313)	69	105	20	119
Liang H et al. *Proc SABCS* 2007 (n = 260)	125	85	3	47
Lo S et al. *J Clin Oncol* 2010 (n = 83)	20	20	3	40
Oratz R et al. *J Oncol Pract* 2007 (n = 68)	19	14	3	32
Thanasoulis T et al. *Proc ASBS* 2008 (n = 78)	8	30	2	38

- Before RS testing: 568 (62%) of patients were recommended to be treated with adjuvant CT+HT.
- After RS testing: 312 (34%) of patients were recommended to be treated with adjuvant CT+HT.

Hornberger J, Chien R. *Proc SABCS* 2010;Abstract P2-09-06.

Probabilities of CT + HT

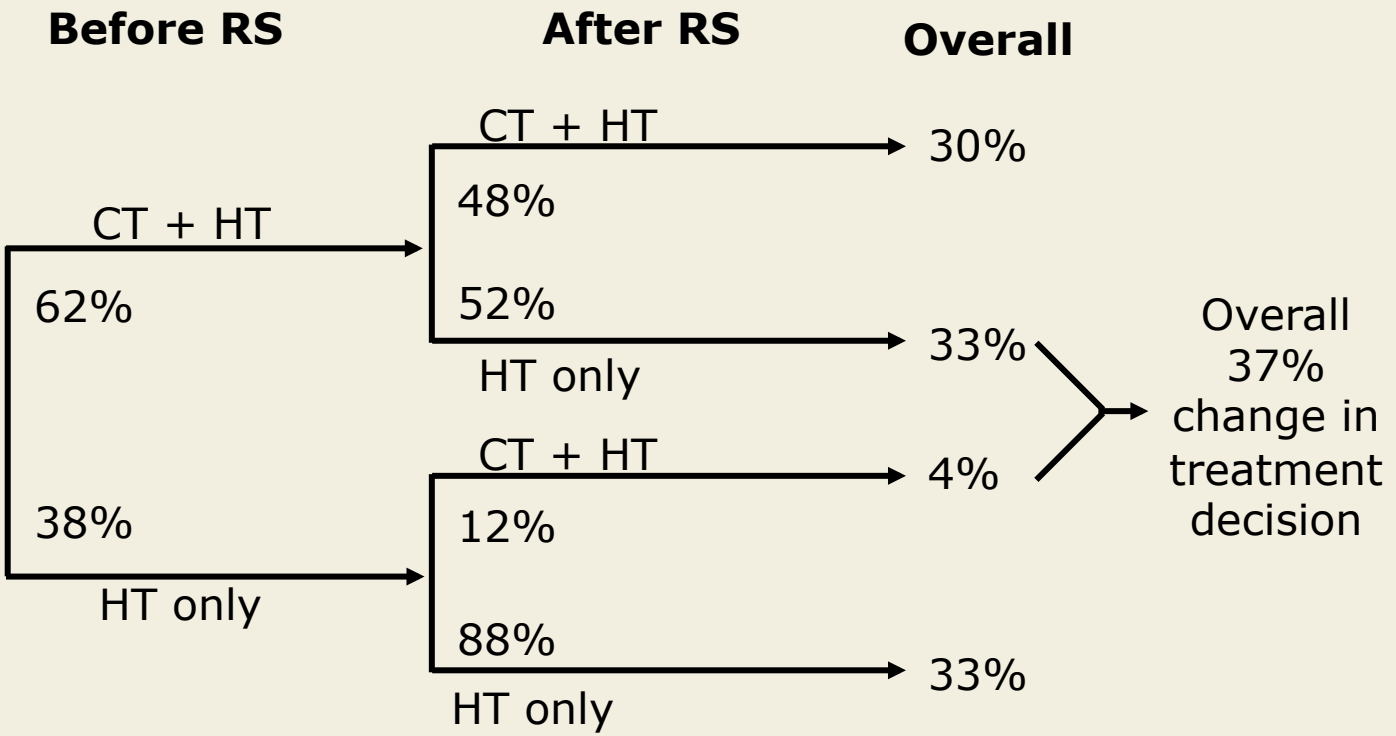
	Before RS	After RS	Difference
Asad J et al. *Am J Surg* 2008	74%	40%	-35%
Henry L et al. *J Surg Oncol* 2009*	45%	28%	-17%
Klang S et al. *Value in Health* 2010	56%	28%	-27%
Liang H et al. *Proc SABCS* 2007	81%	49%	-32%
Lo S et al. *J Clin Oncol* 2010	48%	28%	-20%
Oratz R et al. *J Oncol Pract* 2007	49%	32%	-16%
Thanasoulis T et al. *Proc ASBS* 2008	49%	13%	-36%
All studies	62%	34%	-28%
Excluding Liang H et al.	55%	28%	-27%

