

Breast Cancer™

U P D A T E

Conversations with Clinical Research Leaders
Bridging the Gap between Research and Patient Care

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Breast Cancer Update for Surgeons

A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic techniques, agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing breast surgeon must be well informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update for Surgeons* utilizes one-on-one discussions with leading breast cancer investigators. By providing access to the latest research developments and expert perspectives, this CME program assists breast surgeons in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer in order to incorporate these data into management strategies in the adjuvant and neoadjuvant disease settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors in the adjuvant and neoadjuvant settings, and discuss the risks and benefits of sequencing adjuvant aromatase inhibitors after tamoxifen.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE FOR SURGEONS*

The purpose of *Breast Cancer Update for Surgeons* Issue 2 is to support these global objectives by offering the perspectives of Drs Silverstein, Howell, Cody and Paik on the integration of emerging clinical research data into the management of breast cancer.

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This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. BreastCancerUpdate.com/Surgeons includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in [blue underlined text](#).

Table of Contents

- 2 **Editor's Note: Images from the retrospectroscope and prospectroscope**

- 5 **Melvin J Silverstein, MD**
Professor of Surgery and Henrietta C Lee Chair in Breast Cancer Research
USC-Keck School of Medicine
Director, Harold E and Henrietta C Lee Breast Center
USC/Norris Comprehensive Cancer Center and Hospital
Los Angeles, California

- 8 **Anthony Howell, MD**
Professor of Medical Oncology
University of Manchester
Manchester, England

- 12 **Hiram S Cody III, MD**
Attending Surgeon
Breast Service, Department of Surgery
Memorial Sloan-Kettering Cancer Center
Professor of Clinical Surgery
Weill Medical College of Cornell University
New York, New York

- 15 **Soonmyung Paik, MD**
Director, Division of Pathology
National Surgical Adjuvant Breast and Bowel Project
Pittsburgh, Pennsylvania

- 18 **Post-test**

- 19 **Evaluation**

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Editor's Note

Images from the retrospectroscope and prospectroscope

A recent tumor panel discussion I moderated at the 2005 Miami Breast Cancer Conference included a fascinating case that foreshadows a major paradigm shift in this disease. The 43-year-old premenopausal woman whose case was presented by her South Florida-based medical oncologist was diagnosed several years ago with a small lesion on mammography. This proved to be a 0.7-cm, ER/PR-positive, HER2-negative, infiltrating ductal carcinoma. The axillary node dissection was negative.

After much discussion about whether any adjuvant therapy was indicated in what was considered a low-risk situation based on tumor size and histology, this woman elected to receive tamoxifen alone. Two years later, bone metastases were detected and a biopsy confirmed recurrence. The patient is now receiving palliative systemic management.

What is particularly interesting about this case is that the patient's medical oncologist retrieved the original tumor block and was able to obtain an *Oncotype DX*TM assay, which revealed a high recurrence score. (This was done for academic purposes without charge to the patient.)

In retrospect, had this assay and the results from the latest relevant research data set been available at the time of this patient's initial diagnosis, and had the patient received relatively nontoxic adjuvant chemotherapy (ie, CMF or M → F), the likelihood of her relapsing would have decreased by about 75 percent. Put in more direct terms, three out of every four women and their families in this situation might have been spared the profound sadness and infirmity associated with metastatic breast cancer.

In this issue of *Breast Cancer Update for Surgeons*, we again visit Soon Paik, one of the brilliant architects — along with Genomic Health medical oncologist Steven Shak — who developed perhaps the most important breast cancer clinical research database in the last decade. I interviewed Soon at the 2003 San Antonio Breast Cancer Symposium where he initially presented the results from the NSABP initiative with Genomic Health, and I again chatted with him at this past December's meeting. Both visits were quite memorable, and the most recent interview is included in this program.

Every physician treating breast cancer patients must fully understand this research because it has direct and important implications for daily patient care. Put very simply, women with estrogen or progesterone receptor-positive, node-

negative tumors must be informed of the option of having an *Oncotype* DX assay performed on their tumor tissue. Until recently, many insurers and governmental reimbursement agencies balked at paying the \$3,000 plus tab for this test, but with the emergence of Soon's most recent findings, these bureaucrats will now be standing in line to pay.

Taken at a pure monetary level, the assay has now become the best investment in town because fewer patients will receive costly adjuvant chemotherapy up front, and less resources will be invested in palliative regimens later on. The human savings are even more astonishing and impossible to quantify.

Every day I hear about more personal situations in which this assay has been utilized effectively, not only to identify patients who *will* benefit from receiving chemotherapy but also patients who *will not* benefit. A case in point is the woman who transcribes the research leader interviews for this audio series. This petite 60-year-old very talented ball of fire has a completely untouched head of dark, wavy hair, mainly because of the *Oncotype* DX assay.

In December, while recuperating from breast cancer surgery, this woman — who is a true master of her trade — decided to return to work, and one of her first assignments was to transcribe Dr Paik's interview. Having recently learned of her pathology results (ER/PR-positive, node-negative), she instantly recognized the personal relevance of Soon's findings and spoke with her surgeon, who called me. After hearing of these latest data, he ordered the assay.

