The Role of the Surgeon in the Interdisciplinary Management of Early Breast Cancer

Proceedings and Interviews from a CME Symposium at the 10th Annual Meeting of The American Society of Breast Surgeons

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Featuring discussion of 24 cases submitted from the practices of American Society of Breast Surgeons members

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The Role of the Surgeon in the Interdisciplinary Management of Early Breast Cancer

A Continuing Medical Education Program

OVERVIEW OF ACTIVITY

Historically, surgery has been the primary method for treating breast cancer. More recently, the diagnostic, surgical and medical management of breast cancer has escalated in complexity because of advancements in technology and clinical experience in addition to the availability of novel pharmaceutical agents. Thus, the care of breast cancer has evolved toward a multifaceted approach necessitating input from a variety of interdisciplinary experts. This paradigm shift has created the opportunity for extensive knowledge exchange among oncologic subspecialties and the challenge of ensuring that major clinical advances influencing local and systemic treatment algorithms are effectively disseminated among the cross-functional team members. To bridge the gap between research and patient care, this CME activity utilizes one-on-one interviews and a panel discussion with leading breast cancer investigators. By providing access to the latest research developments and expert perspectives, this program assists breast surgeons in the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Integrate the rational use of tumor biomarkers and tissue-based genomic assays into the individualized selection of therapy for early invasive breast cancer.
- Counsel patients with Stage 0 to III breast cancer about the value of sentinel lymph node biopsy and its influence on local and systemic treatment decisions.
- Appraise the efficacy and safety of partial breast irradiation, and discuss with eligible patients clinical trials evaluating this technique.
- Recognize the benefits and limitations of magnetic resonance imaging in the diagnosis, assessment and prognosis of breast cancer.
- Develop an evidence-based algorithm for the initial management of localized, hormone receptor-positive breast cancer in pre- and postmenopausal patients, focusing on duration and sequence of endocrine treatment and on patient adherence with oral antineoplastic agents.
- Individualize the use of neoadjuvant and/or adjuvant trastuzumab-based therapy for patients with HER2-positive breast cancer.
- Recall the design of ongoing clinical trials evaluating new treatment strategies for early breast cancer, and refer or enroll appropriate patients for participation.

ACCREDITATION STATEMENT

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EDITOR'S NOTE

On April 23, 2009 in San Diego our CME group was thrilled once again to participate in The American Society of Breast Surgeons Annual Meeting. In March 2009, we worked with the Society's team to send out an email inviting The American Society of Breast Surgeons membership to participate in a survey that would help determine the content of our meeting. One hundred and eleven busy surgeons took time from their crammed schedules to respond.

One of our main objectives was to determine the respondents' familiarity with and perspectives on important recent publications, data sets and major ongoing clinical trials. To that end, we provided a list of journal articles and meeting presentations from the past year that many of the clinical investigators who are featured on our breast cancer education programs identified as significant contributions to the field. We then asked participants to tell us if they knew about the data sets and their opinions concerning how essential the research is to physicians in practice (see annotated bibliography below). During the meeting, our faculty discussed many of the papers and ongoing trials deemed most critical. In addition, we asked respondents to submit interesting cases from their practices with specific management questions for the faculty. In the accompanying audio program, 24 of the cases were discussed by our faculty during the meeting or in individual interviews after the meeting.

So... Enjoy and learn!

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
August 10, 2009

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www.ResearchToPractice.com/BreastSurgeons09

Local Therapy

44% **77%** Haffty BG et al. **Timing of chemotherapy after MammoSite Radiation Therapy System breast brachytherapy: Analysis of The American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry trial.** *Int J Radiat Oncol Biol Phys* 2008;72(5):1441-8.

Chemotherapy initiated more than three weeks after the final MammoSite® procedure was associated with better cosmetic outcomes and a lower rate of radiation recall.

28% **84%** Patel RR et al. **Clinical outcome analysis in "high-risk" versus "low-risk" patients eligible for National Surgical Adjuvant Breast and Bowel B-39/ Radiation Therapy Oncology Group 0413 trial: Five-year results.** *Int J Radiat Oncol Biol Phys* 2008;70(4):970-3.

Percent familiar with paper/trial; R Ongoing clinical trial
Percent interested in paper/trial (responses of 4 or 5 on a 1-5 scale)

After five years, no difference was found between "high-risk" and "low-risk" disease treated with multicatheter interstitial brachytherapy or MammoSite with regard to local control rate, crude local recurrence rate and overall survival.

95% **88%** **NSABP-B-39: A randomized Phase III study of conventional whole breast irradiation versus partial breast irradiation**

A Phase III trial (N = 4,300) of whole breast irradiation versus partial breast irradiation (multicatheter brachytherapy or MammoSite balloon catheter or 3D conformal external-beam radiation) for patients who have undergone surgery for DCIS or Stage I/II breast cancer.