*All studies except Henry et al had statistically significant differences in CT recommendation before and after RS testing.

- Results: Net reduction of CT+HT recommendation of 28%

Hornberger J, Chien R. *Proc SABCS* 2010;Abstract P2-09-06.

Effect of Recurrence Score on Treatment Plans



- RS led to 37% change in treatment decisions overall.
- RS testing led to 52% switch in treatment recommendations in patients who were initially recommended to adjuvant CT+HT.
- RS testing led to 12% switch in treatment recommendations in patients who were initially recommended to HT only.

Hornberger J, Chien R. *Proc SABCS* 2010;Abstract P2-09-06.

Decision Impact of the 21-Gene Breast Cancer Recurrence Score in Clinical Practice

Rx Plan Before RS	Rx Plan After RS	N = 912 (%)
CT	CT	271 (30%)
HT only	HT only	303 (33%)
HT only	CT	41 (4%)
CT	HT only	297 (33%)

37%

Hornberger J, Chien R. *Proc SABCS* 2010;Abstract P2-09-06.

Discussion

- Overall reduction of CT recommendation or use is approximately 28%.
- One study (Liang H et al. *Proc SABCS* 2007) reported treatment recommendation based on NCCN guidelines against the RS.
  - Mean chemotherapy difference of 27% with this study excluded from analysis.
- The RS led to approximately 37% change in treatment decision.
- This meta-analysis summarizes the experience with RS in both academic institutions and community-based centers.

Limitations:

- Data are predominately US-based and may not reflect the regional variation in chemotherapy use around the world.
- Data from recently published prospective TRANSGEICAM study were not available at the time of this analysis.
  - Reported 15.5% of patients switched from CT+HT to HT and 12.7% of patients switched from HT-only to CT+HT (Albanell J et al. *Proc ESMO* 2010).

Hornberger J, Chien R. *Proc SABCS* 2010;Abstract P2-09-06.

Conclusions

- This meta-analysis shows approximately 27-28% reduction in the recommendation of chemotherapy after Onco*type* DX assay Recurrence Score testing.

- Overall, the RS changed more than a third of treatment decisions:
  - 33% of the overall population switched from CT+HT to HT only after RS testing.
  - 4% of the overall population switched from HT only to CT +HT after RS testing.

Hornberger J, Chien R. *Proc SABCS* 2010;Abstract P2-09-06.

Investigator Commentary: Meta-Analysis of the Effect of the Onco*type* DX Assay on Clinical Decision-Making

In this meta-analysis of seven published reports with approximately 1,000 patients, the investigators attempted to evaluate the effect of the Recurrence Score on clinical decision-making. They demonstrated consistently that the use of the Recurrence Score resulted in less administration of adjuvant chemotherapy.

