5 Minute JournalClub

Molecular Characterization of Breast Cancer Core Biopsy Specimens by RT-PCR Gene Expression Analysis

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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

- Compare the molecular characterization of breast cancer by RT-PCR gene expression analysis of core biopsy and surgical resection specimens.

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FACULTY — 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:

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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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Molecular Characterization of Breast Cancer Core Biopsy Specimens by RT-PCR Gene Expression Analysis

Presentation discussed in this issue

Anderson JM et al. **Molecular characterization of breast cancer core biopsy specimens by gene expression analysis using standardized quantitative RT-PCR.** San Antonio Breast Cancer Symposium 2009;**Abstract 6021**.

Slides from a presentation at SABCS 2009 and transcribed comments from recent interviews with Adam M Brufsky, MD, PhD (12/23/09) and Rowan T Chlebowski, MD, PhD (1/14/10)

Introduction

- Core biopsies are the initial diagnostic procedure of choice for breast masses identified by imaging or physical examination.
- The Onco*type* DX♦ assay process, which involves RT-PCR to evaluate the expression of 21 prespecified genes, was optimized to require small amounts of tumor tissue (*Clin Chem* 2007;53:1084).
- **Current study objectives:**
  - To determine if core biopsy specimens are comparable to surgical resection specimens in their sufficiency as well as in the results obtained.

Anderson JM et al. SABCS 2009;Abstract 6021.

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Study Methods

- Submissions to Genomic Health Clinical Laboratory for Onco*type* DX assay were obtained from July 2005 through May 2009.
  - Specimens (n=103,863) were stratified by core biopsy vs surgical resection specimen.
- Specimens were analyzed by pathology review and reverse transcriptase polymerase chain reaction.
- Causes of failure were derived from standard laboratory operating procedures and failure types.
  - Insufficient invasive tumor: <5% invasive carcinoma or <2.0 mm carcinoma
  - PCR process failure: PCR unable to be completed
  - Insufficient RNA: insufficient RNA extracted from the formalin-fixed paraffin-embedded tumor tissue specimen
  - Other: unavailable slide, scant tissue in block, incomplete requisition

Anderson JM et al. SABCS 2009;Abstract 6021.

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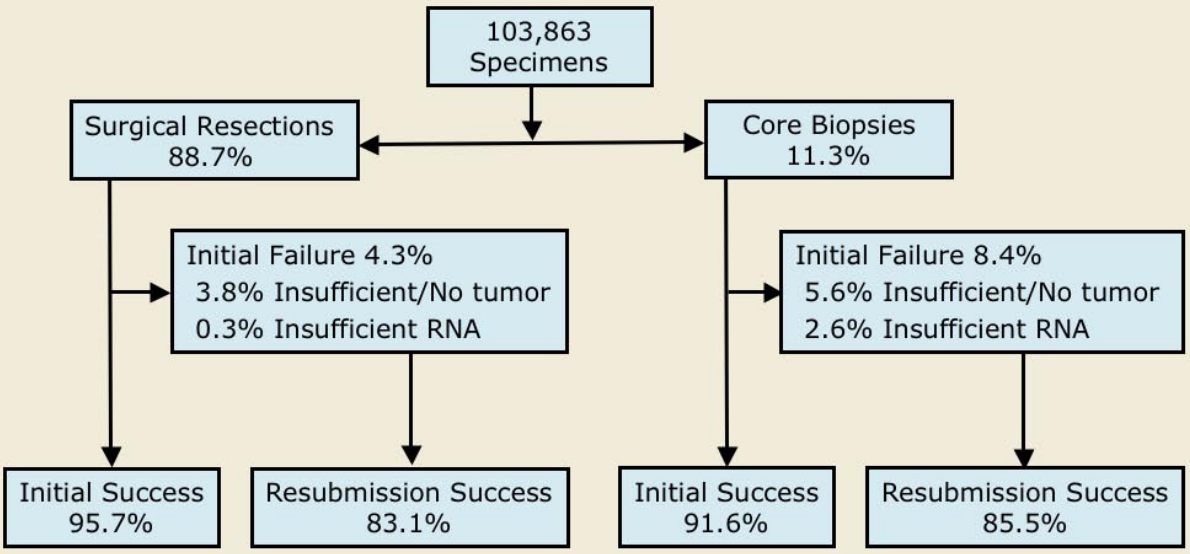
Results



Overall Success Rate > 97% in both

Anderson JM et al. SABCS 2009;Abstract 6021.