59% **64%** Clarke-Pearson EM et al. **Quality assurance initiative at one institution for minimally invasive breast biopsy as the initial diagnostic technique.** *J Am Coll Surg* 2009;208:75-8.

A single-institution audit in 2007 revealed that 40 percent of patients (N = 465) who underwent a breast operation for a benign or cancerous lesion had an excisional biopsy as the initial diagnostic procedure.

78% **61%** Silverstein M. **Where's the outrage?** *J Am Coll Surg* 2009;208:78-9.

Commenting on the study by Clarke-Pearson and colleagues, Dr Silverstein states, "When it comes to breast cancer, the operating room is for treatment, not diagnosis. The goal for those of us who treat breast cancer should be to go to the operating room one time to perform the correct therapeutic (not diagnostic) procedure. Breast center sanctioning organizations: Make certain that the breast centers that you approve have an open biopsy rate for diagnosis that is less than 10% and preferably less than 5%, or don't sanction them."

Endocrine Therapy

55% **77%** Ingle JN et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: Meta-analyses of randomized trials of monotherapy and switching strategies.** Oral Presentation. SABCS 2008;**Abstract 12**.

Meta-analysis revealed that adjuvant aromatase inhibitor (AI) therapy (cohort 1, up-front AIs or cohort 2, tamoxifen → AIs) produced significantly lower recurrence rates compared to five years of tamoxifen for postmenopausal patients with ER-positive breast cancer.

58% **70%** Mouridsen HT et al. **BIG 1-98: A randomized double-blind phase II study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Oral Presentation. SABCS 2008;**Abstract 13**.

Updated results of BIG 1-98 suggest superior overall survival with letrozole compared to tamoxifen for postmenopausal women with endocrine-responsive breast cancer, concluding that adjuvant therapy should start with an AI and that patients can be switched to tamoxifen after two years if necessary.

36% **68%** Cuzick J et al. **Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: A retrospective analysis of the ATAC trial.** *Lancet Oncol* 2008;9(12):1143-8.

Patients who developed new vasomotor symptoms or joint symptoms within the first three months of adjuvant anastrozole or tamoxifen experienced a 16 percent relative reduction in risk of recurrence compared to patients who did not develop symptoms.

57% **70%** **ACOSOG-Z1031: Exemestane, letrozole or anastrozole as treatment for postmenopausal women who are undergoing surgery for Stage II or Stage III breast cancer**

A Phase III trial (N = 375) designed to determine which AI administered as neoadjuvant therapy should be chosen as the agent in a future study that will compare neoadjuvant AI treatment to chemotherapy.

66% 71% **NSABP-B-42: A clinical trial to determine the efficacy of five years of letrozole compared to placebo in patients completing five years of hormonal therapy**

A Phase III trial (N = 3,840) designed to determine whether prolonged adjuvant hormonal therapy will improve disease-free survival of postmenopausal women with endocrine receptor-positive breast cancer who have completed five years of an AI or five years of a combination of up to three years of tamoxifen followed by an AI.

Genomic Predictors of Prognosis and Response to Therapy

71% 91% 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).** Oral Presentation. SABCS 2007;**Abstract 10**.

RT-PCR analysis of specimens from SWOG-8814 (N = 367) revealed that the Oncotype DX® Recurrence Score® was prognostic for postmenopausal patients with positive nodes who were treated with tamoxifen and predictive of added chemotherapy benefit for patients whose tumors had a high Recurrence Score.

49% 89% Dowsett M et al. **Risk of distant recurrence using Oncotype DX in postmenopausal primary breast cancer patients treated with anastrozole or tamoxifen: A TransATAC study.** Oral Presentation. SABCS 2008;**Abstract 53**.

Retrospective analysis of specimens from the monotherapy arms of the ATAC trial (N = 1,308) demonstrated that the Oncotype DX Recurrence Score is an independent predictor of the risk of distant recurrence for patients with node-negative and node-positive disease treated with either anastrozole or tamoxifen.

77% 78% **Program for the Assessment of Clinical Cancer Tests (PACCT-1) — A trial assigning individualized options for treatment: The TAILORx trial**

In this Phase III, partially randomized study (N = 10,046), patients with previously resected, axillary node-negative breast cancer are assigned to one of three treatment groups based on their risk of distant recurrence as determined by the Oncotype DX assay.

44% 68% **MINDACT: Microarray In Node-negative Disease may Avoid Chemo-Therapy**

A prospective, randomized study comparing the 70-gene signature to the common clinical pathological criteria in selecting patients for adjuvant chemotherapy in node-negative breast cancer.

Anti-HER2 Therapy

34% 88% Rakkhit R et al. **Significant increased recurrence rates among breast cancer patients with HER2-positive, T1a,bN0M0 tumors.** SABCS 2008;**Poster 701**.

