Predicting Prognosis in Women with Early Breast Cancer

28TH ANNUAL
San Antonio Breast Cancer Symposium
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In women with early breast cancer, tools that predict both a prognosis and benefit from adjuvant chemotherapy are invaluable to both clinicians and patients. In women with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen, a 21-gene assay was recently found by the NSABP to predict the 10-year distant recurrence rate and the benefit associated with adjuvant chemotherapy. Additional data on this assay will be presented at this meeting. Another valuable resource is the Adjuvant! Online computer program, developed by Dr Peter Ravdin, which allows for the calculation of outcomes in women with early breast cancer. In a presentation at the 2004 ASCO meeting, the predictions from Adjuvant! were found to be comparable to actual outcomes observed in patients from British Columbia. These and future tools that predict outcomes should aid in making decisions about adjuvant therapies.

ONCO*TYPE* DX 21-GENE RECURRENCE SCORE ASSAY

Sixteen cancer and five reference genes from three studies

Proliferation
Ki-67
STK15
Survivin
CCNB1 (cyclin B1)
MYBL2

HER2
GRB7
HER2

Estrogen
ER
PGR
BCL2
SCUBE2

GSTM1

CD68

Reference
ACTB (ß-actin)
GAPDH
RPLPO
GUS
TFRC

Invasion
MMP11 (stromolysin 3)
CTSL2 (cathepsin L2)

BAG1

Recurrence score =

+0.47	x	GRB7 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	Recurrence score (0 - 100)
Low risk of recurrence	<18
Intermediate risk of recurrence	≥18 and <31
High risk of recurrence	≥31

SOURCES: Paik S. Presentation. San Antonio Breast Cancer Symposium 2003;Abstract 16; Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

NSABP-B-14 TAM BENEFIT STUDY IN PATIENTS WITH NODE-NEGATIVE, ER-POSITIVE DISEASE

ARM 1	Placebo
ARM 2	Tamoxifen

Objective: Determine whether the 21-gene recurrence score assay captures prognosis, response to tamoxifen or both

KAPLAN-MEIER ESTIMATES OF THE 10-YEAR DISTANT RECURRENCE RATE ACCORDING TO A 21-GENE RECURRENCE SCORE (N = 668)

Risk group	Percent of patients	10-year distant recurrence rate	95% confidence interval
Low (RS < 18)	51	6.8%	4.0-9.6
Intermediate (RS = 18-30)	22	14.3%	8.3-20.3
High (RS ≥ 31)	27	30.5%	23.6-37.4

RS = recurrence score
$p < 0.001$ for comparison between high- and low-risk groups

SOURCE: Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

COMPARISON OF OUTCOMES PREDICTED BY ADJUVANT! AND ACTUAL OUTCOMES OBSERVED BY THE BREAST CANCER OUTCOMES UNIT (BCOU) IN BRITISH COLUMBIA (N = 4,083)

Parameter	Adjuvant! predicted	BCOU observed	Difference between predicted and observed*
10-year OS	71.7%	72.0%	-0.3%
10-year BCSS			
Overall	83.2%	82.5%	+0.7%
No therapy	89.1%	90.1%	-1.0%
T	81.2%	79.4%	+1.8%
C	74.6%	73.7%	+0.9%
T + C	75.2%	70.6%	+4.6%
10-year EFS	71.0%	70.1%	+0.9%

OS = overall survival; BCSS = breast cancer-specific survival
T = tamoxifen; C = chemotherapy; EFS = event-free survival
* All *p*-values are nonsignificant.

SOURCE: Olivotto IA et al. *J Clin Oncol* 2005;23(12):2716-25.

NSABP-B-20 CHEMOTHERAPY BENEFIT STUDY IN PATIENTS WITH NODE-NEGATIVE, ER-POSITIVE DISEASE

ARM 1	Tamoxifen + MF
ARM 2	Tamoxifen + CMF
ARM 3	Tamoxifen

Objective: Determine the magnitude of the chemotherapy benefit as a function of the 21-gene recurrence score assay

B-20 EVALUATION PATIENTS (N = 651) SIMILAR TO ALL PATIENTS (N = 2,299)

	Number of eligible patients			
	Tamoxifen	Tamoxifen+MF	Tamoxifen+CMF	Total
All B-20	770	763	766	2,299
GHI-B-20 (% of all B-20)	227 (29.5%)	203 (26.6%)	221 (28.9%)	651 (28.3%)

GHI-B-20 study subjects were similar to all B-20 patients.