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Results (continued)

	RS < 18	RS 18-30	RS > 30
Core Biopsy Specimen	58.8%	28.6%	12.6%
Surgical Resection Specimen	52.3%	35.6%	12.1%

	Mean RS	Average RNA Yield (µg)	Manual Micro-dissection Rate to Remove Non-tumor Tissue
Core Biopsy Specimen	18.9	2.5	3.9%
Surgical Resection Specimen	19.7	4.2	33%

The distribution of quantitative ER, PR and Her2 were similar in core biopsy and surgical resection specimens

Anderson JM et al. SABCS 2009;Abstract 6021.

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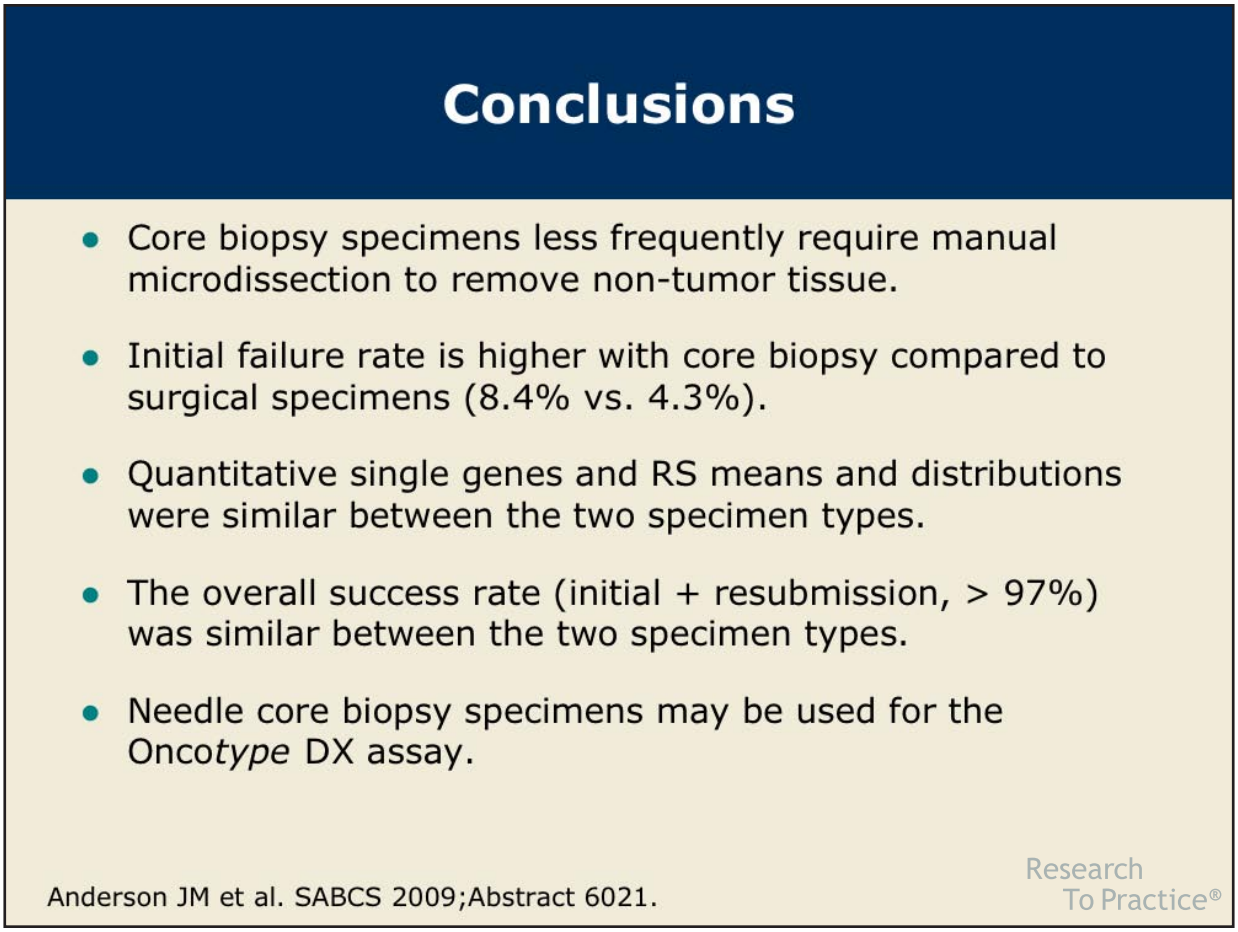