In a review of T1a,bN0M0 breast cancer in patients who had not received adjuvant chemotherapy or trastuzumab (N = 965), investigators found that 10 percent of tumors one centimeter or smaller were HER2-positive and the five-year recurrence rate was 23 percent in these patients, concluding that HER2 positivity is a powerful negative prognostic factor in such cases.

Percent familiar with paper/trial; Ongoing clinical trial
Percent interested in paper/trial (responses of 4 or 5 on a 1-5 scale)

36% 73% Gianni L et al. **Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer: Primary efficacy analysis of the NOAH trial.** Oral Presentation. SABCS 2008;**Abstract 31**.

Among patients with locally advanced, HER2-positive breast cancer, randomly assigned to preoperative chemotherapy with or without trastuzumab (N = 327), both the overall response rate (ORR) and the pathologic complete response (pCR) rate were significantly higher for patients who received trastuzumab — 89 versus 77 percent for ORR and 39 versus 20 percent for pCR.

50% 46% R **NSABP-B-41: Neoadjuvant therapy with trastuzumab, lapatinib or the combination administered with weekly paclitaxel after AC**

A Phase III trial (N = 522) of neoadjuvant therapy with four cycles of AC followed by four cycles of weekly paclitaxel and trastuzumab or lapatinib or trastuzumab with lapatinib.

17% 53% Vukelja S et al. **A phase II study of trastuzumab DM1, a first-in-class HER2 antibody-drug conjugate, in patients with HER2+ metastatic breast cancer.** Oral Presentation. SABCS 2008;**Abstract 33**.

Among patients with progressive metastatic disease within 60 days of receiving HER2-directed therapy, the overall objective response rate with T-DM1 was 39.3 percent, demonstrating that T-DM1 has single-agent activity in patients previously treated with trastuzumab or lapatinib.

Adjuvant Bisphosphonates

43% 84% Gnant M et al. **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009;360(7):679-91.

The addition of zoledronic acid to adjuvant endocrine therapy resulted in a 36 percent relative reduction in the risk of cancer recurrence in premenopausal patients with ER-positive breast cancer.

41% 56% R **SWOG-S0307: Zoledronate, clodronate or ibandronate in women with Stage I, Stage II or Stage III breast cancer**

A Phase III trial (N = 4,500) designed to evaluate disease-free and overall survival of women with resected primary Stage I to III adenocarcinoma of the breast treated with adjuvant zoledronate versus clodronate versus ibandronate.

Neoadjuvant Systemic Therapy

34% 84% Classe JM et al. **Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: Results of Ganglion Sentinelle et Chimiothérapie Neoadjuvante, a French prospective multicentric study.** *J Clin Oncol* 2009;27(5):726-32.

The detection and false-negative rates and accuracy of sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy are comparable to those of SLNB without neoadjuvant chemotherapy.

38% 92% Gomez RE et al. **Sentinel node biopsy performed in the neoadjuvant setting for breast cancer: Results from the I-SPY TRIAL (CALGB 150007/150012 & ACRIN 6657).** SABCS 2008;**Poster 202**.

The sentinel lymph node identification rate after neoadjuvant chemotherapy was 100 percent for patients with clinically negative nodes before the therapy compared to 80 percent for the patients with clinically positive nodes before the therapy.

Percent familiar with paper/trial; R Ongoing clinical trial
Percent interested in paper/trial (responses of 4 or 5 on a 1-5 scale)

Sentinel Lymph Node Biopsy

DR MAMOUNAS: I believe that removing an appropriate number of sentinel nodes is the single most important factor in reducing one's false-negative rate. In most of the multicenter trials, the average number was 2.5 to 2.9. However, we shouldn't go overboard removing nodes because other studies have shown not much benefit is gained in removing more than four or five nodes.

The key is to be meticulous and, after removing the sentinel node, examine the axilla with a probe. That's my technique, and I typically remove four or five nodes.

It's essentially a selective lymphadenectomy in the hope of obtaining the best of both worlds — decreased morbidity and a low false-negative rate.

Magnetic Resonance Imaging (MRI)

DR MAMOUNAS: I don't use MRI routinely for patients with breast cancer. My belief is that the technique should be used selectively when a tumor cannot be defined readily by mammogram and ultrasound. For example, for a patient with dense breast tissue in whom we don't know how much disease is present, I believe MRI is reasonable, particularly when considering neoadjuvant chemotherapy.

Likewise, in general I don't recommend screening MRI. However, the guidelines recommend that MRI be considered for certain patients, such as those who have dense breasts or have a lifetime risk for breast cancer of 25 percent or higher. In patients with BRCA mutations who choose to keep their breasts and undergo chemoprevention, I recommend MRI annually.

Another indication for MRI is prior to prophylactic mastectomy. If a patient's risk is high enough to warrant a mastectomy, then I'm concerned about the possibility of occult cancer and I order MRI before surgery in place of sentinel lymph node biopsy.

