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Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

INTERVIEWS

Eleftherios P Mamounas, MD, MPH

Julie R Gralow, MD

Eric P Winer, MD

Stephen B Edge, MD

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Breast Cancer Update for Surgeons
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Historically, surgery has represented the primary mode of treatment for women with early breast cancer. The diagnostic, surgical and medical management of breast cancer, however, has escalated in complexity due to the numerous advances in novel technologies and pharmaceuticals. Hence, the multifaceted treatment of breast cancer now requires the input of an interdisciplinary group of expert providers. This paradigm shift has created the challenge of ensuring that major clinical advances in local and systemic breast cancer therapy are effectively disseminated among all members of the cross-functional team. To bridge the gap between research and patient care, Breast Cancer Update for Surgeons utilizes one-on-one interviews with leading breast cancer investigators to place the latest research developments in practical context. By providing access to cutting edge data and expert perspectives, this CME program assists breast surgeons in the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Summarize the clinical indications for neoadjuvant systemic therapy, and recall tumor-specific factors that correlate with complete pathologic response.
- Develop an algorithm for the adjuvant treatment of node-negative, HER2-positive early breast cancer.
- Use national guidelines to ensure accurate and reliable assessment and interpretation of breast cancer ER and HER2 values reported by local laboratories.
- Counsel postmenopausal patients with hormone receptor-positive early breast cancer about the benefits and risks of initial adjuvant therapy with an aromatase inhibitor, tamoxifen or a sequence of both agents.
- Identify the rationale for and benefits associated with extended adjuvant endocrine therapy, and employ this approach for appropriately selected patients with hormone receptor-positive early breast cancer.
- Evaluate the utility of tissue-based genomic assays for therapeutic decision-making and, when applicable, use them in the selection of individualized treatment approaches for patients with ER-positive breast cancer.
- Apply the results of emerging data with adjuvant bisphosphonates when recommending treatment options for premenopausal women with ER-positive early breast cancer.
- Utilize emerging data on intraoperative sentinel lymph node evaluation and complete axillary dissection for documented micrometastases in current surgical practice.
- Assess the clinical utility of preoperative magnetic resonance imaging in evaluating the need for mastectomy versus lumpectomy.

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INTERVIEW

Eleftherios P Mamounas, MD, MPH

Dr Mamounas is Medical Director of Aultman Cancer Center and Professor of Surgery at Northeastern Ohio Universities College of Medicine in Canton, Ohio.

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Track 2 Tumor phenotype and response to neoadjuvant therapy

Track 3 Genomic analyses as predictors of pathologic response to neoadjuvant therapy

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Track 17 Proposed NSABP trial of adjuvant trastuzumab for patients with HER2 IHC 1+ or 2+ BC

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: How does breast cancer phenotype influence your neoadjuvant strategy?

DR MAMOUNAS: Information gathered during the past few years indicates that different breast cancer phenotypes respond differently to neoadjuvant chemotherapy. Patients with triple-negative or HER2-positive disease have higher pathologic complete response (pCR) rates, which can be in the range of 50 to 60 percent with some of the more modern trastuzumab-based regimens for HER2-positive disease (Buzdar 2007; [1.1]).

However, pCRs are infrequent among patients with endocrine-responsive disease — high ER and PR — particularly those with invasive lobular carcinomas. For such a patient with extensive lobular carcinoma, it's unlikely that you will obtain a pCR and change the type of procedure performed. You can probably downsize the tumor, but it's unlikely that you'll convert the patient from requiring a mastectomy to needing only a lumpectomy.

DR LOVE: To what extent have genomic analyses been evaluated in terms of predicting pCR with neoadjuvant therapy?

DR MAMOUNAS: They have been assessed in a couple of small studies. The first one, from Luca Gianni's group in Milan, showed that in 89 patients with 11 pCRs, a correlation existed between pCR and the Onco*type* DX Recurrence Score®: The higher the Recurrence Score, the higher the probability of achieving a pCR (Gianni 2005; [1.2]).

