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HOW TO USE THIS MONOGRAPH

This is a CME activity that 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 on pages 18-20 or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program and the website, **BreastCancerUpdate.com**, where you will find 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 **red underlined text**.

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

Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.
- Counsel postmenopausal patients with estrogen receptor-positive tumors about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant setting.
- Describe the current guidelines for, and ongoing clinical trials of, local and regional therapy for noninvasive and invasive breast cancer.

Issue 3, 2003, of *Breast Cancer Update for Surgeons* consists of discussions with five research leaders on a variety of important topics including: local and systemic therapy of DCIS, intraoperative radiation therapy, adjuvant endocrine therapy, mammography trials and breast conservation.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 3

Upon completion of this activity, participants should be able to:

- Distinguish subsets of patients with DCIS for whom radiation therapy may not be necessary.
- Determine the role of estrogen receptor testing for patients with DCIS.
- Counsel patients about the controversies regarding the value of screening mammography.
- Describe the results of the ATAC trial and implications in treating postmenopausal women with ER-positive breast cancer.
- Describe ongoing clinical trials of aromatase inhibitors for DCIS and chemoprevention; counsel appropriate patients about participation.
- Counsel patients about the risks and benefits of mastectomy versus breast-conserving surgery.

ACCREDITATION STATEMENT

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Melvin Silverstein, MD	**Consultant:** Ethicon Endosurgery
Gershon Locker, MD	**Consultant/Speakers' Bureau:** AstraZeneca Pharmaceuticals LP
Blake Cady, MD, FACS	No financial interests or affiliations to disclose.
Hyman Muss, MD	**Grants/Research Support:** Roche Laboratories Inc **Consultant:** Roche Laboratories Inc, AstraZeneca Pharmaceuticals LP, Genentech Inc **Speakers' Bureau:** AstraZeneca Pharmaceuticals LP

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
exemestane	Aromasin®	Pfizer Inc
letrozole	Femara®	Novartis Pharmaceuticals Corporation
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP

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SAVE THE DATE

October 19-23, 2003	**American College of Surgeons 89th Annual Clinical Congress** Lakeside Center, McCormick Place Chicago, IL ***www.facs.org***
December 3-6, 2003	**26th Annual San Antonio Breast Cancer Symposium** Henry B. Gonzalez Convention Center San Antonio, TX ***www.sabcs.org***
February 25-28, 2004	**21st Annual Miami Breast Cancer Conference** Loews Miami Beach Hotel Miami Beach, FL ***www.cancerconf.com***
March 18–21, 2004	**Society of Surgical Oncology 57th Annual Cancer Symposium** New York Marriott Marquis New York, NY ***www.surgonc.org***
April 23-25, 2004	**28th Annual American Society of Breast Disease Symposium 2004** The Westin Copley Place Boston, MA ***www.asbd.org***

Editor's Note

Gender Differences in Interpretation of Research Data

"Every woman wants to be beautiful and desirable, no matter what her age. And unfortunately, breasts are the 'deal'; they make you a woman. That's what you think. Women want to be pretty and whole, regardless of their age. Women in their 70s are still working. They're active. They're dating. They're getting married. They need to be beautiful all the time."

— 77-year-old breast cancer survivor treated with breast-conservation

"My doctor explained all the options. He said, 'You don't necessarily have to lose your breast. We can just take the tumor out, but you will need radiation.' That was one of the deciding factors. The thought of having to go to the hospital five days a week to have radiation didn't appeal to me. So, that's when I said, 'Just take the breast. I've got another one. I want to live. And I'll deal with it from there.'"

— 37-year-old breast cancer survivor treated with mastectomy

Our medical education group recently held an editorial meeting with 35 community-based surgeons and four faculty members (Drs Patrick Borgen, Kevin Fox, Generosa Grana and Terry Mamounas). While our audio series focuses on the clinical perspectives of breast cancer research leaders, we are also very interested in the viewpoints of surgeons at the front line of patient care. To enhance the discussion, we showed video clips from interviews with breast cancer survivors. One of the most discussed was a series of comments on breast-conserving surgery (see above).

Many studies — including a new data set from the ATAC adjuvant trial that is discussed in this program by Dr Gershon Locker — have demonstrated considerable variation in the use of breast conservation. The most significant factor is the physician's attitude when presenting the options.

Our *Breast Cancer Update* working group meeting quickly demonstrated a dichotomy about this issue. Most of the attendees and faculty members indicated that they present lumpectomy to their patients as the preferred alternative. This is based on research data demonstrating equivalent survival with presumed decreased morbidity and psychosocial distress. However, a vocal minority of physicians in attendance staunchly supported mastectomy as a reasonable and equivalent option. In fact, one surgeon had chosen mastectomy when she, herself, was diagnosed with breast cancer some years ago.