On one hand, these findings are not surprising because the Recurrence Score performs well in identifying patients in the low- to intermediate-risk zone who do not need chemotherapy. A back-of-the-envelope calculation would quickly suggest that it should lower the use of adjuvant chemotherapy. On the other hand, it's a nice confirmation of that expectation and this is important to third-party payers and other regulators — because even an expensive test that spares patients chemotherapy will quickly pay for itself, because of the relatively high cost of chemotherapy.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

Prognostic Value of Genomic Analysis After Neoadjuvant Chemotherapy for Breast Cancer

Mayer EL et al.

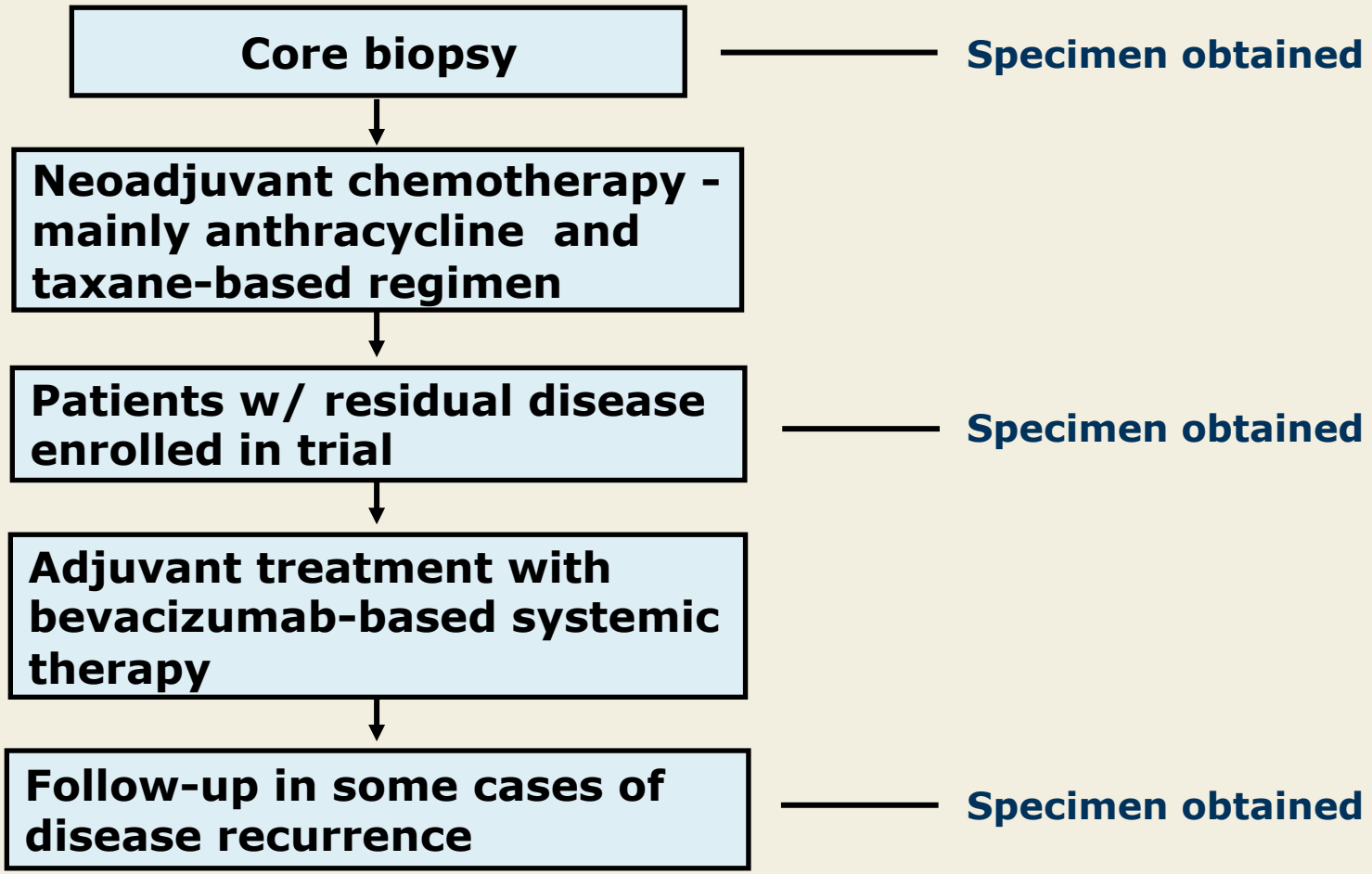
Proc SABCS 2010;Abstract P3-10-13.