1.1

Neoadjuvant Paclitaxel (P) Followed by FEC with or without Concurrent Trastuzumab (H) for HER2-Positive Operable Breast Cancer

	P + FEC	P + FEC + H		
	(n = 19)	First cohort (n = 23)	Second cohort (n = 22)	Combined (n = 45)
Pathologic complete response (95% CI)	26.3% (9-51)	65.2% (43-84)	54.5% (32.2-75.6)	60% (44.3-74.3)
One-year disease-free survival (95% CI)	94.7% (85.2-100)	100% (85.2-100)	100% (83.9-100)	100% (92-100)

CI = confidence interval

SOURCE: Buzdar AU et al. *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

1.2

Onco*type* DX Recurrence Score (RS) Predicts Pathologic Complete Response (pCR) to Neoadjuvant Chemotherapy for Locally Advanced Breast Cancer

"The RS has been validated to quantify the risk of recurrence in tamoxifen-treated patients with node-negative, ER-positive breast cancer. We show here that RS strongly correlated with pCR. This has a provocative clinical implication, namely, that patients with high RS values, who are most likely to experience recurrence, are the very patients most likely to receive the greatest clinical benefit from chemotherapy treatment. It will be important to further evaluate this concept in future studies."

SOURCE: Gianni L et al. *J Clin Oncol* 2005;23(29):7265-77. **Abstract**

It's not all that unexpected because we know about the correlation in the adjuvant setting (Paik 2006). Also, we know that some of the genes included in the Onco*type* DX assay (ie, HER2, proliferation genes, ER and PR) have been associated with a benefit from chemotherapy.

Track 5

DR LOVE: Would you discuss where we are in terms of data on the timing of sentinel lymph node biopsy (SLNB) for patients receiving neoadjuvant therapy?

DR MAMOUNAS: We have information on SLNB after neoadjuvant chemotherapy but not as much as we have in the up-front setting. When you evaluate the literature collectively, you see that the false-negative rate for SLNB in patients who have received neoadjuvant chemotherapy is in the same range as the false-negative rate when you perform the SLNB up front — between eight and 10 percent (Classe 2009; Tausch 2006; Mamounas 2005).

Intuitively, it makes sense to use SLNB after neoadjuvant chemotherapy to take advantage of its downstaging effect, assuming you believe SLNB works as well after neoadjuvant chemotherapy and you don't lose information that may guide you with locoregional management. One of the arguments made by the radiation oncologists is that we may lose information that is important for making decisions regarding radiation therapy.

Track 6

DR LOVE: Aman Buzdar's study (Buzdar 2007; [1.1, page 4]), evaluating an anthracycline concurrent with trastuzumab for HER2-positive disease in the neoadjuvant setting, received a lot of attention. Will those results be taken forward?

DR MAMOUNAS: They are being confirmed by ACOSOG-Z1041 (1.3), in which patients are randomly assigned to receive trastuzumab concurrent with FEC and paclitaxel or FEC first followed by paclitaxel/trastuzumab. One arm essentially mimics the MD Anderson regimen (Buzdar 2007), and the other arm mimics the Intergroup and NSABP-B-31 regimen with the anthracycline administered first followed by trastuzumab/paclitaxel (Romond 2005).

DR LOVE: Do you think using the anthracycline concurrently with trastuzumab makes a difference in terms of antitumor effect?

DR MAMOUNAS: My bias is that it does. This might be due to the continuation of trastuzumab for a longer duration in that setting, or because synergism exists when it is administered with an anthracycline. I'm not sure why, but the data from MD Anderson have demonstrated the highest pCR rates. Even in the extended series, the pCR rate was approximately 55 percent (Buzdar 2007; [1.1, page 4]).

As another example, Michael Untch reported on a Phase II study of EC followed by paclitaxel/trastuzumab in 230 patients with HER2-positive breast cancer. The pCR rate in that study was approximately 40 percent (Untch 2005). So a small difference may exist between pCR rates of 40 percent and those of 55 to 60 percent.

1.3

Combination Neoadjuvant Chemotherapy and Paclitaxel (T) with Trastuzumab (H) for HER2-Positive Operable Breast Cancer

Protocol IDs: ACOSOG-Z1041, CTSU
Date Activated: July 2007
Target Accrual: 270 (Open)

Eligibility

HER2-positive (IHC 3+ or FISH) invasive breast cancer (≥2 cm) with known ER/PR status

Other therapy: Patients with ER/PR-positive disease receive a minimum of five years of hormonal therapy.

Study Contacts

American College of Surgeons Oncology Group
Aman Buzdar, MD, Protocol Chair
Tel: 800-392-1611
Kelly Hunt, MD, Protocol Co-chair
Tel: 800-392-1611

SOURCE: www.clinicaltrials.gov. Accessed March 12, 2009.

Track 13

DR LOVE: Are there any new data sets with respect to adjuvant endocrine therapy that are relevant to physicians in practice?

DR MAMOUNAS: At the 2008 San Antonio Breast Cancer Symposium, we heard the results from the BIG 1-98 trial comparing the sequence of tamoxifen followed by an aromatase inhibitor to an aromatase inhibitor up front or an aromatase inhibitor for two years followed by tamoxifen. The bottom line is that no difference was found between the three different strategies (Mouridsen 2008; [1.4]).