Partial Breast Irradiation

DR HYAMS: The NSABP-B-39 trial evaluates partial breast irradiation in an objective manner because it allows external-beam radiation therapy, catheter brachytherapy and the MammoSite. I don't believe we have enough data yet in a cross comparison of trials to say which of these approaches is more effective.

Catheter brachytherapy developed a "bum rap" because of how it was used. It can still cause problems if it is not carefully delivered because of the potential for catheter site scarring,

which can be worsened if the seeds are in close proximity. However, with good technique that shouldn't be an issue. The same, of course, is true with tools like MammoSite. It's important to make certain that an adequate distance is present between the skin and the cavity. All of these approaches require that the surgeon and radiation oncologist work closely together.

DR MAMOUNAS: We use partial breast irradiation outside of the NSABP-B-39 trial only in select cases, such as for patients who have a contraindication to whole breast irradiation. For example, we have a patient who received mantle radiation years ago for Hodgkin disease and now presents with ductal carcinoma in situ (DCIS). I believe she would be a good candidate for this approach.

We also use partial breast irradiation for patients with a local ipsilateral recurrence if their lumpectomy was long ago, such as 10 years. In those cases, we administer 3D conformal external-beam radiation therapy to the lumpectomy area only. We have seen — and Mel Deutsch in Pittsburgh has published — reasonable local control rates among these patients, and we are able to avoid mastectomy (Deutsch 2002).

I have used this approach for two dozen patients and haven't seen any complications except severe fibrosis initially, which eventually resolves although it may take two to four years. The cosmetic result is compromised because the breast has undergone surgery and radiation therapy twice, but the patients who have this procedure prefer that to mastectomy. ■

SELECT PUBLICATION

Deutsch M. **Repeat high-dose external beam irradiation for in-breast tumor recurrence after previous lumpectomy and whole breast irradiation.** *Int J Radiat Oncol Biol Phys* 2002;53(3):687-91.

ENDOCRINE THERAPY

Adjuvant Endocrine Therapy for Postmenopausal Women

DR FOX: If we take the philosophy that we will want to offer the patient the best therapy, then aromatase inhibitors have been proven repeatedly to be superior to tamoxifen for postmenopausal patients.

The superiority is modest, and the improvement in survival is quite possibly statistically negligible.

However, I'm not certain that survival should always be our primary consideration in justifying one therapy versus another.

One issue that needs to be emphasized is that the advantage of an aromatase inhibitor is to lower the risk of a variety of undesirable outcomes. An in-breast recurrence, contralateral breast cancer or developing metastatic breast cancer are all undesirable events for a patient to endure.

In an 85-year-old, for whom the costs of aromatase inhibitors may be prohibitive, then tamoxifen is a less expensive alternative and I have had to prescribe it more often than

I like to admit in those situations. However, for an 85-year-old with severely compromised bone health who is at risk for falls, the justification for an aromatase inhibitor begins to wear thin. In patients who are at high risk for osteoporotic fracture for a variety of factors, other than simply low bone density, tamoxifen is also a suitable alternative to an aromatase inhibitor.

Duration of Adjuvant Endocrine Therapy

DR HOLMES: How to treat a postmenopausal patient with ER-positive, node-positive disease after five years of an aromatase inhibitor is a difficult question because until we have the data, we're flying by the seat of our pants.

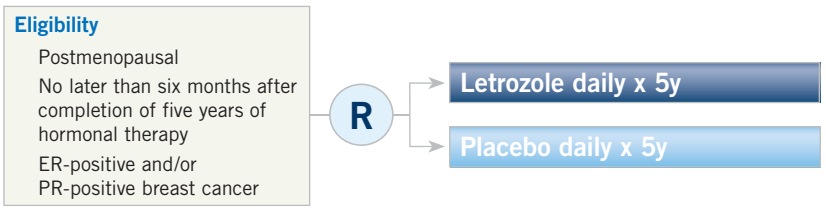
With a patient who is at high risk, such as a woman who had multiple positive nodes, I discuss the fact that prolonged blockade appeared to be helpful in the MA17 trial (Goss 2005), and if she isn't experiencing any significant problems, then I recommend she continue therapy for at least five years. Meanwhile, we'll have more data from trials addressing this issue (NSABP-B-42; [1.1]), and we'll monitor the patient's lipids, bones and vitamin D levels.

1.1

NSABP-B-42: Adjuvant Letrozole After Completion of Five Years of Hormonal Therapy with Either an Aromatase Inhibitor or Tamoxifen Followed by an Aromatase Inhibitor

Target Accrual: 3,840 over 5.25 years

Date Activated: August 14, 2006



SOURCE: NCI Physician Data Query, July 2009.

Endocrine Therapy-Related Symptoms and Risk of Recurrence

DR FOX: I find Cuzick's data on endocrine therapy-related symptoms and the risk of recurrence provocative (Cuzick 2008; [1.2]).