Methods

- Patients were recruited from the Dana-Farber Cancer Institute 05-055 Phase II trial of adjuvant bevacizumab-based therapy for patients with residual disease after neoadjuvant therapy.
  - Accrual between 2005 and 2008
  - Sample size: 162 patients
- Formalin-fixed paraffin-embedded tissue blocks obtained at the following timepoints:
  - Baseline core biopsy
  - Residual tissue from surgery
  - Time of metastatic recurrence
- ER, PR and HER2 determined by IHC and/or FISH for all samples.
- Standard Onco*type* DX® testing was performed on all samples.

Mayer EL et al. *Proc SABCS* 2010;Abstract P3-10-13.

Study Design



Mayer EL et al. *Proc SABCS* 2010;Abstract P3-10-13.

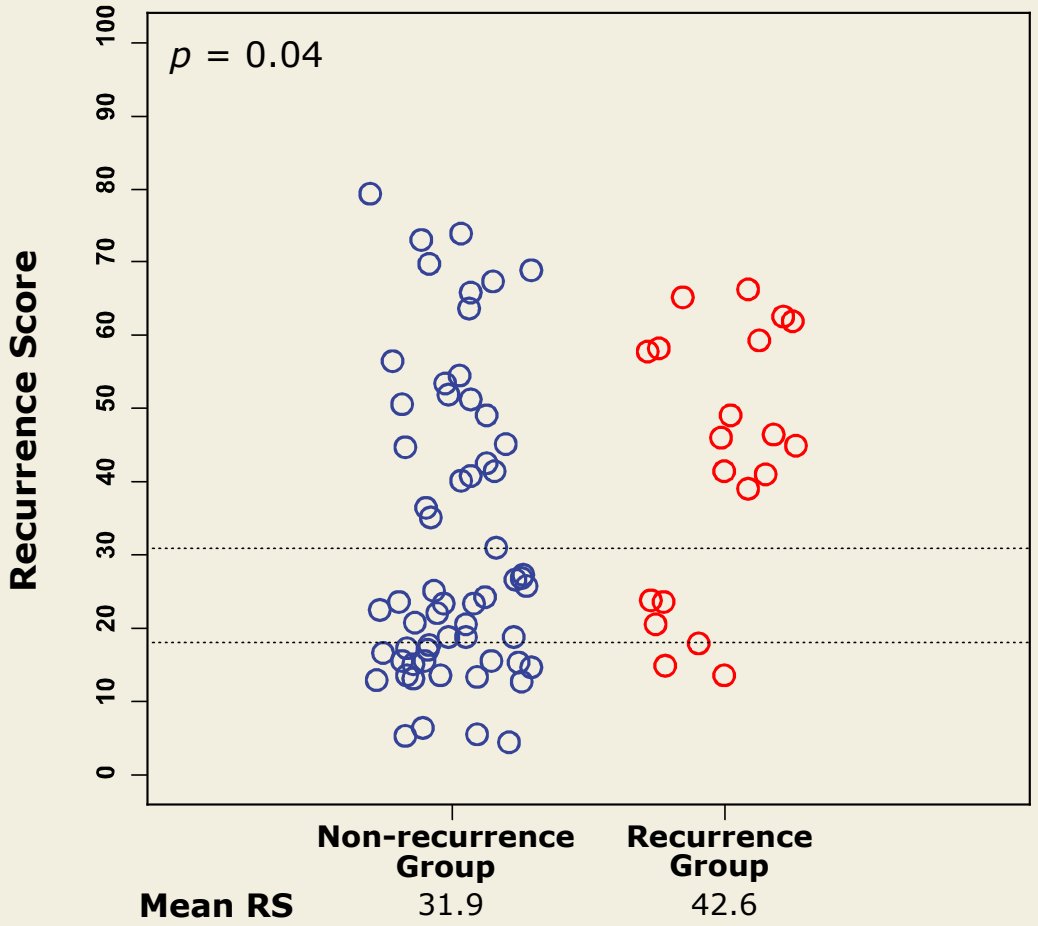