Studying the curves, it appears that the patients receiving letrozole up front fared a little better. Those receiving tamoxifen up front fared a little worse, but when these patients were switched to letrozole the rate of failure changed, and the lines became parallel.

It is interesting that the patients who were receiving letrozole first and were then switched to tamoxifen fared as well as those receiving letrozole for five years (Mouridsen 2008; [1.4]). ■

1.4

BIG 1-98: Letrozole Monotherapy or in Sequence with Tamoxifen as Adjuvant Therapy for Postmenopausal Women with Hormone Receptor-Positive Early Breast Cancer

	Letrozole monotherapy* (n = 1,546)	Letrozole → tamoxifen† (n = 1,540)	Tamoxifen → letrozole† (n = 1,548)
Five-year disease-free survival	87.9%	87.6%	86.2%
Hazard ratio (95% CI) Letrozole versus sequence	—	0.96 (0.76-1.21)	1.05 (0.84-1.32)

* Median follow-up: 76 months; † Median follow-up: 71 months; CI = confidence interval

SOURCE: Mouridsen HT et al. San Antonio Breast Cancer Symposium 2008;**Abstract 13**.

SELECT PUBLICATIONS

Buzdar AU et al. **Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen.** *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

Classe JM et al. **Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: Results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study.** *J Clin Oncol* 2009;27(5):726-32. **Abstract**

Gianni L et al. **Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer: Primary efficacy analysis of the NOAH trial.** San Antonio Breast Cancer Symposium 2008;**Abstract 31**.

Gianni L et al. **Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer.** *J Clin Oncol* 2005;23(29):7265-77. **Abstract**

Mamounas EP et al. **Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: Results from National Surgical Adjuvant Breast and Bowel Project protocol B-27.** *J Clin Oncol* 2005;23(12):2694-702. **Abstract**

Mouridsen HT et al. **BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 13**.

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Tausch C et al. **Sentinel lymph node biopsy after preoperative chemotherapy for breast cancer: Findings from the Austrian Sentinel Node Study Group.** *Ann Surg Oncol* 2008;15(12):3378-83. **Abstract**

Untch M et al. **A multicenter phase II study of preoperative epirubicin, cyclophosphamide (EC) followed by paclitaxel (P) plus trastuzumab (T) in Her2 positive primary breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 1064**.

Von Minckwitz G et al. **Integrated meta-analysis on 6402 patients with early breast cancer receiving neoadjuvant anthracycline-taxane +/- trastuzumab containing chemotherapy.** San Antonio Breast Cancer Symposium 2008;**Abstract 79**.

INTERVIEW

Julie R Gralow, MD

Dr Gralow is Director of Breast Medical Oncology at Seattle Cancer Care Alliance/University of Washington and Associate Professor of Medical Oncology at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, Washington.

Tracks 1-13

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss where we are with ER and HER2 testing?

DR GRALOW: We don't know the best way to test for ER or HER2 at this point. Data emerging from some of our trials, in which we're comparing local to central laboratory results, suggest that many factors can affect testing.

With respect to ER, the percentage of cells staining and the intensity of the stain matter, not simply whether a result is positive or negative. I believe that some trials are starting to sort out low versus high ER. We generally use the Allred scoring system at our institution, which I find to be more reflective of

the quantity of ER present. For a patient whose tumor has many cells staining for ER with a high intensity, I'm more likely to omit chemotherapy and use endocrine therapy — compared to the patients with tumors that are more borderline, for whom I add the endocrine agent to the treatment regimen — but I won't be relying on it as the sole therapy.

From a surgical perspective, we have to be cognizant of the fact that tissue fixation is critical and if a sample is not put in fixative in an appropriate amount of time, all bets are off in terms of the results. It can entirely alter the ER and HER2 staining. When this occurs, we don't necessarily know how to treat the patient.

DR LOVE: Another issue is the use of RT-PCR to assess quantitative ER and HER2, which is what's reported with the Onco*type* DX assay. Are you utilizing those numbers?

DR GRALOW: Absolutely. When I receive the Recurrence Score, I study it. Of course, in general, I'm not ordering Onco*type* DX assays for patients who are known to have HER2-positive breast cancer. The data suggest that most of those patients are at high risk, and I'll administer trastuzumab anyway.

Tracks 4-6

DR LOVE: Would you discuss the results from the ABCSG-12 study reported by Dr Gnant (Gnant 2009) and your ongoing trial, SWOG-S0307, evaluating adjuvant bisphosphonates?