It wasn't the intent of the ATAC trial, but be that as it may, it was not an observation made in only a few dozen patients. This observation was made in more than 3,000 people, so this pattern may have some substance.

They identified all the patients who claimed to have no vasomotor or musculoskeletal symptoms at the time of randomization and then recorded their self-reported symptoms at the first three-month visit. The propor-

tion of patients who reported these symptoms was approximately one third, which I believe is appropriate to our clinical perception, and those patients experienced a reduction in the risk of recurrence out to seven or eight years of follow-up.

The hazard ratios were substantial. It almost seems to be an undeniable phenomenon. I believe it is entirely legitimate to use these data to coax patients into being adherent to therapy when they're discouraged because of toxicities.

1.2

ATAC Trial: Annual Breast Cancer Recurrence Rate According to Endocrine Symptoms Reported at Three-Month Follow-Up

	Anastrozole (n = 1,967)	Tamoxifen (n = 1,997)	Overall (n = 3,964)	Hazard ratio* (95% CI)	*p*-value
Vasomotor symptoms	1.7%	2.4%	2.1%	0.84 (0.71-1.00)	0.04
Joint symptoms	1.6%	1.9%	1.7%	0.60 (0.5-0.72)	<0.0001
Neither side effect	2.8%	3.5%	3.2%	1.0†	—

* Hazard ratios adjusted for age, body mass index, previous use of hormone replacement therapy, nodal status, tumor grade and tumor size; † Reference group; CI = confidence interval

SOURCE: Cuzick J et al. *Lancet Oncol* 2008;9(12):1143-8.

Adherence with Oral Endocrine Therapy

DR FOX: Many patients have an inherent reluctance to take medication, and with their frequent desire to please the physician I believe we're often misled regarding adherence. Conversely, we don't press the issue hard enough in clinical practice. The most staggering piece of information I've seen in this regard was when Steve Jones presented the TEAM trial data in San Antonio (Jones 2008). When they enumerated in an open-label trial the percentage of patients at two and three quarters who weren't taking their medicine, it was 30 percent on the tamoxifen arm and 20 percent for patients receiving exemestane.

That's a staggering number when coupled with the study Ann Partridge presented at San Antonio about two years ago, in which prescription filling was staggeringly decreased after one year and after two years (Partridge 2006). It seemed that a large minority of patients were no longer even filling their prescriptions. We haven't developed a reliable mechanism for ensuring adherence in our clinic other than our relatively casual day-to-day encouragement. I see it as a big problem.

Adjuvant Endocrine Therapy for Premenopausal Patients

DR FOX: Internationally, philosophical differences abound with regard to endocrine therapy for premenopausal patients. In the United States, many

oncologists still adhere to the assumption that the standard endocrine therapy for a premenopausal woman is tamoxifen. We still do not have proof that any other maneuver is better.

It's easy to assume that the combination of ovarian ablation and tamoxifen will never prove to be inferior to tamoxifen alone, but the issue is whether the combination will ever prove to be superior. Until the SOFT trial is completed, I've been disinclined to administer ovarian ablation therapy because the consequences of that maneuver should not be taken lightly, whether it's temporary or permanent.

It has not been our general practice at the University of Pennsylvania to recommend ovarian ablation therapy as part of a standard hormonal strategy for a very young patient, but I do acknowledge that many, many oncologists feel otherwise.

DR LOVE: What about a woman in her forties who gets chemotherapy, immediately stops menstruating and has a postmenopausal profile by blood work? You decide to administer tamoxifen, wait two years and she hasn't had a period. Will you keep the tamoxifen going?

DR FOX: I believe that the correct thing to do is to continue tamoxifen therapy. Ian Smith wrote a paper a few years ago in the *Journal of Clinical Oncology* demonstrating that about one fourth of women under those circumstances who receive aromatase inhibitors will resume menstruating (Smith 2006). In our practice, going back to 2003 or 2004, we were inclined many times to make the switch from tamoxifen to aromatase inhibitors under the circumstances that you described, only to find that fully one third of the patients resumed menstrual periods, had ovarian function and should have been maintained on tamoxifen. So I would be extremely hesitant about switching.

DR LOVE: If the patient has multiple node-positive breast cancer and completes five years of tamoxifen, would you keep the tamoxifen going or would you consider an aromatase inhibitor at that point, assuming she still had no menses and had a postmenopausal profile?

DR FOX: I would feel much more comfortable switching to an aromatase inhibitor at that point. The likelihood that she'll recover ovarian function and render the drug ineffective is low. Her risk of recurrence at five years is still substantial with five positive nodes, and I would have no misgivings about switching her to an aromatase inhibitor.