Clinical Samples Summary

	Samples	Patients
Included in data analysis	116	80
Core biopsy samples	47	—
Surgical excision samples	67	—
Core biopsy and surgical specimen pairs	68	34
Recurrence specimen	2	2

- A total of 20 patients experienced distant recurrence.
- A majority of patients were ER-positive and/or PR-positive and HER2-negative.

Mayer EL et al. *Proc SABCS* 2010;Abstract P3-10-13.

Distribution of Recurrence Score (RS) Values



n = 80 samples
47 core biopsies
33 surgical specimens

- A high RS was positively associated with distant recurrence

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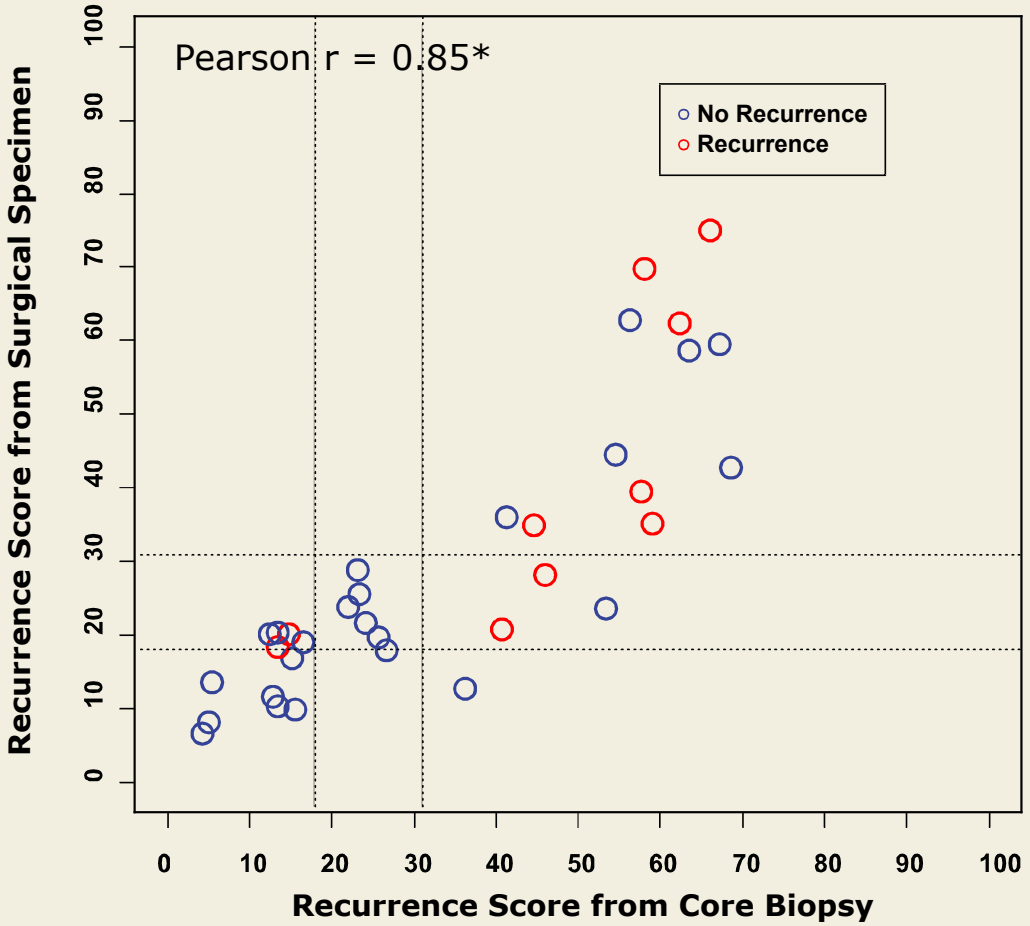
Comparison of RS Values from Patients with Core Biopsy and Surgical Specimens (n = 34)