When the results suggested a low chance of recurrence, the patient and her surgeon decided to forego adjuvant chemotherapy. Now, before beginning her day deciphering rapid-fire talkers and investigators with accents from all over the globe, she munches a daily anastrozole pill that will further reduce her already low risk of recurrence.

The landmark research collaboration that spared this woman the rigors of adjuvant chemotherapy is just the first of what is likely to be a long series of similar studies with many other new and perhaps less costly predictive assays.

The NSABP initiative utilized a new technology developed by Genomic Health to evaluate a 21-gene panel in paraffin-embedded tumor tissue. Essentially, the *Oncotype* DX assay was able to determine that about half of the patients were in a favorable risk stratum with less than a seven percent chance of recurrence on tamoxifen. These numbers are likely to be even lower with aromatase inhibitors (AIs), as discussed in this program by Tony Howell, principal investigator of the ATAC trial.

The most recent NSABP data set presented by Soon documented a profound effect of adjuvant chemotherapy on the risk of relapse in the higher-risk subset. One might imagine that today, if the 43-year-old patient presented at the 2005 Miami Breast Cancer Conference tumor panel discussion had been identified as being in the high-risk category, she might not only have received adjuvant chemotherapy, but perhaps more aggressive adjuvant endocrine therapy than just tamoxifen. Specifically, ovarian ablation or suppression plus tamoxifen

might have been considered for this patient, or even the option of an aromatase inhibitor added to ovarian suppression, although minimal clinical trial data currently support this strategy.

In general, a variety of clinical trials continue to demonstrate an advantage for AIs over tamoxifen in postmenopausal women, either in the up-front setting — as with anastrozole in ATAC — or after two or five years of adjuvant tamoxifen, as documented in a number of trials. The next generation of studies is addressing the role of AIs with ovarian suppression in premenopausal patients and the optimal duration of adjuvant AI therapy.

During my oncology fellowship in the late 1970s, tamoxifen became the beacon of targeted therapy, first in metastatic disease, then as adjuvant therapy for invasive disease and then DCIS, and finally as chemoprevention in women at high risk.

Now, after decades in the unique role as the optimal available endocrine therapy, this amazing SERM has finally been displaced by aromatase inhibitors for postmenopausal women. Tony Howell also reviews evolving research demonstrating that while the three available aromatase inhibitors have similar antitumor effects, interesting differences are beginning to emerge related to the risk of side effects and long-term sequelae, including cardiovascular disease.

The other two speakers interviewed in this program, surgeons Mel Silverstein and Chip Cody, discuss recent developments in local therapy for breast cancer, particularly related to decreasing morbidity. Partial breast irradiation and sentinel node biopsy are particularly noteworthy. While these strategies may not affect tumor control, the morbidity and inconvenience to the patient are considerably decreased compared to conventional breast irradiation and axillary node dissection.

It is always distressing to consider patients diagnosed just prior to research advances because these people have narrowly missed the opportunity to benefit. However, when one considers such cases retrospectively, we are better able to understand the human value of clinical and translational research, and thinking prospectively, we have hope that cancer therapy will become increasingly effective with fewer side effects and long-term complications for our patients.

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Select publications

Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. [Abstract](#)

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. [Abstract](#)

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. [Abstract](#)

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](#)

Estrogen receptor results and benefit from adjuvant tamoxifen in patients with DCIS

In NSABP-B-24, patients with DCIS had excision and radiation therapy and were randomly assigned to adjuvant tamoxifen or placebo. A statistical benefit in the local recurrence rate was observed for patients who received adjuvant tamoxifen (Fisher 1999).

Dr Craig Allred evaluated approximately 600 cases from NSABP-B-24. Patients with ER-positive disease derived benefit from treatment, whereas patients with ER-negative disease did not benefit (Allred 2002; [1.1]).



1.1 NSABP-B-24: Frequency and Relative Risk of First Breast Cancer Events in Patients with DCIS

	ER-positive		ER-negative	
	Tamoxifen (n=237)	Placebo (n=243)	Tamoxifen (n=62)	Placebo (n=84)
All events	10%	23%	23%	26%
Ipsilateral	7%	13%	18%	18%
Contralateral	3%	8%	5%	6%
Other	0%	2%	0%	2%
Relative risk for all breast cancer events	0.41 (↓ 59%)		0.80 (↓ 20%)	
p-value	0.0002		0.51	

SOURCE: Allred D et al. **ER status and response to tamoxifen in ductal carcinoma in situ (DCIS): Findings from NSABP protocol B-24.** Presentation. San Antonio Breast Cancer Symposium 2002; **Abstract 30.**

Dr Silverstein is a Professor of Surgery and Henrietta C Lee Chair in Breast Cancer Research at USC-Keck School of Medicine and Director of the Harold E and Henrietta C Lee Breast Center at USC/Norris Comprehensive Cancer Center and Hospital in Los Angeles, California.