In fact, for in patients at the highest risk of recurrence, arbitrarily setting the bar at 10 positive nodes or higher, who complete five years of tamoxifen and have continued to menstruate I have, on occasion, instituted ovarian suppression therapy and prescribed an aromatase inhibitor as part of the sequential therapy for what would be a total of 10 years. ■

SELECT PUBLICATIONS

Cuzick J et al. **Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: A retrospective analysis of the ATAC trial.** *Lancet Oncol* 2008;9(12):1143-8.

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.

Jones SE et al. **Results of the first planned analysis of the TEAM (tamoxifen exemestane adjuvant multinational) prospective randomized phase III trial in hormone sensitive postmenopausal early breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 15**.

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**.

Partridge AH et al. **Adherence with adjuvant anastrozole therapy among women with early stage breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 4044**.

Smith IE et al. **Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: Caution and suggested guidelines.** *J Clin Oncol* 2006;24(16):2444-7.

GENOMIC PREDICTORS OF PROGNOSIS AND RESPONSE TO THERAPY

Role in ER-Positive, Node-Negative Breast Cancer

DR FOX: My colleagues and I were relatively fast adopters of the Onco*type* DX assay after Paik's early presentations (Paik 2004).

We wanted a way to identify patients for whom chemotherapy was or was not appropriate, and they've demonstrated that the assay can predict the value of chemotherapy in women with node-negative, ER-positive breast cancer (Paik 2006; [2.1]).

In early 2005 we began to apply the test for patients who met the eligibility criteria for the NSABP-B-20 trial, evaluating tamoxifen with or without chemotherapy in women with ER-positive, node-negative primary invasive breast cancer.

After a couple of years we examined our practice habits to determine how often we ordered the Onco*type* DX assay, whether we were abiding by the test results and if we were following the guidelines set by the NSABP.

We learned that we tended to order the assay less often for older patients and patients with large tumors (Patel 2007). We also found that we were good at abiding by the results. Patients with scores lower than 18 received no chemotherapy more than 85 percent of the time.

Conversely, patients with scores higher than 31 received chemotherapy approximately 90 percent of the time. The intermediate group received chemotherapy about 40 percent of the time.

Our principal finding was that the overall application of chemotherapy in that group of patients decreased by half, which was consistent with the Onco*type* DX assay in that about half of the patients receive a score lower than 18 (Patel 2007).

2.1

Effect of Adding Chemotherapy (Chemo) to Tamoxifen According to Oncotype DX Recurrence Score for Women with ER-Positive, Node-Negative Disease

10-year distant recurrence-free survival

Risk group	Tamoxifen (n = 227)	Tamoxifen with chemo (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.

Role in ER-Positive, Node-Positive Breast Cancer

DR FOX: The strategy of administering adjuvant chemotherapy to patients with node-positive breast cancer has been entrenched in what we do for so long that it will be difficult to steer oncologists off that track. Conversely, I don't think any sensible oncologist doubts that for a subset of patients with node-positive disease chemotherapy is a colossal waste of time. Utilization of the Oncotype DX assay for patients with positive nodes gives weight to this notion.

The problem with the trial that evaluated Oncotype in node-positive disease is that it used a chemotherapy regimen considered inferior to what we use today (Albain 2007; [2.2]). In addition, the number of women with low scores was not high. Finally, the study was limited to postmenopausal women and some believe that the relative benefits of chemotherapy may be greater for younger patients.

We've been hesitant to use Oncotype thus far for patients with node-positive disease. We've used it in cases in which the perceived risks of chemotherapy might provide us with justification for withholding chemotherapy. However, that has been a relatively small number of patients.

2.2

Effect of Adding Chemotherapy to Tamoxifen for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer According to Oncotype 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**.

TransATAC Study

DR COBLEIGH: The TransATAC study found that the Onco*type* DX Recurrence Score was prognostic for patients who received an aromatase inhibitor and for those who received tamoxifen. It also demonstrated that the Recurrence Score was prognostic in node-positive and node-negative disease (Dowsett 2008; [2.3]).

I have rarely used the Onco*type* DX assay for patients with positive nodes. One scenario might be a patient having one to three positive nodes and being adamantly opposed to chemotherapy — to give her more courage. Most often, it's been for patients with tiny micrometastases and otherwise negative axillary nodes. ■

2.3

TransATAC: Proportion of Patients Treated with Anastrozole or Tamoxifen Who Are Free of Distant Recurrence at Nine Years by Onco*type* DX Recurrence Score (RS) Group: Analysis of Nodal Status

	Low	Int	High	High vs low	Int vs low
Node-negative (n = 513, 229, 130)	96%	88%	75%	HR* = 5.2	HR* = 2.5
Node-positive (n = 160, 94, 52)	83%	72%	51%	HR* = 2.7	HR* = 1.8

* HR = hazard ratio for RS group, adjusted for tumor size, grade, age and treatment

SOURCE: Dowsett M et al. San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

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**.

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.

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.

Patel H et al. **Utilization of Onco*type* DX in node-negative, ER-positive breast cancer patients.** *Proc ASCO* 2007;**Abstract 11067**.