DR GRALOW: ABCSG-12 was a study involving 1,800 premenopausal women who all received an adjuvant LHRH analog and were randomly assigned to tamoxifen or an aromatase inhibitor. No benefit was found with the aromatase inhibitor versus tamoxifen. A second randomization was to zoledronic acid or nothing (Gnant 2009). ABCSG-12 was powered to evaluate disease-free survival for both the endocrine and bisphosphonate questions. The surprise was that only six doses of zoledronic acid during three years reduced recurrences or events by approximately 36 percent (Gnant 2009; [2.1]).

The ongoing Intergroup/NSABP adjuvant trial, SWOG-S0307 (2.2), uses a standard arm of clodronate — a nonaminobisphosphonate — compared to two more potent aminobisphosphonates, ibandronate and zoledronic acid. Ibandronate is used at bone-metastasis doses, not osteoporosis doses. Zoledronic acid is administered monthly for six months and then quarterly. Patients on all three arms receive a bisphosphonate for three years. The trial is accruing rapidly to reach its goal of 4,500 patients.

In the AZURE trial, which is also evaluating bisphosphonates, approximately 200 of the 3,360 patients received preoperative chemotherapy. Half of these patients received simultaneous preoperative zoledronic acid, whereas half did not. The surgery results were presented at the 2008 San Antonio Breast Cancer Symposium. The primary endpoint was residual invasive disease in the breast, and pCR was another endpoint (Winter 2008).

With multivariate corrections, the group that didn't receive zoledronic acid had approximately 40 millimeters of residual tumor on average, whereas the group that received zoledronic acid had slightly less than 30 millimeters of residual tumor. These were large tumors to start with. In general, the pCR rates were low. They were roughly six percent in the group not treated with zoledronic acid and 11 percent in the group receiving zoledronic acid, with a *p*-value of about 0.03 (Winter 2008).

2.1

ABCSG-12: Zoledronic Acid (ZDA) Added to Adjuvant Endocrine Therapy Prolongs Disease-Free Survival (DFS) for Premenopausal Patients with ER-Positive Early Breast Cancer

	First DFS event per patient, n	
	ZDA (n = 899)	No ZDA (n = 904)
Locoregional recurrence	10	20
Distant recurrence	29	41
Contralateral breast cancer	6	10
Secondary cancer	9	10
Death without prior recurrence	0	2

Hazard ratio (95% CI) for DFS, versus no ZDA = 0.64 (0.46-0.91), $p = 0.01$

SOURCE: Gnant M et al; ABCSG-12 Trial Investigators. *N Engl J Med* 2009;360(7):679-91. **Abstract**

2.2

Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer

Protocol IDs: SWOG-S0307, CTSU
Date Activated: July 2005
Target Accrual: 4,500 (Open)

Eligibility

Stage I to Stage III breast cancer with standard adjuvant therapy

Study Contacts

SWOG
Julie R Gralow, MD and Robert Livingston, MD, Tel: 205-288-7722
Other participating cooperative groups: NCCTG, ECOG, NSABP, CALGB and NCIC CTG

SOURCE: NCI Physician Data Query, March 2009.

This was not a planned analysis, and it evaluated a small subset from the AZURE trial. However, I believe that these results suggest a direct effect of zoledronic acid on the tumor in the breast. This is not definitive, but it is hypothesis generating.

Track 11

DR LOVE: What have we learned during the past few years about the long-term history of ER-positive disease?

DR GRALOW: During the first five years, the population with ER-positive disease has a somewhat lower risk of relapse compared to the group with ER-negative disease. After 20 to 25 years, the risk is comparable because the patients with ER-positive disease have a constant, small but real rate of relapse that lasts forever.

The patients with ER-negative disease have a much higher rate of relapse in the short term and then a much lower rate of relapse moving forward. So patients with ER-positive disease may still see a benefit from prolonged endocrine therapy. NCIC-MA17 demonstrated a survival benefit for five years of letrozole after five years of tamoxifen for patients with node-positive disease (Goss 2005).

We currently have studies evaluating whether five more years of adjuvant endocrine therapy are beneficial for women who have finished five years of an aromatase inhibitor, whether or not they received any tamoxifen (2.3). ■

2.3

Ongoing Phase III Trials Evaluating Extended Adjuvant Aromatase Inhibitor Therapy for Postmenopausal Patients with ER-Positive Early Breast Cancer Who Completed Five Years of Adjuvant Endocrine Therapy

Protocol ID	Number of patients	Randomization
NSABP-B-42	3,840	Letrozole vs placebo x 5y
NCIC-MA17R	1,800	Letrozole vs placebo x 5y
SALSA	3,500	Anastrozole x 2y vs 5y

SOURCE: www.clinicaltrials.gov. Accessed March 18, 2009.

