5 Minute JournalClub

Effect of a 21-Gene RT-PCR Assay on Treatment Recommendations for Patients with Node-Positive, ER-Positive Breast Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Recognize the therapeutic impact of the Onco*type* DX Recurrence Score on the clinical management of node-positive, ER-positive early breast cancer.

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IN THIS ISSUE:

- **SWOG analysis** again demonstrates lack of benefit of adjuvant chemotherapy for patients with node-positive tumors and low Recurrence Scores®
- **Survey demonstrates** similar clinical practice impact of Onco*type* DX for patients with node-positive tumors to that previously seen with node-negative tumors
- **Onco*type* DX results from core biopsies** similar to those from excisional biopsies

The current Phase III adjuvant breast cancer research platform to a great extent was shaped by the deep passion and commitment of two legendary clinical investigators, the NSABP's Dr Bernard Fisher and Dr Gianni Bonadonna from the Milan Cancer Institute. Bernie was actually the first person interviewed when the *Breast Cancer Update* audio series was launched in 1988, and not long after, I met up with the very suave Dr Bonadonna, who resembled a classic Italian movie star much more than a world-class scientist. Beginning in the late 1960s, these fiery and inspirational leaders persuaded an international audience to support clinical trials evaluating the then-heretical idea of giving chemotherapy to patients who might already be cured. Bonadonna managed to obtain support for the logical approach of adjuvant combination chemotherapy (CMF), while Bernie struggled just to study L-PAM.

At this year's San Antonio meeting I met Dr Bonadonna's protégé, Dr Luca Gianni, who last year at the meeting presented the NOAH study that was just published in the *JCO* and demonstrated Buzdar-like results of neoadjuvant chemo with a trastuzumab/anthracycline-containing regimen for locally advanced HER2-positive disease. With the excellent Italian research infrastructure developed by Dr Bonadonna and others, including Dr Umberto Veronesi, Dr Gianni has led a number of important studies of pre-op therapy, including one of the few to investigate Onco*type* DX as a predictor of response to neoadjuvant chemotherapy. (As one might guess, it predicted path CRs.) At the end of our chat, Dr Gianni casually mentioned that his cooperative group (Fondazione Michelangelo) was running a trial randomizing patients with ER-positive, HER2-negative, node-positive tumors and low Recurrence Scores to hormone therapy alone or preceded by chemotherapy.

Upon hearing these words, I swallowed and asked, just to be sure: "So this is essentially a TAILORx-like study for patients with node-positive tumors?" His answer was simply, "Yes." Walking back to the "Marriott attached to the mall," I ran into Dan Hayes and asked if he knew that the Italians had pulled off what the US cooperative groups had been trying to implement since Kathy Albain presented the initial 2007 San Antonio SWOG node-positive data set on Onco*type* DX. It was news to Dan, who seemed frustrated by the glacier-like trial development and review process in the United States.

Meanwhile, *Lancet Oncology* had teamed up with Dr Albain, the SWOG investigators and San Antonio and arranged to publish electronically the definitive "node-positive" Onco*type* paper at 5:30 PM CST, the moment that Dr Christos Sotiriou walked to the podium on the first day of the meeting to discuss the poster findings. This new SWOG analysis has the same message as the initial one: Patients with low and maybe intermediate Recurrence Score tumors don't seem to benefit from chemotherapy. However, there is uniform support for a prospective trial very much like the one Dr Gianni described that will attempt to prospectively validate the clinical utility of the Recurrence Score for patients with node-positive tumors.

Our Patterns of Care surveys show that US-based oncologists are already using Onco*type* DX for some patients with node-positive tumors, and this new data set is likely to increase reliance on this practice-changing assay. Hopefully, the test will help guide physicians to enroll their patients with node-positive, low Recurrence Score tumors on clinical trials of novel therapies that might lower the risk of disease progression. This shouldn't be too difficult with the current PARP inhibitor mania and other promising approaches, such as the use of high-dose megestrol acetate to stimulate production of the NM23-H1 antimetastatic factor. One might also envision the utility of Onco*type* DX for some older patients or those with comorbidities, with node-positive tumors and high Recurrence Scores who might otherwise be inclined to skip treatment but might reconsider with an assay predicting high efficacy.