ANTI-HER2 THERAPY

Neoadjuvant Anti-HER2 Therapy

DR HOLMES: The MD Anderson trial evaluating neoadjuvant chemotherapy with or without trastuzumab reported nearly a 67 percent patho-

logic complete response (pCR) rate in the first cohort, but then the next cohort demonstrated a slightly lower response. Thus, the overall pCR rate was 60 percent (Buzdar 2007; [3.1]). The controversy is that the investigators used an anthracycline and trastuzumab together, and the concern is increased cardiotoxicity. That same approach was used in the NOAH trial (Gianni 2008; [3.2]).

I believe neoadjuvant therapy is a reasonable option because of the biologic information it provides for the appropriate patient. Most patients do not receive neoadjuvant therapy, however, because generally the surgeon sees them first.

3.1

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.

3.2

Neoadjuvant Chemotherapy with Trastuzumab for Patients with Locally Advanced, HER2-Positive Breast Cancer: Primary Efficacy Data

Pathologic complete response rate for primary tumors: Intent-to-treat population

	Chemotherapy + trastuzumab	Chemotherapy	*p*-value
HER2-positive tumors	43%	23%	0.002

Chemotherapy + trastuzumab versus chemotherapy

Probability	HR	95% CI	*p*-value
Event-free survival	0.56	0.36-0.85	0.006
Overall survival	0.65	0.34-1.23	0.18

SOURCE: Gianni L et al. San Antonio Breast Cancer Symposium 2008;**Abstract 31**.

Anti-HER2 Therapy for Smaller, Node-Negative Tumors

DR FOX: I often treat small, HER2-positive, node-negative breast cancer with chemotherapy and trastuzumab. I wouldn't withhold therapy based on the notion that a patient has a good prognosis because her tumor is small. The idea that the size of an invasive tumor trumps everything

else in treatment decision-making has long been entrenched in what we do. However, HER2-positive cancer, even a small tumor, can be a notorious misbehaver.

DR COBLEIGH: Most of the data we have on treating breast cancer smaller than one centimeter are with T1B tumors. We have little information on T1A tumors and virtually no data from randomized clinical trials. What we do know from the Vancouver database and from recent data presented at San Antonio is that patients with HER2-positive, T1B tumors have poor prognoses (Chia 2008; Rakkhit 2008).

I believe we should offer treatment at least to patients with T1A tumors, if they're healthy. I do not generally administer trastuzumab as a single agent because we have no information on that. I use what we know works, such as combining chemotherapy with trastuzumab.

Treatment for HER2-Positive DCIS

DR COBLEIGH: Approximately 55,000 patients are diagnosed with DCIS each year in this country. Recent research indicates that two kinds of DCIS exist: low-grade DCIS, which is often ER-positive, and higher-grade lesions, which are often HER2-positive.

We also know now that the combination of antibodies targeted toward growth factor receptors produces a better result when administered with radiation therapy than radiation therapy alone. Cetuximab and concurrent radiation therapy has been FDA approved for patients with head and neck cancer, and in vitro information indicates that HER2-positive breast cancer is more sensitive to the combination of radiation therapy and trastuzumab than to radiation therapy alone.

The NSABP-B-43 trial is evaluating radiation therapy with or without two doses of trastuzumab for patients with HER2-positive DCIS resected by lumpectomy. The primary endpoint is local control with the goal of preserving more breast tissue. ■

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.

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.

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**.

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**.

ABCSG-12 Trial

DR FOX: The Austrian ABCSG-12 trial evaluated premenopausal women with hormone receptor–positive breast cancer who were randomly assigned to ovarian suppression with tamoxifen versus ovarian suppression with anastrozole. The most recent presentation reported no difference in recurrence rates when tamoxifen and anastrozole were compared (Gnant 2009).

In a second randomization, the patients either did or did not receive twice-yearly infusions of zoledronic acid. The reported risk of recurrence was decreased for the women who received the bisphosphonate (4.1). It's difficult to translate these data into clinical practice because those patients were not being treated in accordance with our own standards — that is, they didn't receive chemotherapy. Therefore, we have not yet incorporated bisphosphonates as a routine part of postoperative treatment for our patients who are premenopausal.

However, those of us who follow this development closely would like to see something come of it because the infusion of zoledronic acid two times a year is not a big deal. It's not overly expensive or toxic, and no major health consequences are known. If it produces a relative reduction in recurrence risk of one third, it will be difficult to not use it in clinical practice. We're all waiting for the AZURE study to be presented, which is more of a real-life examination of bisphosphonates. ■

4.1

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.

SELECT PUBLICATION

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.