SELECT PUBLICATIONS

Gnant M et al; ABCSG-12 Trial Investigators. **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009;360(7):679-91. **Abstract**

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

Winter MC et al. **The addition of zoledronic acid to neoadjuvant chemotherapy may influence pathological response — Exploratory evidence for direct anti-tumor activity in breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 5101**.

INTERVIEW

Eric P Winer, MD

Dr Winer is Thompson Investigator in Breast Cancer Research and Director of the Breast Oncology Center at Dana-Farber Cancer Institute and is Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-10

Select Excerpts from the Interview

Track 2

DR LOVE: How can a surgeon be assured of optimal HER2 testing for his or her patients?

DR WINER: I believe the single most important variable is the laboratory. The labs that perform these tests repeatedly tend to produce more accurate results.

A surgeon who practices in a small hospital where testing for HER2 is sporadic should consider sending specimens out to a reference lab. Additionally, a decision must be made about what to call HER2-positive. Assuming it's a reliable lab, an immunohistochemistry (IHC) test result of 3+ HER2 positivity is positive — period, end of story.

A FISH ratio greater than two is positive. If you want to say it has to be 2.2, based on the guidelines, that's fine.

Track 3

DR LOVE: Would you discuss the available clinical trial data for patients with small, node-negative, HER2-positive breast cancer?

DR WINER: A data set from MD Anderson with approximately 1,000 patients suggested that patients with small — defined as less than one centimeter — node-negative, HER2-positive disease had more than a 20 percent risk of disease recurrence during the first five years of follow-up (Rakkhit 2008). This was substantially higher than it was for patients with other disease subtypes.

Patients with triple-negative disease were also at higher risk than patients with ER/PR-positive, HER2-negative disease but were not at as high a risk as those with HER2-positive disease (3.1). This analysis did not evaluate treatment, so no conclusion could be drawn in terms of the efficacy of treatment. The point is that these patients are at high enough risk to justify some treatment.

At the Dana-Farber Harvard Cancer Center and 10 other centers around the country, we are conducting the 07-199 trial, which is a rather large study of 400 patients with small, node-negative, HER2-positive tumors. All patients will receive 12 weeks of paclitaxel and trastuzumab, followed by completion of one year of trastuzumab. We define small as any tumor smaller than three centimeters, although most of the patients in this study have tumors that are smaller than two centimeters.

This trial will not answer the questions of whether trastuzumab/paclitaxel is better than no therapy or whether trastuzumab/paclitaxel is better than either agent alone, but it will provide us with a sense of the natural history of these cases with small tumors being treated with relatively nontoxic chemotherapy regimens.

If we see a recurrence rate of 10 percent in this patient population, we will consider the treatment a failure. We are hoping for a recurrence rate that is less than five or six percent.

3.1

Recurrence-Free Survival (RFS) and Distant Recurrence-Free Survival (DRFS) in Subgroups of Patients with Small (≤1 cm), Node-Negative Breast Cancer

	Five-year estimate	
	RFS	DRFS
Breast cancer subgroup	$p < 0.0001$	$p < 0.0001$
HER2-positive	77.1%	86.4%
Triple-negative	85.2%	95.6%
ER/PR-positive	95.2%	97.5%

SOURCE: Rakkhit R et al. San Antonio Breast Cancer Symposium 2008;**Abstract 701**.

Track 9

DR LOVE: What are your thoughts on the duration of adjuvant hormonal therapy?

DR WINER: This is a very important area of research. It's clear that for patients with ER/PR-negative disease, if they experience a recurrence, it usually occurs in the first five years. For patients with ER/PR-positive disease, recurrences remain a problem for five, 10 and 15 years. Much of the benefit we will provide is by extending hormonal therapy. I believe that is one of the reasons that Paul Goss's MA17 trial evaluating letrozole after tamoxifen is so important (Goss 2006; [3.2]).

Nancy Lin and I wrote an editorial in the *Journal of Clinical Oncology* recently in which we identified the need for better predictors of who's at risk for late recurrence (Lin 2008). To some extent the predictors of late recurrence may be different from the predictors for early risk of recurrence in patients with ER/PR-positive disease.