Role of adjuvant radiation therapy in older patients with small, ER-positive, node-negative, invasive tumors

The standard in the United States today is to treat invasive cancer conservatively with excision and radiation therapy. Two recent articles published in the *New England Journal of Medicine* — one from Canada by Dr Fyles and the other from Boston by Dr Hughes — evaluated women 50 years of age and older (Fyles 2004) and 70 years of age and older (Hughes 2004) who were randomly assigned to excision and tamoxifen with or without radiation therapy. Most of the patients had ER-positive, T1 (≤ 2 cm) tumors.

As expected, patients receiving radiation therapy had a lower local recurrence rate, but the absolute magnitude of that reduction was quite small. In Dr Hughes' study, it was only three or four percent (Hughes 2004); in the Canadian study, it was seven or eight percent (Fyles 2004). Although the local recurrence rate was higher without radiation therapy, overall survival was identical for patients treated with or without radiation therapy.

Since those articles were published, I've treated a few women who were 65 to 75 years of age with well-excised, nonaggressive, ER-positive tumors. I showed those patients the literature, and they were interested. Two of them elected not to receive radiation therapy, and I think more patients with similar disease profiles will begin to consider declining radiation.

The alternative, however, might be to use MammoSite® radiation therapy, so you're not withholding potentially life-saving radiation. Although I believe little difference will occur in survival, a significant difference will occur in local recurrence, which can be a very depressing, demoralizing event.

Image-detected breast cancer

I recently directed the Second International Consensus Conference on image-detected breast cancer. The first one was held in 2001 and was published in the *Journal of the American College of Surgeons* six months later (International Breast Cancer Consensus Conference 2001). At this recent second conference, the executive editor of the *Journal of the American College of Surgeons* was present, along with about 23 experts from all over the world. We discussed a variety of subjects: ductal carcinoma in situ, minimally invasive small tumors, minimally invasive breast biopsy and MRI.

Thirty years ago, image-detected lesions virtually did not exist. Almost all patients had palpable lesions, and more than half had positive nodes. For all practical purposes, DCIS did not exist. In 1978, the American College of Surgeons conducted a survey and found that less than one percent of all breast tumors were DCIS. Now, 25 to 30 years later, DCIS accounts for 21 percent of all the new breast cancer cases, of which 90 percent are nonpalpable and are detected mammographically.

The average size of an invasive breast cancer has decreased from about 3.5 to 4 centimeters 30 years ago to 10 to 15 millimeters today. We suddenly have tumors that we can't feel in perfectly normal asymptomatic women without any physical

findings. The abnormalities are almost always detected mammographically. Initially, in the 1980s and 1990s, all of these patients were taken to the operating room for an open wire-directed excision.

Today, I think that's a bad idea. At the Second International Consensus Conference, we made a strong statement that the optimal way to biopsy this type of lesion is with a minimally invasive breast biopsy using an image-directed needle. The operating room should be reserved for definitive treatment, and we should attempt to subject patients to no more than one surgery.

Role of MRI in patients with breast cancer

At the Second International Consensus Conference on image-detected breast cancer, vigorous debate arose about the role of MRI. Without a doubt, this tool is coming of age. It was only of minor interest at the 2001 conference, and it was of tremendous interest at the 2005 conference.

Many uses for MRI are now accepted. For example, most patients who present with axillary metastases and an unknown primary lesion have breast cancer. Seventy to 80 percent of the time you'll locate the primary tumor with an MRI, but not with any other tool. MRI is also valuable in evaluating patients with implants and in determining the extent of disease before and after neoadjuvant chemotherapy.

In every patient in whom I utilize a needle biopsy and mammography to diagnose infiltrating cancer, I try to follow up with an MRI. Many times the MRI will reveal more extensive disease in another quadrant or the other breast. A decision about what to do should not be based solely on the MRI. If disease is revealed elsewhere that precludes breast preservation, a biopsy should be performed and MRI-guided biopsy may be necessary. If the patient is adamant about saving her breast, histologic proof of disease somewhere other than in the breast is needed before committing the patient to a mastectomy.

Select publications

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** San Antonio Breast Cancer Symposium 2002; [Abstract 30](#).

Fisher B et al. **Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial.** *Lancet* 1999;353(9169):1993-2000. [Abstract](#)

Fyles AW et al. **Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer.** *N Engl J Med* 2004;351(10):963-70. [Abstract](#)

Hughes KS et al; Cancer and Leukemia Group B; Radiation Therapy Oncology Group; Eastern Cooperative Oncology Group. **Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer.** *N Engl J Med* 2004;351(10):971-7. [Abstract](#)

International Breast Cancer Consensus Conference. **Image-detected breast cancer: State of the art diagnosis and treatment.** *J Am Coll Surg* 2001;193(3):297-302. No abstract available

ATAC trial: Findings at 68 months

Disease-free survival and overall survival

The 68-month data from the ATAC trial indicate continued improvement in disease-free survival in patients receiving anastrozole versus tamoxifen (Howell 2005) — 3.3 percent absolute difference in recurrence rate and a 17 percent improvement in the hazard ratio for relapse in hormone receptor-positive patients. Anastrozole improves the time to distant recurrence.