What's maybe even more important is what can be accomplished with an appropriate community-based research infrastructure and effective leadership as demonstrated by the Milan group and, for that matter, by the Austrians, whose zoledronic acid adjuvant study was among the most important new data sets in the field in recent years. Drawing from a smaller population than in the state of Florida, the Milan group believes it can complete what is most definitely a landmark study. To get results quicker, maybe the NSABP should consider joining in. It would be the perfect partnership, considering how these two groups and their founding fathers truly helped move the field forward for the benefit of patients.

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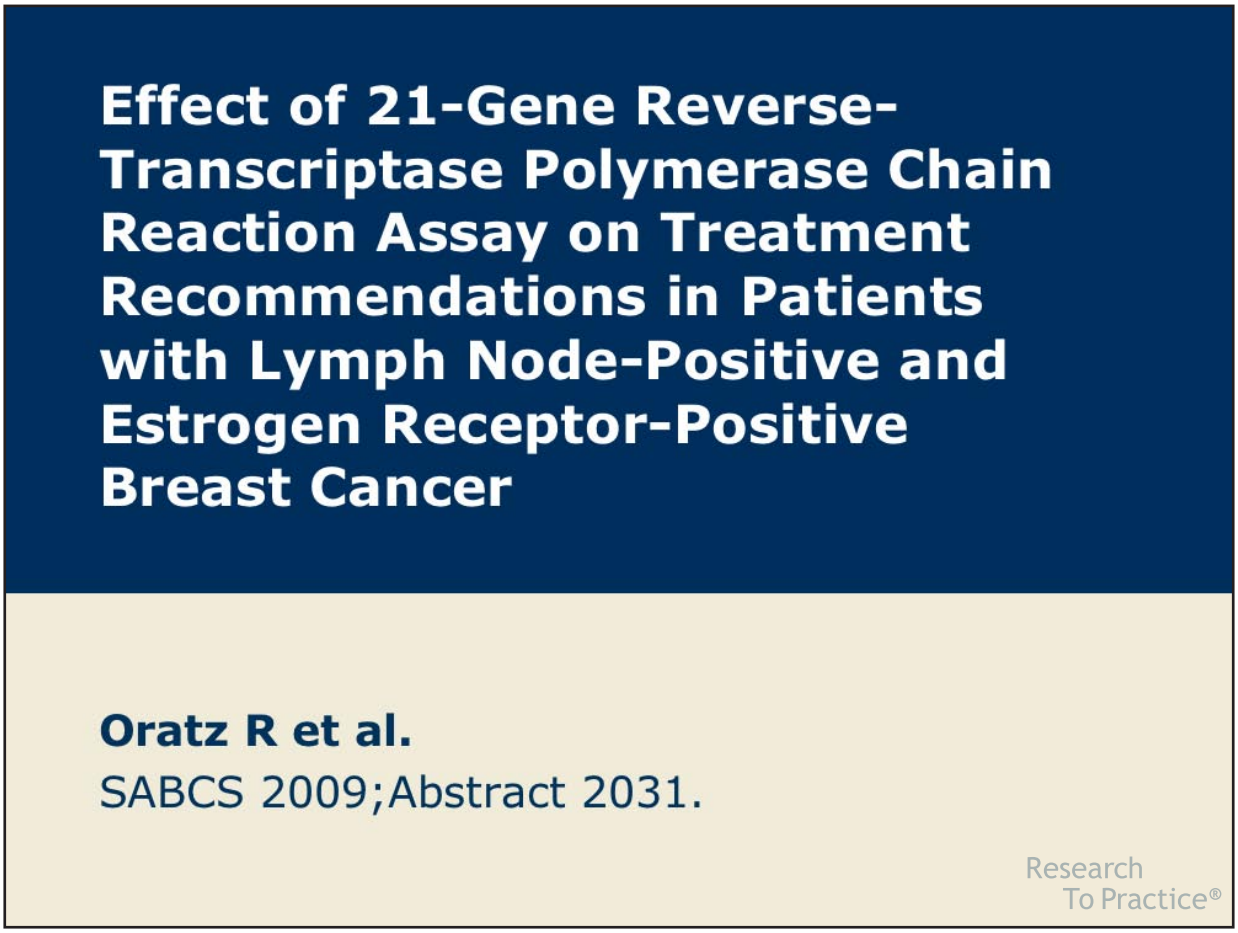
Effect of a 21-Gene RT-PCR Assay on Treatment Recommendations for Patients with Node-Positive, ER-Positive Breast Cancer

Presentation discussed in this issue

Oratz R et al. **Effect of 21-gene recurrence score results on treatment recommendations in patients with lymph node-positive, estrogen receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2009;**Abstract 2031**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Adam M Brufsky, MD, PhD (12/23/09)