DR BRUFSKY: There have been questions raised about the use of the Onco*type* DX® assay when performed on core biopsy specimens. Can you obtain enough RNA? How does one know if the core biopsy hasn't found a pocket that doesn't predict for the whole tumor? Anderson and colleagues conducted a descriptive trial and examined the rate of assay failure when core biopsy specimens versus surgical resection specimens were used. They also addressed reasons for assay failure. Did the specimen contain enough tumor? Was there insufficient RNA? Concordance with core biopsy Onco*type* DX versus the whole tumor was also examined.

DR CHLEBOWSKI: The initial failure rate with surgical resections was 4.3 percent and the initial failure rate with core biopsies was 8.4 percent. When they went back and tried a second sample, they achieved success rates into the high nineties with both sample types. The upshot of this is that a core specimen will almost invariably provide sufficient data to make an analysis and possibly enough data to perform the assay a second time if there is an initial failure.

I believe that's encouraging. If your practice is to want to obtain the ER/PR, HER2 and as much information as possible from the core, this would be a good way of doing it.

DR BRUFSKY: When levels of ER/PR and HER2 were determined by RT-PCR, the core biopsy samples appeared to provide equivalent results to the surgical specimens. I still believe, however, that you have to be in the right part of the tumor on a core.

DR LOVE: In what kind of clinical situation would you want to do Onco*type* DX on a core?

DR BRUFSKY: If you are trying to determine if you want to administer to a patient neoadjuvant chemotherapy to achieve pathologic complete response (CR). This would be a patient with small breasts, a tumor on the larger size, around three centimeters or so, and Ki-67 around five to 10 percent. Luca Gianni's paper correlated pathologic CR to Onco*type* DX score. The higher the score, the higher the pathologic CR rate with chemotherapy. I would do the assay on a core biopsy specimen if you wanted to get a sense of whether someone will have a real response to chemotherapy.

DR LOVE: Would you rather determine ER by IHC or RT-PCR?

DR BRUFSKY: RT-PCR, but I believe the most important reason to use Onco*type* is not for ER/PR, which I want to do, but it is really to get a sense of grade, which is subjective. Onco*type* gives a lot of information on that in addition to ER/PR and HER2.

DR LOVE: It seems that this would have implications for the neoadjuvant setting. Have you ever used this assay in that setting?

DR CHLEBOWSKI: We haven't, but that is an important point. It appears that you get an answer almost all the time with the core biopsy sample. You would not be giving up much of anything by doing the assay in the neoadjuvant setting and then administering your therapy afterwards.

Dr Brufsky is Associate Professor of Medicine and Associate Division Chief of Hematology/Oncology at the University of Pittsburgh, Co-Director of the Comprehensive Breast Cancer Center and Associate Director for Clinical Investigation at the University of Pittsburgh Cancer Institute in Pittsburgh, Pennsylvania.

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