The relative reduction in breast cancer mortality with anastrozole was 13 percent, and a nonsignificant improvement in time to breast cancer death was demonstrated in ATAC; however, no statistically significant difference in overall survival was demonstrated between patients receiving anastrozole versus tamoxifen.

In NSABP-B-14, which enrolled only patients with node-negative disease, we didn't see a mortality improvement until after approximately seven years of follow-up. In the ATAC trial, 39 percent of patients had node-positive disease and the remainder had primarily node-negative disease. We're at six years with ATAC and it may be a year or two before any mortality improvement is demonstrated. We expect it to occur because we see both a distant disease-free survival improvement and a breast cancer survival improvement, albeit not significant, with anastrozole.

Two-year recurrence rate and effects of anastrozole

A peak in recurrence occurs at two years for patients on tamoxifen, and it's similar to the peak we see in patients who receive no treatment. We see this peak in all patients on tamoxifen, but especially in patients who have node-positive disease. This two-year peak was blunted by anastrozole. This is important because if patients start with tamoxifen, some will relapse on tamoxifen who would not have relapsed on anastrozole, and we've lost those patients. In addition, we see increased toxicity with tamoxifen during those first two and a half years, so from both the efficacy and toxicity standpoints, it is probably better to begin adjuvant hormonal therapy with an aromatase inhibitor. In the ATAC trial, contralateral breast cancer was reduced by 50 percent with anastrozole,



which is similar to the data from other aromatase inhibitor trials. That's a 50 percent reduction compared to tamoxifen and an estimated 75 percent reduction compared to no treatment.

Toxicity

At the 2004 San Antonio meeting, we presented updated toxicity data including new data on the rate of hysterectomy (2.1), which was 5.1 percent in patients on tamoxifen but only 1.3 percent in patients on anastrozole (Howell 2004). The rate of endometrial cancer was 0.8 percent with tamoxifen and 0.2 percent with anastrozole, so clearly endometrial cancer doesn't account for all of the increase seen in the hysterectomy rate. This suggests that some women are undergoing unnecessary hysterectomies. I believe this issue makes anastrozole favorable despite its higher cost.

Another issue is the joint symptoms we see with aromatase inhibitors. In the data reported, tamoxifen had approximately a 29 percent joint symptom rate compared to 36 percent with anastrozole. Matt Ellis' group presented an interesting abstract in San Antonio indicating that women with these symptoms may have low vitamin D levels and giving them vitamin D improves some of the joint symptoms. These are early data and more studies are underway, but if we could solve this joint problem with vitamin D, it would be extraordinary.

We know from the ATAC trial that more serious adverse events are associated with tamoxifen than with anastrozole and, despite the joint symptoms, patients tend to stay on anastrozole more than they stay on tamoxifen, which is an important efficacy issue.

Bone density

In the 68-month follow-up of the ATAC trial, the fracture rates were 7.7 percent with tamoxifen versus 11 percent with anastrozole (Howell 2005). We saw no increase in hip fractures with anastrozole, which is important, but the fracture rate with anastrozole is still a concern. The other issue is fracture rate over time. I presented the data after six years, and the annual fracture rate is approximately 1.5 percent to two percent with tamoxifen and 2.5 percent with anastrozole. What surprised me was that during the fifth year of the trial, the fracture rate was lower in the anastrozole group than in the tamoxifen group, although not significantly lower. It seems that as soon as anastrozole is stopped, the fracture rate goes down.

We had a bone subprotocol in which we evaluated lumbar spine and trochanter bone mineral density over time. In the first year, an approximately 2.5 percent drop in bone mineral density occurred in patients on anastrozole. At two years, it was slightly more than a four percent drop.

This is similar to the IES data with exemestane and the MA17 data with letrozole, so the impact on bone mineral density is a class effect of aromatase inhibitors, not limited to anastrozole, and we need to learn how to manage it (Coleman 2004, Perez 2004).

In San Antonio, Michael Gnant presented the extraordinary Austrian data on using zoledronic acid to prevent bone mineral loss in premenopausal patients (Gnant 2004). Patients were randomly assigned to receive goserelin plus tamoxifen or goserelin plus anastrozole, and then a subrandomization assigned patients to zoledronic acid or not. In this study, they found that the 14 percent loss of bone mineral density on anastrozole over three years was completely abrogated by administering zoledronic acid.