Women with high-grade ER/PR-positive disease are probably at higher risk of early recurrence. It's the women with lower-grade disease, I suspect, who are at greater risk of late recurrence, but we still know much less about this issue than we would like. ■

3.2 **MA17: Extended Adjuvant Letrozole After Five Years of Tamoxifen**

"The updated analyses of the [MA17] trial results (median follow-up, 2.5 years) confirm that letrozole significantly reduced the risk of recurrent breast cancer (42%) regardless of the patient's nodal status or receipt of prior chemotherapy, and significantly reduced the risk of distant metastasis (40%). Importantly, letrozole as extended adjuvant therapy achieved a significant improvement in overall survival in women with node-positive disease. Mortality was reduced by 39% among the approximately 2,500 women with node-positive disease randomized in the study. Letrozole showed minimal side effects compared with placebo; adverse effects on bone metabolism of uncertain clinical significance were the most noteworthy side effect."

SOURCE: Goss PE. *Semin Oncol* 2006;33(2 Suppl 7):8-12. **Abstract**

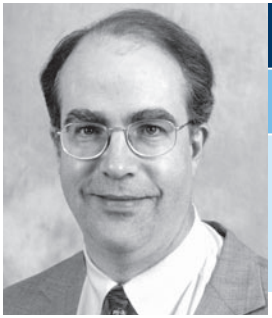
SELECT PUBLICATIONS

Chia S et al. **Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers.** *J Clin Oncol* 2008;26(35):5697-704. **Abstract**

Goss PE. **Preventing relapse beyond 5 years: The MA.17 extended adjuvant trial.** *Semin Oncol* 2006;33(2 Suppl 7):8-12. **Abstract**

Lin NU, Winer EP. **Optimizing endocrine therapy for estrogen receptor-positive breast cancer: Treating the right patients for the right length of time.** *J Clin Oncol* 2008;26(12):1919-21. No abstract available

Rakkhit R et al. **Significant increased recurrence rates among breast cancer patients with HER2-positive, T1a,bN0M0 tumors.** San Antonio Breast Cancer Symposium 2008;**Abstract 701**.



INTERVIEW

Stephen B Edge, MD

Dr Edge is Chair of the Department of Breast and Soft Tissue Surgery at Roswell Park Cancer Institute and Professor of Surgery at State University of New York at Buffalo in Buffalo, New York.

Tracks 1-13

Track 1	Influence of preoperative MRI on mastectomy rates
Track 2	Counseling women about the risk of local recurrence with mastectomy versus lumpectomy
Track 3	Clinical use of preoperative MRI
Track 4	Role of completion axillary-node dissection
Track 5	Timing of SLNB relative to neoadjuvant therapy
Track 6	Intraoperative evaluation of sentinel lymph nodes
Track 7	Data with partial breast irradiation (PBI)
Track 8	Clinical use of adjuvant radiation therapy after mastectomy
Track 9	SLNB for patients with DCIS
Track 10	Clinical use of the Onco*type* DX assay in ER-positive, node-negative or node-positive BC
Track 11	Inaccuracies in HER2 and ER testing
Track 12	Long-term natural history of ER-positive early BC
Track 13	Support for patients deciding between mastectomy and lumpectomy

Select Excerpts from the Interview

Tracks 1, 3

DR LOVE: Would you discuss the recent report that suggested that mastectomy rates may be increasing in the United States?

DR EDGE: The resurgent use of mastectomy for the treatment of breast cancer is an area of interest. The seminal report is a single-institution series with all sorts of potential biases, but they reported that the use of mastectomy increased with the increased use of MRI (Katipamula 2008).

The proportion of women with Stage 0, I and II breast cancer at the Mayo Clinic who underwent mastectomy was 45 percent in 1997, and that dropped to 30 percent by 2003. At that time, physicians started using MRI more aggressively for staging breast cancer. The rate of mastectomy has increased to approximately 43 percent of breast cancer cases in the last reported year, which was 2006. The use of MRI increased from around 10 percent in 2003 to 23 percent in 2006. Women who underwent MRI had mastectomy rates that

approached 60 percent. Of course, you have a potential selection bias in who underwent MRI.

By comparison, the rate of mastectomy in the NCCN Oncology Outcomes Database is unchanged for the same time frame. However, anecdotally, most of us are seeing more patients coming in and talking about mastectomy and even considering bilateral mastectomy in settings in which, five years ago, the issue probably would not have been raised.

DR LOVE: Would you discuss the use of MRI in clinical practice and your approach to using it?

DR EDGE: Debates on the pros and cons of MRI now take place at all of the meetings. Remember, all of the outcome data regarding low single-digit local failure rates with breast-conserving surgery were from patients treated in the pre-MRI era. Of course, these patients were also treated in the whole-breast radiation therapy era. However, we have to question what we are gaining with MRI. We use MRI for patients with larger tumors, for women with dense breasts and for tumors of which we don't know the size because they're embedded in areas of dense glandular tissue.