POST-TEST

The Role of the Surgeon in the Interdisciplinary Management of Early Breast Cancer

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the MD Anderson neoadjuvant study reported by Buzdar and colleagues, approximately _____ of patients with HER2-positive breast cancer who received chemotherapy and trastuzumab demonstrated a pathologic complete response.**
   a. 20 percent
   b. 30 percent
   c. 40 percent
   d. 60 percent

2. **In the MA17 trial, continuing letrozole after completion of adjuvant tamoxifen _____ result in improved efficacy compared to placebo.**
   a. Did
   b. Did not

3. **Though the Onco*type* DX assay has been integrated into the clinical management of node-negative tumors, recent data have emerged suggesting its potential utility in the management of node-positive tumors.**
   a. True
   b. False

4. **In the TransATAC analysis, the Onco*type* DX Recurrence Score predicted the likelihood of distant metastatic disease through nine years of follow-up for patients with node-negative and node-positive breast cancer treated with _____.**
   a. Anastrozole
   b. Tamoxifen
   c. Anastrozole or tamoxifen

5. **The NSABP-B-39 trial, which compares whole breast irradiation to partial breast irradiation (PBI), includes which of the following PBI techniques?**
   a. Brachytherapy
   b. MammoSite
   c. 3D conformal external-beam radiation
   d. All of the above

6. **In the NSABP-B-42 trial, postmenopausal women who have completed five years of adjuvant hormonal therapy within the past six months for hormone receptor-positive, early invasive breast cancer are randomly assigned to receive _____ versus placebo for five years.**
   a. Tamoxifen
   b. Fulvestrant
   c. An aromatase inhibitor
   d. Any of the above

7. **Cuzick and colleagues demonstrated that women who reported new vasomotor or joint symptoms within the first three months of adjuvant treatment with anastrozole or tamoxifen experienced a greater response to endocrine therapy than women without these symptoms.**
   a. True
   b. False

8. **NSABP-B-43 is evaluating radiation therapy with or without _____ for patients with HER2-positive DCIS resected by lumpectomy.**
   a. Gefitinib
   b. Lapatinib
   c. Trastuzumab
   d. T-DM1

9. **Gnant and colleagues reported that in a trial for premenopausal women that evaluated ovarian suppression with tamoxifen or anastrozole, alone or combined with zoledronic acid, patients who received bisphosphonate therapy experienced which of the following?**
   a. Reduction in contralateral breast cancer
   b. Reduction in locoregional recurrence
   c. Reduction in distant metastases
   d. All of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

The Role of the Surgeon in the Interdisciplinary Management of Early Breast Cancer

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

How would you characterize your level of knowledge on the following topics?

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

	BEFORE	AFTER
Prognostic and predictive value of genomic assays in clinical decision-making	4 3 2 1	4 3 2 1
Use of whole breast versus partial breast irradiation therapy	4 3 2 1	4 3 2 1
Extending adjuvant hormonal therapy beyond five years for patients with ER-positive disease	4 3 2 1	4 3 2 1
Optimal adjuvant systemic therapy for patients with HER2-positive breast cancer	4 3 2 1	4 3 2 1
Use of neoadjuvant systemic therapy, including timing of sentinel lymph node biopsy	4 3 2 1	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 learning objectives (LOs) by circling the appropriate selection:

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

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

- Integrate the rational use of tumor biomarkers and tissue-based genomic assays into the individualized selection of therapy for early invasive breast cancer. . . . . 4 3 2 1 N/M N/A
- Counsel patients with Stage 0 to III breast cancer about the value of sentinel lymph node biopsy and its influence on local and systemic treatment decisions. 4 3 2 1 N/M N/A
- Appraise the efficacy and safety of partial breast irradiation, and discuss with eligible patients clinical trials evaluating this technique. . . . . 4 3 2 1 N/M N/A
- Recognize the benefits and limitations of magnetic resonance imaging in the diagnosis, assessment and prognosis of breast cancer. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based algorithm for the initial management of localized, hormone receptor-positive breast cancer in pre- and postmenopausal patients, focusing on duration and sequence of endocrine treatment and on patient adherence with oral antineoplastic agents. . . . . 4 3 2 1 N/M N/A
- Individualize the use of neoadjuvant and/or adjuvant trastuzumab-based therapy for patients with HER2-positive breast cancer. . . . . 4 3 2 1 N/M N/A
- Recall the design of ongoing clinical trials evaluating new treatment strategies for early breast cancer, and refer or enroll appropriate patients for participation.. 4 3 2 1 N/M N/A

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 faculty and moderator for this educational activity

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
Melody A Cobleigh, MD	4	3	2	1	4	3	2	1
Kevin R Fox, MD	4	3	2	1	4	3	2	1
Frankie A Holmes, MD	4	3	2	1	4	3	2	1
David M Hyams, MD	4	3	2	1	4	3	2	1
Eleftherios P Mamounas, MD, MPH	4	3	2	1	4	3	2	1
Moderator	**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 faculty and moderator for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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Breast Cancer® UPDATE

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