2.1 ATAC Trial 68-Month Analysis: Adverse Events*

	Anastrozole (percent)	Tamoxifen (percent)	Odds ratio (anastrozole vs tamoxifen)	p-value
Drug-related AE	60.9	68.4	—	<0.0001
Drug-related SAE	4.7	9.0	—	<0.0001
AE leading to withdrawal	11.1	14.3	—	0.0002
Hot flashes	35.7	40.9	0.80	<0.0001
Vaginal bleeding	5.4	10.2	0.50	<0.0001
Vaginal discharge	3.5	13.2	0.24	<0.0001
Endometrial cancer	0.2	0.8	0.29	0.02
Hysterectomy	1.3	5.1	—	<0.0001
Ischemic cerebrovascular events	2.0	2.8	0.70	0.03
Venous thromboembolic events	2.8	4.5	0.61	0.0004
Joint symptoms/arthritis	35.6	29.4	1.32	<0.0001
Fractures†	11.0	7.7	1.49	<0.0001

AE = adverse events; SAE = serious adverse events

* Adverse events on treatment or within 14 days of discontinuation

† Fractures occurring before recurrence (includes patients no longer on treatment)

SOURCES: Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. [Abstract](#)

Howell A. Presentation. San Antonio Breast Cancer Symposium 2004; [Abstract 1](#).

Deep vein thrombosis, stroke and cardiovascular events

In the ATAC trial, 4.5 percent of patients on tamoxifen had deep vein thrombosis, whereas approximately 2.8 percent of patients on anastrozole developed this side effect. These results are comparable to similar studies and to the rate seen in women on hormone replacement therapy. We also continue to see a reduction in ischemic cerebrovascular events with anastrozole versus tamoxifen — two percent versus 2.8 percent, respectively.

In my opinion, the important data are the new and slightly worrisome findings on cardiac events in the aromatase inhibitor trials. In ATAC, the rate of events was 4.1 percent with anastrozole and 3.4 percent with tamoxifen. The increase with anastrozole was not significant — the *p*-value was 0.12. The IBCSG-1-98 data presented at the St Gallen's meeting also reported on Grades III to V cardiac events. The rates were 3.6 percent in patients on letrozole compared to 2.5 percent in patients on tamoxifen, with 26 versus 13 myocardial deaths, respectively (BIG 1-98 Collaborative Group 2004). In San Antonio, Coombes reported the IES trial had a statistically significant increase — 20 myocardial infarctions in patients on exemestane and eight in patients on tamoxifen (Coombes 2004). This issue needs to be carefully monitored.

IBCSG-1-98: Letrozole versus tamoxifen up front or sequentially

The IBCSG-1-98 efficacy data at 30 months look almost identical to the ATAC data at 33 months, favoring the aromatase inhibitor over tamoxifen (BIG 1-98 Collaborative Group 2004). There is a 21 percent reduction in disease-free survival in IBCSG-1-98 and a 22 percent reduction in ATAC. Time to recurrence is an 18 percent reduction in IBCSG-1-98 and a 17 percent reduction in ATAC. There appears to be a greater survival advantage in the BIG trial — a 14 percent reduction in death versus only a three percent reduction in ATAC, although we need to see what happens with further follow-up. The hazard ratio for overall survival was 0.97 for ATAC and 0.86 for IBCSG-1-98. The distant disease-free survival, which is possibly a surrogate for breast cancer survival, is also similar to ATAC.

Select publications

BIG 1-98 Collaborative Group. **Letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. BIG 1-98: A prospective randomized double-blind Phase III study.** [Abstract](#)

Coleman RE et al. **Intergroup Exemestane Study: 1 year results of the bone sub-protocol.** San Antonio Breast Cancer Symposium 2004; [Abstract 401](#).

Coombes RC et al. **The Intergroup Exemestane Study: A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen-updated survival analysis.** San Antonio Breast Cancer Symposium 2004; [Abstract 3](#).

Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen: Bone density subprotocol results of a randomized multicenter trial (ABCSG-12).** San Antonio Breast Cancer Symposium 2004; [Abstract 6](#).

Howell A, on behalf of the ATAC Trialists' Group. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen.** San Antonio Breast Cancer Symposium 2004; [Abstract 1](#).

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. [Abstract](#)

Perez EA et al. **Effect of letrozole versus placebo on bone mineral density in women completing 5 years (yrs) of adjuvant tamoxifen: NCIC CTG MA.17b.** San Antonio Breast Cancer Symposium 2004; [Abstract 404](#).

Quality control with sentinel lymph node biopsy

Without question, sentinel lymph node biopsy (SLNB) is equivalent to axillary dissection in its sensitivity for detecting nodal metastases and maintaining local control. More importantly, it results in less morbidity. However, SLNB is a procedure that has a learning curve. Early in one's experience, it helps to take a course, to be mentored and to do a series of sentinel node procedures with a backup axillary dissection for validation before performing SLNB alone.



The best data we have suggest that the false-negative rate diminishes with experience, and surgeons should perform about 20 sentinel node procedures with a backup dissection to minimize their false-negatives. When our group began to do sentinel node biopsy, our false-negative rate was about 15 percent. In evaluating those cases, we discovered that at least half of those patients had palpably suspicious nodes at the time of surgery. These were generally patients with a clinically negative axilla.

I believe a key element of the sentinel node procedure is to palpate the axilla after removing the blue and hot nodes. If any nodes are suspicious by palpation, they should also be submitted. By adding palpability to the definition of what constitutes a sentinel node, our own false-negative rate has dropped from 15 percent to four percent.