As the discussion proceeded, I noticed that most of the physicians defending mastectomy were female surgeons, and the sole faculty member agreeing with this perspective was medical oncologist, Dr Genny Grana. These practitioners were in no way claiming that mastectomy resulted in greater survival, but they highlighted what they believed to be a lower rate local recurrence — an event they believed to be emotionally traumatic.

Female physicians had the perception that male physicians might generalize too much about the deeper feelings women have about their breasts. They also felt that some women, such as the physician who was a breast cancer survivor, find less difficulty than imagined when facing mastectomy.

This conversation is particularly relevant to comments in the enclosed program by Drs Mel Silverstein and Blake Cady, both of whom believe that women with early breast cancer often receive too much local therapy. Dr Cady notes that local recurrence may be a predictor of poor prognosis, but it is not an independent determinant of breast cancer mortality. He does acknowledge that patients may wish to minimize their risk of local recurrence by choosing, for example, postsurgical radiation therapy.

These discussions are a reminder that clinical research often provides new therapeutic options that may be perceived differently by individual patients and physicians. Additionally, these perceptions may vary with age, culture and, perhaps, gender. In this program, Dr Hy Muss, a leading investigator in the field of breast cancer in the elderly, notes that many physicians believe that older women are less interested in breast-conservation than younger women. However, surveys about this issue contradict that perception.

In patients with breast cancer, the choice of primary surgery is only one example of a plethora of controversial decisions for which multiple options are supported by research evidence. Another major issue involves the choice of adjuvant systemic therapy. The interviews with Drs Muss and Locker highlight several recent research studies that have made decision-making about the use of adjuvant chemotherapy and endocrine treatment much more complex. New results from a CALGB trial in women with node-positive tumors suggest a survival advantage to "dose-dense" chemotherapy, which is given every two weeks. However, there are only three years of follow-up and no other confirmatory trials have been reported. The ATAC trial is another important recently reported study that has complicated adjuvant treatment decisions. This historic study demonstrates a disease-free survival advantage for anastrozole compared to tamoxifen in postmenopausal women, but not enough deaths have been observed to comment on mortality.

Our editorial board agreed that when clinical research data supports multiple acceptable options, patients should be allowed to actively participate in treatment decisions. In that regard, it is interesting to consider a new initiative our education group has launched to learn more about how women with breast cancer perceive treatment trade-offs. Over the next four months, we will conduct a series of three "Breast Cancer Town Meetings," in which breast cancer survivors who were diagnosed at least one year ago will utilize electronic keypads to "vote" on a variety of treatment-related issues. Our first meeting was held in New York City on May 17, 2003. Select results are presented below and have also been submitted as an abstract to the 2003 San Antonio Breast Cancer Symposium.

The most striking observation from this initial endeavor was the strong reinforcement of prior patient surveys indicating that women are very motivated to accept therapies that offer the likelihood of even modestly reducing the chance of cancer recurrence and mortality. Even relatively toxic treatments seem to be acceptable to patients for relatively minimal improvements in cancer-related outcome.

The overriding concern of cancer control must be considered in the debate about local breast cancer therapy. No matter how much we reassure patients that local recurrence is not an independent predictor of mortality, the thought of "treatment failure" is frightening to every patient. Perhaps, for some women, the emotional downside of concern about local recurrence may outweigh the cosmetic benefit of less extensive surgery.

—Neil Love, MD

Mandelblatt JS et al. **Measuring and predicting surgeons' practice styles for breast cancer treatment in older women.** *Med Care* 2001;39:228-42. **Abstract**

Weinberg E et al. **The influence of gender of the surgeon on surgical procedure preference for breast cancer.** *Am Surg* 2002;68(4):398-400. **Abstract**

Breast Cancer Town Meeting: Keypad Polling Results

During a day-long meeting, a multidisciplinary panel* verbally presented the potential risks and benefits of commonly utilized adjuvant therapies for a series of hypothetical scenarios of women with primary breast cancer as they would counsel similar patients in their practice. Breast cancer survivors responded via electronic keypads to a series of related questions.

Selection of Adjuvant Therapy for Four Hypothetical Cases of Breast Cancer in a 65-year-old Woman

ER status	Risk of BC death without adjuvant therapy	**Chemotherapy	Tamoxifen	***Anastrozole
ER-positive	10%	50%	46%	41%
ER-positive	20%	64%	49%	42%
ER-negative	20%	87%	-	-
ER-positive	60%	83%	41%	51%

BC = Breast Cancer, all women HER2-negative

* **Town Meeting Panelists:** Patrick Borgen, MD; Kevin Fox, MD; Generosa Grana, MD; Gabriel Hortobagyi, MD and Marisa Weiss, MD

** 65% of survivors would want to receive chemotherapy for an absolute survival benefit of 2%; 56% of survivors would want to receive chemotherapy for an absolute benefit of 1%.