* RS was highly correlated before and after exposure to chemotherapy (95% CI 0.72-0.92)

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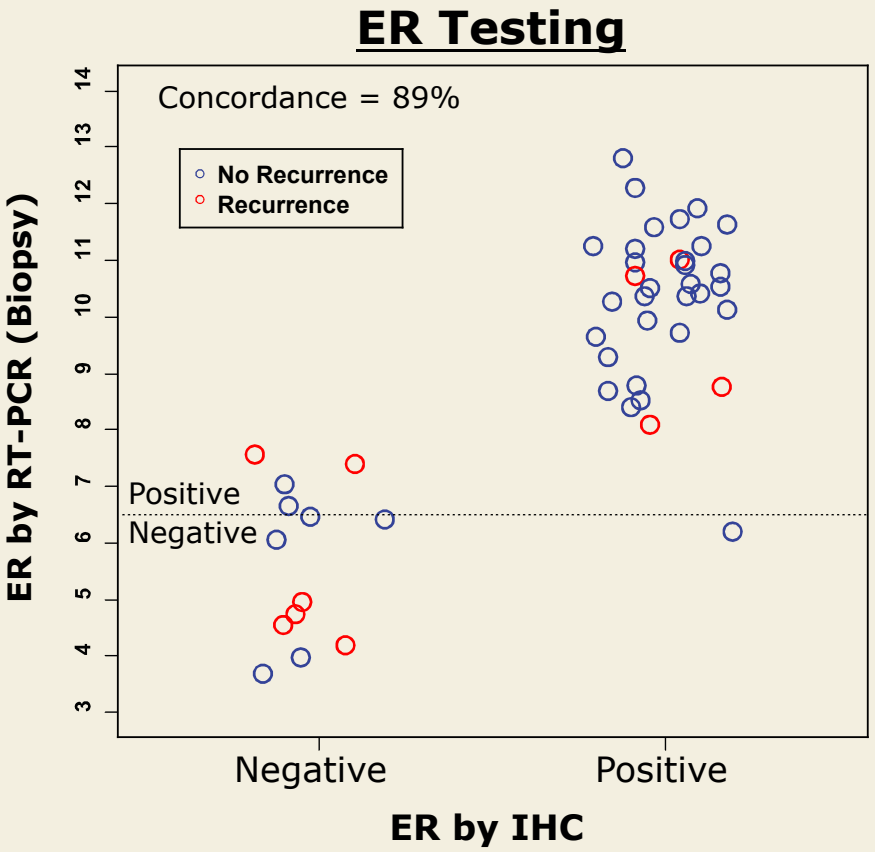
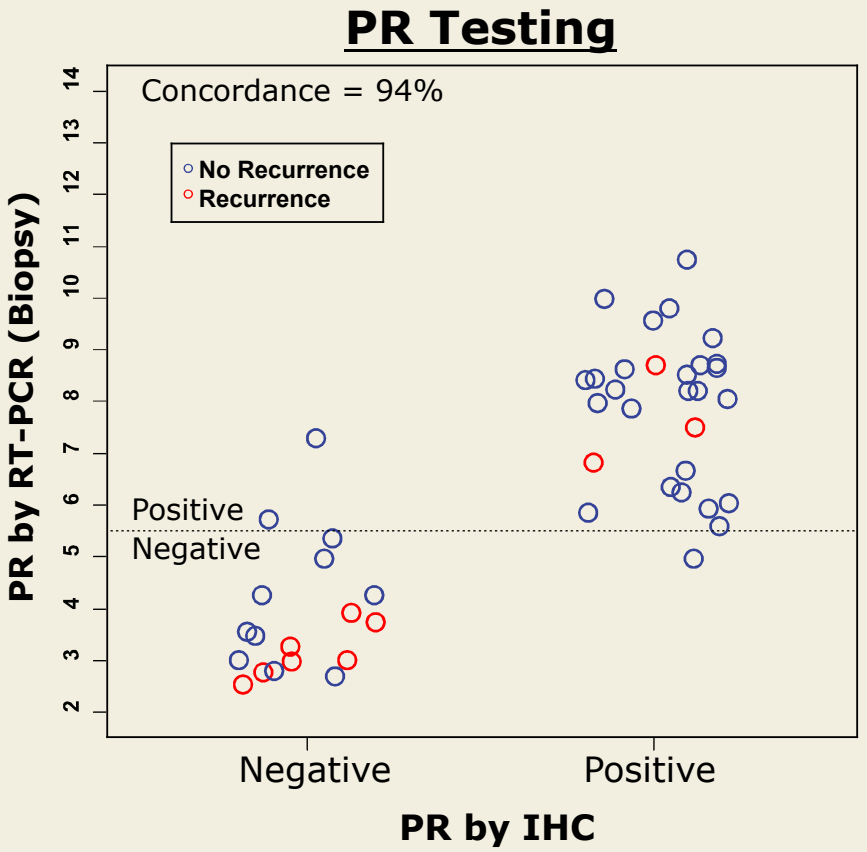
Concordance of ER/PR Testing by IHC vs RT-PCR in Prechemotherapy Samples