Introduction

- The Onco*type* DX® Recurrence Score® (RS) assay reliably estimates the risk of distant recurrence in individual patients with node-negative (N-) ER-positive (ER+) early breast cancer (BC).
- The RS also allows for the identification of specific patients with N-/ER+ BC who are unlikely to benefit from chemotherapy.
- Recent studies have demonstrated similar prognostic and predictive utilities of the RS in patients with node-positive (N+)/ER+ BC (*Lancet Oncol* 2010;11:55, SABCS 2008;Abstract 53).
- **Current study objectives:**
  - Identify reasons for ordering the Onco*type* DX assay in N+/ER+ BC
  - Determine whether the results, when obtained, have affected adjuvant treatment recommendations

Oratz R et al. SABCS 2009;Abstract 2031.

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Methods

- Web-based survey targeting medical oncologists (MO) who ordered Onco*type* DX RS for patients with N+/ER+ BC.
  - 1,017 MO invited to participate between May and June 2009
  - Survey closed after 150 successful responses
  - N=160 total surveys included in analysis
- Descriptive analyses summarized frequency and percentage distributions of the survey responses, classifying patients by RS low (<18), RS intermediate (18-30), and RS high (≥31).
- Treatment recommendations categorized as hormonal therapy (HT) alone or chemotherapy (CT) + HT.
- Changes in treatment recommendation defined as:
  - Decreased intensity: CT + HT → HT alone
  - Increased intensity: HT alone → HT + CT

Oratz R et al. SABCS 2009;Abstract 2031.

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Physician Demographics (n = 160)

Practice Setting	%
Academic medical center	25.0
Commmunity (multi-/single-specialty or solo practice)	71.3
Other	3.8
Geographic Region	**%**
East	25.6
Midwest	23.1
South	27.5
West	23.8
Years in Practice*	
Mean/median	14.5 yrs/11 yrs

* 3 missing values

Oratz R et al. SABCS 2009;Abstract 2031.

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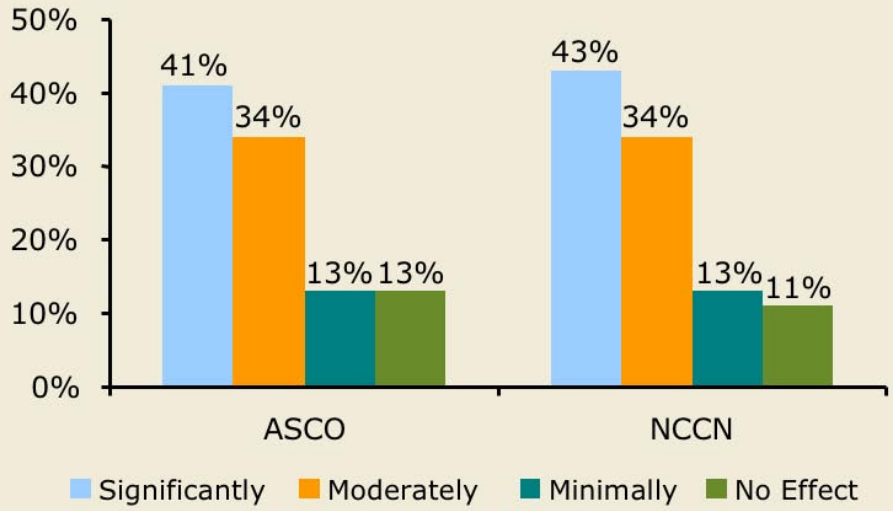
Anticipated Extent of Increased Use of Oncotype DX by Physicians for N+/ER+ Disease if it is Included in Clinical Practice Guidelines



Over 70% of MOs surveyed would adopt use of the Oncotype DX assay for node-positive BC if use of the assay were to be recommended for this subtype by ASCO or NCCN guidelines.

Oratz R et al. SABCS 2009;Abstract 2031.