*** Survivors who had not been treated with tamoxifen were more likely to select anastrozole.

Melvin Silverstein, MD

Professor of Surgery and Henrietta C Lee Chair in Breast Cancer Research,
University of Southern California, Keck School of Medicine

Director, Harold E and Henrietta C Lee Breast Center, University of Southern California, Norris Comprehensive Cancer Center and Hospital

Edited comments by Dr Silverstein

Increased detection of DCIS

In 1978, the American College of Surgeons conducted a survey demonstrating that 200 out of 24,000 cases of breast cancer were DCIS — less than one percent. The incidence of DCIS exploded in the mammographic era. By screening women, we discovered microcalcifications and other architectural distortions that we otherwise never would have known were present. Some of those women would have developed invasive breast cancer six to ten years later. Now, we intercede in the neoplastic continuum five to ten years earlier. Today, DCIS represents 21 percent of all new cancers. In 2003, we will detect 57,000 cases of DCIS and 211,000 cases of invasive breast cancer.

DCIS as more than a high-risk marker for breast cancer

DCIS is the precursor lesion to invasive breast cancer. Roland Holland, the renowned Dutch pathologist, examined 100 consecutive invasive breast cancers, which he thoroughly sampled with multiple slides for each. In 98 out of 100 cases, he found a DCIS component in at least one of the slides. This is compelling evidence that DCIS is a precursor lesion. It does not mean all DCIS will develop into invasive breast cancer, rather all invasive breast cancers were probably born from DCIS.

Our personal series has almost 1,100 patients with DCIS, of whom 10 percent have developed a contralateral breast cancer — approximately 50 percent are invasive and 50 percent are DCIS. That's a high number considering the median follow-up is only about eight years in those patients, which translates into about a one percent risk per year. This is consistent with the view that DCIS is also a high-risk marker for contralateral breast cancer.

Clinical trials evaluating anastrozole for the treatment of DCIS

NSABP-B-35 and IBIS-II are both evaluating anastrozole versus tamoxifen for postmenopausal women with ER/PR-positive DCIS. Those are exciting trials,

and based on the existing data, I believe these trials will eventually show anastrozole to be superior to tamoxifen, with fewer side effects. In patients with invasive breast cancer, my impression is that anastrozole has less toxicity, and medical oncologists at the University of Southern California (USC) view it as the adjuvant hormonal therapy of choice in postmenopausal women with ER-positive invasive disease.

Which patients with DCIS need radiation therapy?

We know from Roland Holland's work that DCIS tends to be a segmental disease, and it usually involves only one ductal system. It lends itself to local therapy, although complete excision is difficult because the DCIS we treat today cannot be seen or felt. Preoperatively, I map out the DCIS as well as I can with mammography and MRI. I also use ultrasound, because sometimes we'll find a mass not visualized on X-ray. I use multiple wires to widely excise the DCIS and submit all of the tissue sequentially. The margins are analyzed and if they are clear by 10 millimeters or more, we don't treat those patients. I have a large number of patients like this, and at 12 years of follow up, the local recurrence rate is less than eight percent.

Radiation therapy in our series, as with the NSABP, reduces local recurrence by about 50 percent, but that is a relative reduction. If a patient has a 30 percent risk of local recurrence after surgery, radiation will reduce it to 15 percent, and I recommend it. On the other hand, if I widely excise a lesion and reduce the recurrence risk to 6 to 8 percent, radiation therapy will decrease it to 3 to 4 percent, and then I don't think it's worth it.

Reducing the risk of recurrence with radiation therapy does not translate into a survival benefit. If we look at the published prospective randomized trials, there's no difference in breast cancer-specific or overall survival between women treated by excision alone versus excision followed by radiation therapy. In my series, I now have about 1,100 patients with DCIS who received three different treatments. Although they're selected, there's no difference whatsoever in terms of survival. The only difference is for local recurrence. About one-half of local recurrences are invasive and about 10 percent of those patients will die, so we're talking about small benefits. You would have to treat a few hundred patients to save one life.

MammoSite® in the management of patients with DCIS

I've been regarded as an anti-radiation therapy advocate for years, but the new MammoSite® protocol for DCIS might change my mind. I believe the MammoSite® will solve many of the problems with traditional therapy, because treatment is only five days instead of five or six weeks, it doesn't irradiate the entire breast, and it's not expected to have the pulmonary or cardiac complications we see with external beam therapy.