SOURCES: Paik S. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract24; Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

TEN-YEAR DISTANT RECURRENCE-FREE SURVIVAL ACCORDING TO A 21-GENE BREAST CANCER RECURRENCE SCORE

Risk group	Percent of patients	Tamoxifen (n = 227)	Tamoxifen + chemotherapy (n = 424)	*p*-value
Low (RS < 18)	51%	96%	95%	0.76
Intermediate (RS = 18-30)	22%	90%	89%	0.71
High (RS ≥ 31)	27%	60%	88%	0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCES: Paik S. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 24; Paik S. Presentation. San Antonio Breast Cancer Symposium 2003;Abstract 16; Paik S et al. *N Engl J Med* 2004;351(27):2817-26.

SELECT PUBLICATIONS

Goldhirsch A et al. **Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer.** *J Clin Oncol* 2003;21(17):3357-65.

Olivotto IA et al. **Population-based validation of the prognostic model Adjuvant! for early breast cancer.** *J Clin Oncol* 2005;23(12):2716-25.

Paik S. **Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 24.

Paik S. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** Presentation. San Antonio Breast Cancer Symposium 2003;Abstract 16.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

Paik S et al. **Risk classification of breast cancer patients by the Recurrence Score assay: Comparison to guidelines based on patient age, tumor size, and tumor grade.** *Breast Cancer Res Treat* 2004;88(1 Suppl 1);118;Abstract 104.

Piccart MJ et al. **Multi-center external validation study of the Amsterdam 70-gene prognostic signature in node negative untreated breast cancer: Are the results still outperforming the clinical-pathological criteria?** San Antonio Breast Cancer Symposium 2004;Abstract 38.

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91.

*ONCO*TYPE *DX™ ASSAY TO PREDICT RESPONSE TO CHEMOTHERAPY*

We evaluated the NSABP-B-20 chemotherapy arms to address whether the assay predicted chemotherapy responsiveness. We went into that study with an a priori hypothesis, based on the data presented at the 2004 ASCO meeting by Dr Luca Gianni's group in Milan evaluating samples from a neoadjuvant trial they performed with paclitaxel and doxorubicin. They demonstrated a correlation between the Genomic Health recurrence score and pCR rate. The higher recurrence score correlated strongly with the higher pCR rate.

In NSABP-B-20, the results are quite striking and unlike anything I've ever seen. The absolute benefit from chemotherapy is negative in the low-risk group and zero in the intermediate-risk group. In the high-risk group, the absolute improvement in distant recurrence at 10 years is 28 percent, or a relative risk reduction of 75 percent.

The data in the low-risk group are, in a sense, not relevant because the baseline risk after tamoxifen is so low — 6.8 percent — so it's a moot point of whether they need chemotherapy or not. In the intermediate-risk group the confidence interval overlaps with one, so whether patients with intermediate-risk disease gain any benefit or not remains a question.

— Soonmyung Paik, MD.* Breast Cancer Update *2005 (3)

We wanted to determine whether the assay could predict the benefit of chemotherapy, so we examined the data from NSABP-B-20, which randomly assigned patients with receptor-positive, node-negative disease to tamoxifen versus tamoxifen plus CMF chemotherapy versus tamoxifen plus MF chemotherapy. We found that patients at high risk derived benefit from chemotherapy, but patients at low risk, who comprised 50 percent of the cohort, did not appear to derive substantial benefit from the addition of chemotherapy to tamoxifen.

The intermediate group comprised only 20 to 25 percent of the cohort, and we didn't have the power to determine if they benefit from the addition of chemotherapy. We were surprised to find that the relative risk reduction was not uniform — different risk groups did not have the same relative risk reduction. The greatest relative risk reduction was seen in patients at highest risk.

— Norman Wolmark, MD.
Breast Cancer Update *for Surgeons 2005 (1)*

*UTILIZATION OF COMPUTERIZED MODELS AND THE ONCO*TYPE *DX ASSAY*

John Bryant presented data at the last St Gallen meeting evaluating the recurrence score and Adjuvant! Online, and they seem to perform independently to a certain extent. Adjuvant! Online will add to the recurrence score, and the recurrence will add to Adjuvant! Online. Peter Ravdin is working with us to modify Adjuvant! Online to introduce recurrence score. They provide complementary information, which is important for the patient. However, Adjuvant! Online doesn't provide any prediction on benefit from therapy, whereas the recurrence score adds prognostic and predictive value.

— Eleftherios P Mamounas, MD, MPH.
Breast Cancer Update *for Surgeons 2005 (3)*

BENEFITS OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH ER-POSITIVE TUMORS

As with several other recent retrospective studies, Don Berry's presentation at the last San Antonio meeting on sequential trials of adjuvant chemotherapy in CALGB trials, demonstrated that the effects of chemotherapy were substantially greater in patients with ER-negative than ER-positive tumors. A key question is: Do these results apply only to that lineage of chemotherapy or can they be generalized to chemotherapy overall, and how does this relate to the clinical use of adjuvant chemotherapy in patients with ER-positive tumors? This will be a matter of debate for some time to come.

— G Thomas Budd, MD.* Breast Cancer Update *2005 (8)