The learning curve for SLNB may not be as long as we originally thought because it was calculated at a time when the technique hadn't been standardized. The ALMANAC trial has recently published its learning-curve results (Clarke 2004). In that trial, every surgeon was required to complete 40 sentinel node procedures validated by axillary dissection before beginning the trial.

From those 40 validated cases, they demonstrated that when a standard technique was employed from the beginning, most of the false negatives and failed procedures occurred in the first case. Beyond that, few false negatives or failures occurred, so maybe the emphasis should be on a standardized technique rather than the number of cases completed.

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Technical aspects of SLNB

Variation exists in the SLNB technique. An emerging consensus indicates that it is best to use both blue dye and isotope. It appears that subdermal, intradermal and subareolar injections all work well and are probably better than peritumoral injections. Most of the breast and its overlying skin are draining into the same few sentinel nodes anyway.

Sentinel lymph node biopsy requires coordination between nuclear medicine, surgery and pathology. Before performing an SLNB, the nuclear medicine physician, surgeon and pathologist should agree on procedures. Regarding nuclear medicine, I think the one technical point that made the biggest difference for us was injecting the isotope intradermally. That modification has increased our success rate, bringing it close to 100 percent.

With regard to the actual surgery, it is important to perform the sentinel node procedure before completing the rest of the breast operation and to use good three-point retraction in the axilla and keep the tissue under tension. If you do that, it is a simple procedure.

It is also important to remove all blue and all focally hot lymph nodes. We take counts of the nodes *ex vivo*. At the end of the procedure, it is important to palpate the axilla to identify nodes that might be grossly involved by tumor, therefore not picking up the dye or the isotope.

We generally remove an average of two to three sentinel nodes per case. We will occasionally encounter a situation in which the axilla is diffusely hot and we could easily remove eight or 10 nodes; however, we have found that by removing three sentinel nodes we identify 98 percent of the positive lymph nodes.

By removing four sentinel nodes, we identify 99 percent of the positive lymph nodes, so even when the axilla is diffusely hot, you don't have to remove more than three or four sentinel nodes.

Morbidity associated with SLNB versus axillary dissection

At our institution, we conducted a study using a sophisticated instrument to assess postoperative sensation after both SLNB and axillary dissection. We found that SLNB resulted in approximately half the postoperative sensation morbidity that results from axillary dissection; however, we also found that SLNB had definite morbidity. It's important for physicians to emphasize this in their discussions with patients.

Patients may have pain, areas of numbness and injury to the intercostal brachial nerve. Lymphedema — which occurs in approximately 10 to 20 percent of axillary dissection cases — will also occur after SLNB, although much less frequently (approximately one to two percent of cases). Another important aspect to consider is the severity of the morbidity. It's dramatic how much less symptomatology patients have after SLNB than after axillary dissection (3.1).

3.1 ALMANAC Trial Comparing Sentinel Node Biopsy to Conventional Axillary Treatment in Patients with Clinically Node-Negative Invasive Breast Cancer

	Standard axillary procedure	Sentinel node biopsy	p-value
Nodal positivity ¹	23%	26%	—
Arm swelling (patient reported) ^{2*}			
3 months — mild	12%	4%	<0.001 [†]
3 months — moderate or severe	3%	1%	
6 months — mild	14%	4%	
6 months — moderate or severe	3%	0.5%	
Sensory loss (patient reported) ^{1*}			
1 month	62%	18%	<0.0001 [†]
3 months	54%	20%	
6 months	43%	16%	
Sensory loss (physician assessed) ^{2*}			
1 month	42%	14%	<0.0001 [†]
3 months	38%	14%	
6 months	37%	14%	
Drain usage ^{2*}	79%	17%	<0.001 [†]
Mean days of hospital stay ^{2*}	5.4 days	4.1 days	<0.001 [‡]
Return to normal activities in 6 months ^{2*}	93%	96%	<0.001 [‡]

* Intention to treat; [†] Chi-square; [‡] Mann-Whitney test

SOURCES: ¹ ALMANAC trialists'. Presentation. San Antonio Breast Cancer Symposium 2004; [Abstract 15](#).

² Mansel RE et al. Presentation. San Antonio Breast Cancer Symposium 2004; [Abstract 18](#).

Pilot trial of intraoperative brachytherapy

At Memorial Sloan-Kettering, we are currently conducting a pilot study assessing the role of intraoperative brachytherapy. We are using the standard brachytherapy setup that we have used for years with rectal and gynecologic cancer and are delivering a single dose of radiation intraoperatively to the cavity of the breast excision. The study is limited to women over the age of 60 with tumors smaller than two centimeters. With an experience now of approximately 40 patients, we've found that this approach generally works well. It has an advantage in that it is a single intraoperative treatment and not 30 trips for postoperative radiation therapy. However, approximately 10 percent of patients had poor wound healing and required reoperation to excise the irradiated area and reclose the wound.