- Good concordance exists in ER/PR testing by local IHC vs RT-PCR for the prechemotherapy samples (n = 47 core biopsies)

With permission from Mayer EL et al. *Proc SABCS* 2010;Abstract P3-10-13.

Summary

- A high RS appeared to be associated with disease recurrence for the entire study cohort (p = 0.04).
- The RS determined either before or after neoadjuvant chemotherapy also appeared to be associated with disease recurrence (Pearson r = 0.85).
- RT-PCR results for ER/PR/HER2 remained consistent despite interval chemotherapy (data not shown).
- Despite high concordance between IHC and RT-PCR for ER/PR, the observed 6-11% discordance is of unclear origin and may have meaningful clinical consequences.
- Confirmation of the potential prognostic role of postneoadjuvant chemotherapy RS warrants additional study.

Mayer EL et al. *Proc SABCS* 2010;Abstract P3-10-13.

Investigator Commentary: Prognostic Value of Genomic Analysis After Neoadjuvant Chemotherapy

Our group conducted a series of studies in which we evaluated treating a unique and high-risk group of patients with breast cancer who had residual disease after neoadjuvant chemotherapy. On a series of protocols we offered them additional treatments, mostly built around bevacizumab.

We wanted to know how the pre- and post-treatment biopsy Recurrence Scores® correlated and whether we could study the residual tumors with an Onco*type* DX® assay to predict disease recurrence. Our studies were limited by a small sample size, but we showed a good correlation between tumor biopsy preneoadjuvant therapy and postneoadjuvant therapy. So whatever chemotherapy is doing to the tumor, it's not changing its Recurrence Score phenotype that much.

We also showed that if you review the post-treatment biopsy results by Recurrence Score, they remain robust predictors of the chance of disease recurrence in the years ahead. So we saw no real surprises in these findings — rather, it was another demonstration of the power of these molecular diagnostic tests.

Interview with Harold J Burstein, MD, PhD, December 22, 2010