When we find abnormalities, we need to evaluate them further. Frequently we don't see the mammogram or an ultrasound so we're forced to perform an MRI-guided biopsy, which is tedious. It subjects patients to a lot of biopsies, and some may decide it's easier to undergo a mastectomy. Even though you try not to perform a mastectomy on the basis of an MRI finding, the process tends to push some women toward mastectomy.

Track 10

DR LOVE: Would you discuss how use of the Onco*type* DX assay has affected the management of breast cancer? In what situations should the surgeon be ordering it, and in what situations should the patient be referred to a medical oncologist for that decision?

DR EDGE: The data on the use of Onco*type* DX are compelling. If I were a woman with intermediate-size, ER/PR-positive, node-negative breast cancer, I'd want an Onco*type* DX assay performed. I would want to avoid chemotherapy if I had a low score, and I would be comfortable that hormonal therapy alone was sufficient because I would derive no added benefit from chemotherapy (Paik 2004; [4.1]). I would also want to know if I had a high score and thus had a substantial chance of disease recurrence, in which case hormonal therapy alone is insufficient.

I'm uncertain why we would not be using the Onco*type* DX assay, but surgeons aren't always ordering it. We refer patients to medical oncologists because if they will be receiving chemotherapy anyway, then we don't need to order the assay. However, that throws in another two-week delay in obtaining the result. Perhaps our reticence to send out for Onco*type* DX testing should disappear when we see a woman with ER/PR-positive, HER2-negative breast

cancer that is larger than one centimeter with negative nodes, and we should start ordering the assay as we do ER/PR tests because it truly offers advantages to patients.

We have not ordered the Onco*type* DX assay for patients with node-positive breast cancer, but the data are intriguing (Albain 2007; [4.2]). These patients have a substantial risk of recurrence, but some may gain much less benefit from chemotherapy than others. ■

4.1

Effect of Adding Chemotherapy to Tamoxifen According to Onco*type* DX Recurrence Score for Women with ER-Positive, Node-Negative Disease

10-year distant recurrence-free survival

Risk group	Tamoxifen (n = 227)	Tamoxifen with chemotherapy (n = 424)	*p*-value
Low (RS < 18)	97%	96%	0.61
Intermediate (RS = 18-30)	91%	89%	0.39
High (RS ≥ 31)	61%	88%	<0.001

Chemotherapy = MF or CMF; RS = Recurrence Score

SOURCE: Paik S et al. *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

4.2

Effect of Adding Chemotherapy to Tamoxifen for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer According to Onco*type* DX Recurrence Score

10-year disease-free survival estimates

	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low Recurrence Score (<18)	60%	64%
Intermediate Recurrence Score (18-30)	49%	63%
High Recurrence Score (≥31)	43%	55%

SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

SELECT PUBLICATIONS

Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814,INT0100).** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

Dowsett M et al. **Risk of distant recurrence using Onco*type* DX in postmenopausal primary breast cancer patients treated with anastrozole or tamoxifen: A TransATAC study.** San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

Katipamula R et al. **Trends in mastectomy rates at the Mayo Clinic Rochester: Effect of surgical year and preoperative MRI.** *Proc ASCO* 2008;**Abstract 509**.

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. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a study by Aman Buzdar and colleagues of neoadjuvant paclitaxel followed by FEC with trastuzumab in patients with HER2-positive breast cancer, the pCR rate was approximately _____.**
   a. 15 to 20 percent
   b. 25 to 30 percent
   c. 40 to 45 percent
   d. 55 to 60 percent

2. **Luca Gianni and colleagues demonstrated that the Onco*type* DX Recurrence Score correlated with pCR rate among patients receiving neoadjuvant chemotherapy for locally advanced breast cancer.**
   a. True
   b. False

3. **BIG 1-98 evaluated which of the following aromatase inhibitors as monotherapy or sequential therapy with tamoxifen for postmenopausal women with early breast cancer?**
   a. Anastrozole
   b. Letrozole
   c. Exemestane
   d. All of the above
   e. None of the above

4. **NSABP-B-43 is evaluating _____ as a radiosensitizer for women with HER2-positive DCIS who have a lumpectomy and receive radiation therapy.**
   a. Lapatinib
   b. Gefitinib
   c. Trastuzumab
   d. T-DM1

5. **In ABCSG-12, which of the following bisphosphonates was found to reduce the risk of breast cancer recurrence in premenopausal women treated with adjuvant hormonal therapy?**
   a. Clodronate
   b. Ibandronate
   c. Zoledronic acid
   d. All of the above
   e. None of the above