Select publications

Clarke D et al. **The learning curve in sentinel node biopsy: The ALMANAC experience.** *Ann Surg Oncol* 2004;11(3 Suppl):211-5. [Abstract](#)

Oncotype DX™ multigene assay as a prognostic factor in patients treated with tamoxifen

At the 2003 San Antonio meeting, when I presented the initial data on this assay, Dr Kent Osborne raised a question about whether the recurrence score is a prognostic or predictive factor.

Frankly, we didn't really care, as long as it's a prognostic factor in that specific setting of tamoxifen-treated patients, so that we can identify a cohort of patients who don't need chemotherapy.



Using the NCCN or St Galen criteria, in the tamoxifen-treated cohort in NSABP-B-14 we would identify about eight percent of patients who don't need chemotherapy. If we use the Genomic Health assay, we identify 50 percent — a huge increase in the number of patients categorized as low risk and not requiring chemotherapy.

The median 10-year distant failure rate was about 6.8 percent in patients who received tamoxifen with a low recurrence score, but the individual risk ranged from three percent to 12 percent, which is another strength of this test.

Although the NSABP usually refrains from subset analyses, supplementary information accompanying the *New England Journal of Medicine* article (Paik 2004a) details several subset analyses. Questions arose about whether the Oncotype DX assay would work in patients with tumors smaller than one centimeter, patients older than 60 years and other subsets in which the statistical power is much less; however, the overall trends seem to show that the assay works in every subset we evaluated. It always seemed to divide patients into low- or high-risk categories, regardless of histology grade or tumor size.

Prediction of response to chemotherapy with Oncotype DX assay

NSABP-B-20 included women with node-negative, ER-positive disease. It was a three-arm design, and patients were randomly assigned to tamoxifen alone or tamoxifen concurrent with either CMF or methotrexate followed by 5-FU. Our study was a retrospective analysis of that completed trial.

Dr Paik is the Director of the Division of Pathology at the National Surgical Adjuvant Breast and Bowel Project in Pittsburgh, Pennsylvania.

We repeated the *Oncotype DX* assay on the tamoxifen arm to ensure the assay was reproducible, and we demonstrated that it is reproducible, which is encouraging for a clinical assay. We also evaluated the NSABP-B-20 chemotherapy arms to address whether the assay predicted chemotherapy responsiveness. We went into that study with an a priori hypothesis based on data presented at the 2004 ASCO meeting by Dr Luca Gianni’s group in Milan, evaluating samples from a neoadjuvant trial of paclitaxel and doxorubicin.

They demonstrated a correlation between the Genomic Health recurrence score and pCR rate (Gianni 2004). The higher recurrence rate correlated strongly with the higher pCR rate. The overall pCR rate was approximately 25 percent in the patients with high-risk disease, and no pCR occurred in patients with low-risk disease.

We hypothesized that the benefit from chemotherapy in NSABP-B-20 would be almost negligible in patients with low-risk disease and high in patients with high-risk disease. The results of this study are actually quite striking and unlike anything I’ve ever seen (Paik 2004b).

The absolute benefit from chemotherapy is actually negative in the low-risk group and zero in the intermediate-risk group. In the high-risk group, the absolute improvement in distant recurrence at 10 years is 28 percent, or a relative risk reduction of 75 percent (4.1).

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

4.1 Ten-Year Distant Recurrence-Free Survival According to a 21-Gene Recurrence Score

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

Chemotherapy = MF or CMF; RS = recurrence score

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

Implications of the *Oncotype DX* assay study results

These data provide an important paradigm shift in the way we think about clinical trial design and patient management. So far, in most clinical trial designs, we presume that the proportional benefit or incremental gain would be the same

degree in patients with low-risk and high-risk disease. All statistical sample size calculations are based on that assumption, but now we have to change that.

This data set also forces us to think about new clinical trial designs in which we preselect patients who are at high risk, because those are the patients who will benefit from chemotherapy. We already knew from other studies that ER-positive patients do not benefit much from chemotherapy. In the neoadjuvant trials, the pCR rate is much lower in ER-positive tumors. This study definitely shows that based on genes related to proliferation or estrogen receptor, we can actually select patients who are the best candidates for chemotherapy trials.

Potential impact of Oncotype DX on Ravdin's Adjuvant! model

Peter Ravdin notes that in the Adjuvant! program, the relative benefit of chemotherapy is presumed to be equal for patients at higher and lower risk, but it's likely that the estimation of chemotherapy benefit in the group with low-risk disease is an overestimation. Conversely, the benefit in the group with higher-risk disease may be underestimated. I believe our studies with Oncotype DX demonstrate this, and Ravdin's model may need to be slightly modified.

My prediction is that when people see these data, they will want the assay performed because nobody wants to receive chemotherapy when it will not work. I'm sure a lot of competing assays are being developed that will claim to do the same thing. As a clinical trial group, we are interested in supporting all of those studies. In my lab, we are trying to develop competing assays that will be less expensive and based on factors such as histology and estrogen receptors. We must demonstrate in a clinical study in a stepwise fashion as we did with Genomic Health that a marker is reliable and reproducible clinically so that patients will have confidence in the results.