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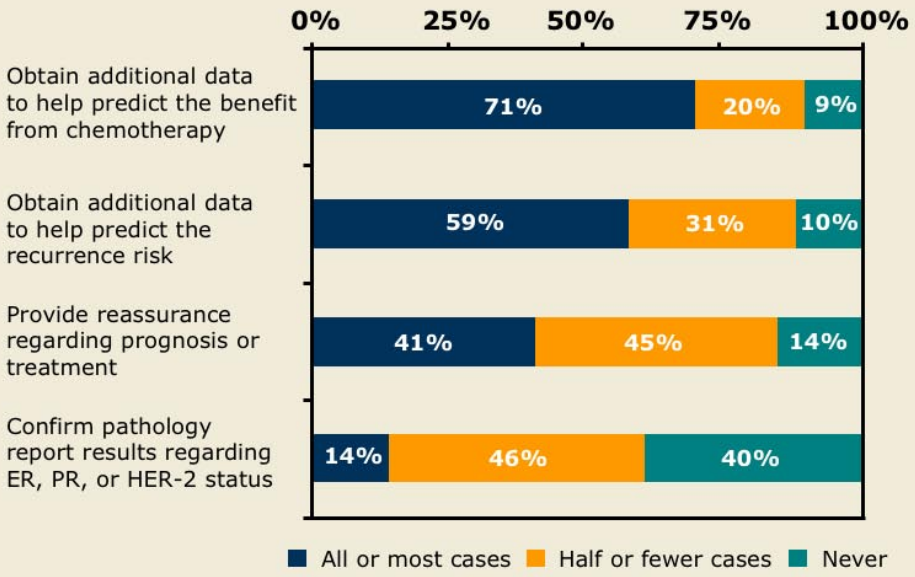
Reasons for Ordering Oncotype DX for N+/ER+ BC



Oratz R et al. SABCS 2009;Abstract 2031.

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Select Characteristics of Patients with N+/ER+ Breast Cancer

Patient Age	**All (n=160)**
Mean	60.2 years
Tumor Classification	
T1 (≤2 cm)	61.9%
T2 (>2 cm but ≤5 cm)	35.0%
T3 (>5 cm)	2.5%
Positive Axillary Lymph Nodes*	
1	68.8%
2	17.5%
3	6.3%

* Excludes micrometastases and isolated tumor cells.

Oratz R et al. SABCS 2009;Abstract 2031.

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Effect of RS on Treatment Recommendation (N = 138*)

Effect on Recommendation	Recurrence Score		
	Low (n=72)	Intermediate (n=53)	High (n=13)
Any change	43	20	7
Decreased intensity	35	11	0
Increased intensity	4	6	3
Other[Ŧ]	4	3	4
No change	29	33	6

Data shown represent number of patients.
* 22 patients did not have treatment recommendations before assay.
Ŧ 11 patients with treatment changes did not fit definitions of decreased or increased intensity.

Oratz R et al. SABCS 2009;Abstract 2031.

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Conclusions

- MO who order Onco*type* DX® for patients with N+/ER+ BC use the RS results much in the same way as they do for N-/ER+ BC.
- In more than half of the cases (n=70), information obtained from the RS resulted in alteration of the initial treatment recommendation.
  - In 66% of these cases, the treatment plan was revised to exclude chemotherapy.
    - Most of these revisions occurred in patients with a low RS.
- Limitations of current analysis:
  - Voluntary web-based survey may yield a biased sample.
  - N+/ER+ patient descriptions may be subject to recall bias.

Oratz R et al. SABCS 2009;Abstract 2031.

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DR BRUFSKY: This study used a questionnaire to sample the opinions of medical oncologists. The medical oncologists questioned were experienced overall — they had an average of almost 15 years in practice — and about 71 percent were community physicians and 25 percent were academics.

If use of the Onco*type* DX assay for patients with node-positive disease was adopted as part of the NCCN guidelines, the uptake in the community would be substantial. Around 77 percent of those surveyed would adopt the Onco*type* DX assay for this use if it became part of the NCCN guidelines. I believe that the uptake could be higher once these data are circulated along with the data that Kathy Albain just published in *Lancet Oncology* (see presentation 1 of this issue).

The main reason it seems that medical oncologists order this assay is to predict the chemotherapy benefit. Not many oncologists seem to use the assay to confirm ER, PR and HER2 status, which I think is another great use for this test.

The average patient for whom an Onco*type* DX assay is ordered seems to be an older patient with a smaller tumor and one positive node.

These results bear out what you find occurring currently if you talk to physicians in clinical practice who order this assay. No oncologist is using it for a patient who has 10 positive nodes or even five positive nodes. The assay isn't ordered for a patient with a tumor that's eight centimeters. It's usually ordered for those T2N1 types of tumors in postmenopausal women.

As these data settle in the community, I believe that you're going to see a real increase in the use of the Onco*type* DX assay in patients with ER-positive and node-positive disease, similar to what has happened in patients with node-negative tumors.

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