6. **Which of the following bisphosphonates is being evaluated in SWOG-S0307?**
   a. Clodronate
   b. Ibandronate
   c. Zoledronic acid
   d. All of the above
   e. None of the above

7. **In MD Anderson's retrospective analysis, the estimated five-year risk of recurrence in patients with small, node-negative, HER2-positive breast cancer was approximately _____.**
   a. Five percent
   b. 10 percent
   c. 20 percent

8. **In the MA17 trial, extended adjuvant letrozole for patients who completed five years of tamoxifen resulted in improvements in _____ for postmenopausal patients with ER/PR-positive, node-positive breast cancer.**
   a. Risk of recurrence
   b. Risk of distant metastases
   c. Overall survival
   d. All of the above

9. **In a single-institution series, the use of preoperative MRI was positively associated with _____.**
   a. Rate of mastectomy
   b. Rate of breast-conserving surgery
   c. None of the above

10. **The Onco*type* DX Recurrence Score predicts benefit or lack of benefit from chemotherapy in postmenopausal patients with ER/PR-positive, node-negative early breast cancer.**
    a. True
    b. False

Post-test answer key: 1d, 2a, 3b, 4c, 5c, 6d, 7c, 8d, 9a, 10a

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update for Surgeons — Issue 1, 2009

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

- **Use of neoadjuvant systemic therapy, including timing of sentinel lymph node biopsy** 4 3 2 1
- **Results from BIG 1-98: Up-front adjuvant therapy with letrozole, tamoxifen or a sequential strategy for postmenopausal women with ER-positive early breast cancer** 4 3 2 1
- **Extending adjuvant hormonal therapy beyond five years for patients with ER-positive disease** 4 3 2 1
- **Results from ABCSG-12, evaluating adjuvant zoledronic acid for premenopausal women with ER-positive, early breast cancer** 4 3 2 1
- **Use of genomic assays to select patients with ER-positive breast cancer for adjuvant chemotherapy** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

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- **Use of neoadjuvant systemic therapy, including timing of sentinel lymph node biopsy** 4 3 2 1
- **Results from BIG 1-98: Up-front adjuvant therapy with letrozole, tamoxifen or a sequential strategy for postmenopausal women with ER-positive early breast cancer** 4 3 2 1
- **Extending adjuvant hormonal therapy beyond five years for patients with ER-positive disease** 4 3 2 1
- **Results from ABCSG-12, evaluating adjuvant zoledronic acid for premenopausal women with ER-positive, early breast cancer** 4 3 2 1
- **Use of genomic assays to select patients with ER-positive breast cancer for adjuvant chemotherapy** 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will be able to:

- Summarize the clinical indications for neoadjuvant systemic therapy, and recall tumor-specific factors that correlate with complete pathologic response. ..... 4 3 2 1 N/M N/A
- Develop an algorithm for the adjuvant treatment of node-negative, HER2-positive early breast cancer. ..... 4 3 2 1 N/M N/A
- Use national guidelines to ensure accurate and reliable assessment and interpretation of breast cancer ER and HER2 values reported by local laboratories. ..... 4 3 2 1 N/M N/A
- Counsel postmenopausal patients with hormone receptor-positive early breast cancer about the benefits and risks of initial adjuvant therapy with an aromatase inhibitor, tamoxifen or a sequence of both agents. ..... 4 3 2 1 N/M N/A
- Identify the rationale for and benefits associated with extended adjuvant endocrine therapy, and employ this approach for appropriately selected patients with hormone receptor-positive early breast cancer. ..... 4 3 2 1 N/M N/A
- Evaluate the utility of tissue-based genomic assays for therapeutic decision-making and, when applicable, use them in the selection of individualized treatment approaches for patients with ER-positive breast cancer. ..... 4 3 2 1 N/M N/A
- Apply the results of emerging data with adjuvant bisphosphonates when recommending treatment options for premenopausal women with ER-positive early breast cancer. ..... 4 3 2 1 N/M N/A
- Utilize emerging data on intraoperative sentinel lymph node evaluation and complete axillary dissection for documented micrometastases in current surgical practice. ..... 4 3 2 1 N/M N/A
- Assess the clinical utility of preoperative magnetic resonance imaging in evaluating the need for mastectomy versus lumpectomy. ..... 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the editor and faculty for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Eleftherios P Mamounas, MD, MPH	4 3 2 1	4 3 2 1
Julie R Gralow, MD	4 3 2 1	4 3 2 1
Eric P Winer, MD	4 3 2 1	4 3 2 1
Stephen B Edge, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

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Professional Designation:

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

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