Select publications

Gianni L et al. **Gene expression profiles of paraffin-embedded core biopsy tissue predict response to chemotherapy in patients with locally advanced breast cancer.** *Proc ASCO* 2004;[Abstract 501](#).

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](#)

Paik S et al. **Expression of the 21 genes in the recurrence score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** San Antonio Breast Cancer Symposium 2004;[Abstract 24](#).

Paik S et al. **Risk classification of breast cancer patients by the recurrence score assay: Comparison to guidelines based on patient age, tumor size, and tumor grade.** San Antonio Breast Cancer Symposium 2004;[Abstract 104](#).

Post-test:

Breast Cancer Update for Surgeons — Issue 2, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In NSABP-B-24, women with ER-negative DCIS derived benefit from adjuvant tamoxifen.
 - a. True
 - b. False
2. In older women with small, ER-positive, node-negative, invasive disease, radiation therapy in addition to adjuvant tamoxifen following excision has been shown to:
 - a. Increase overall survival
 - b. Decrease local recurrences
 - c. All of the above
 - d. None of the above
3. According to the Second International Consensus Conference on image-detected breast cancer, the diagnosis of most breast lesions should be made by:
 - a. An image-directed minimally invasive breast biopsy
 - b. A wire-detected excision
 - c. Either of the above
 - d. None of the above
4. The 68-month data from the ATAC trial demonstrated that patients who received anastrozole experienced significantly:
 - a. Improved disease-free survival
 - b. Improved overall survival
5. The 68-month data from the ATAC trial showed significantly higher hysterectomy rates in patients receiving:
 - a. Anastrozole
 - b. Tamoxifen
6. Dr Luca Gianni's group evaluated samples from a neoadjuvant trial with paclitaxel and doxorubicin and demonstrated a correlation between the Genomic Health recurrence score and the pCR rate.
 - a. True
 - b. False
7. During SLNB, removal of nodes that are palpably suspicious results in a lower false-negative rate.
 - a. True
 - b. False
8. The ALMANAC trial demonstrated that compared to standard axillary dissection, SLNB results in significantly lower rates of:
 - a. Lymphedema
 - b. Sensory loss
 - c. Drain usage
 - d. All of the above
9. The 10-year distant recurrence rate in tamoxifen-treated patients with low recurrence scores from the Genomic Health *OncoType* DX assay was approximately:
 - a. 7 percent
 - b. 14 percent
 - c. 30 percent
10. The 30-month efficacy data from the IBCSG-1-98 trial of letrozole versus tamoxifen:
 - a. Favor letrozole over tamoxifen
 - b. Parallel the 33-month results from the ATAC trial
 - c. Both of the above
 - d. None of the above
11. The relative risk reduction in 10-year distant recurrence in patients with a high recurrence score from the Genomic Health *OncoType* DX assay who were treated with tamoxifen plus chemotherapy is:
 - a. 10 percent
 - b. 25 percent
 - c. 50 percent
 - d. 75 percent
12. Using the Genomic Health assay, what percentage of patients in the tamoxifen-treated cohort of NSABP-B-14 could be identified as low risk and not requiring chemotherapy?
 - a. 8 percent
 - b. 20 percent
 - c. 33 percent
 - d. 50 percent

Evaluation Form:

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5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor N/A = not applicable to this issue of *BCU* for Surgeons

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *BCU* for Surgeons address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer in order to incorporate these data into management strategies in the adjuvant and neoadjuvant disease settings. 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors in the adjuvant and neoadjuvant settings, and discuss the risks and benefits of sequencing adjuvant aromatase inhibitors after tamoxifen. 5 4 3 2 1 N/A
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer. 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse and, when applicable, utilize these to guide therapy decisions. 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Melvin J Silverstein, MD	5 4 3 2 1	5 4 3 2 1
Anthony Howell, MD	5 4 3 2 1	5 4 3 2 1
Hiram S Cody III, MD	5 4 3 2 1	5 4 3 2 1
Soonmyung Paik, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

- Objectives were related to overall purpose/goal(s) of activity. 5 4 3 2 1 N/A
- Related to my practice needs. 5 4 3 2 1 N/A
- Will influence how I practice. 5 4 3 2 1 N/A
- Will help me improve patient care. 5 4 3 2 1 N/A
- Stimulated my intellectual curiosity. 5 4 3 2 1 N/A
- Overall quality of material. 5 4 3 2 1 N/A
- Overall, the activity met my expectations. 5 4 3 2 1 N/A
- Avoided commercial bias or influence. 5 4 3 2 1 N/A

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Breast Cancer™

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This program is supported by education grants from AstraZeneca Pharmaceuticals LP and Genomic Health Inc.

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This program is supported by education grants
from AstraZeneca Pharmaceuticals LP
and Genomic Health Inc.



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Last review date: May 2005
Release date: May 2005
Expiration date: May 2006
Estimated time to complete: 3 hours