There's a good rationale for brachytherapy — 80 or 90 percent of all local recurrences are at or near the primary and are simply residual disease. In those cases, the patient doesn't need whole breast radiation. The MammoSite®

radiates one centimeter around the cavity to a dose of 34 Gy and then another centimeter or two at a lower dose. I expect it will be more effective than external beam therapy in treating the local margins and dealing with 80 to 90 percent of recurrences. I also expect the MammoSite® will reduce the need for re-excision.

Screening mammography in women younger than 50 years of age

I believe strongly in screening mammography and begin screening women at the age of 40 — earlier if the woman is BRCA1/2-positive or has a strong family history of breast cancer. We don't have good data for the benefit of screening mammography in women younger than age 50. Breast cancer occurs less frequently in younger women and because their breasts are denser, it's more difficult to detect subtle changes.

Michael Baum believes that the use of screening mammography in women younger than age 50 does more harm than good. Clearly, when you screen women, it will result in more biopsies being performed. For every 100 biopsies performed, only 20 yield positive results and not all are invasive cancer; many of the cases are DCIS. One may argue we could wait to detect DCIS later, but I believe for every DCIS cured, an invasive cancer may have been prevented. That is the price we pay to detect cancer early.

I'm absolutely convinced by the data from Tabar and others that patients benefit from screening. In our own series, when I compare women with mammography-detected invasive cancers with women who walked in with cancers we could palpate, women with mammography-detected breast cancers have a 15-year survival of over 90 percent, but in those with cancers we could palpate, it's less than 70 percent.

Counterpoint by Michael Baum, MD, ChM, FRCS, FRCR

Mammography in women younger than 50 years of age

The latest Canadian trial results published in the *Annals of Internal Medicine* in September 2002 do not demonstrate an advantage in breast cancer mortality. In fact, there is an excess mortality from breast cancer in women younger than 50 years of age for the first 10 years of the study. This excess mortality in the early years has also been noticed in the overviews of the screening trials.

I had a patient with screening-detected DCIS. After a biopsy, the patient was advised to have surgery, however, she chose not to have treatment. She saw me six to nine months later with a breast full of cancer. That is not the natural history of DCIS, but rather the natural history of perturbed, incompletely excised DCIS. The biological mechanism is perturbation of the tumor or its environment, which induces angiogenesis.

Most *in situ* cancers are latent cancers, and angiogenesis is the trigger from latency to invasion. Likewise, I believe most patients with invasive cancer have

metastases in dynamic equilibrium, which may progress and become life-threatening when the system is perturbed and angiogenesis is induced. Women with latent breast cancer or occult metastases are living close to a chaos boundary, and we perturb the system at our peril.

Informed consent for mammography in women older than 50 years of age

My argument against screening women older than 50 years of age is not that it has no effect, but that we are disingenuous in the way we invite women to be screened. I passionately believe that women should make an informed choice.

With systemic therapy, we bend over backwards to inform women of the absolute benefits. We agonize whether a two or three percent improvement in five-year survival is worth the "side effects," and we counsel our patients this way. We tell women that screening will save their lives and reduce their risk of dying by 20 percent. In absolute terms, we have to screen 1,000 women for 10 years to save one life — one in a thousand. If we told women truthfully, "If I screen you for 10 years, you will have one in a thousand less chance of breast cancer death, but a significant risk of overdiagnosis, false alarms, health insurance issues, unnecessary biopsies and detection of ductal carcinoma in situ, which never would have troubled you," many women would refuse it.

In the United States, I think there is a profit motive. In the United Kingdom, it's social engineering. I think it's almost fascistic to decide what is good for women and coerce them to come forward for screening without telling them the whole truth.

Select publications

Publication discussed by Professor Baum

Miller AB et al. **The Canadian National Breast Screening Study-1: Breast Cancer Mortality after 11 to 16 Years of Follow-up. A randomized screening trial of Mammography in women age 40 to 49 years.** *Ann Intern Med* 2002;137(5):305-15. **Abstract**

Brachytherapy for DCIS

Chow E. **Radiation treatment for breast cancer. Recent advances.** *Can Fam Physician* 2002;48:1065-9. **Abstract**

Frassica DA, Zellars R. **Radiation oncology: The year in review.** *Curr Opin Oncol* 2002;14(6):594-9. **Abstract**

Intra M et al. **Surgical technique of intraoperative radiotherapy in conservative treatment of limited-stage breast cancer.** *Arch Surg* 2002;137(6):737-40. **Abstract**

Reitsamer R et al. **Intraoperative radiotherapy given as a boost after breast-conserving surgery in breast cancer patients.** *Eur J Cancer* 2002;38(12):1607-10. **Abstract**

Vaidya JS et al. **The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer.** *Eur J Surg Oncol* 2002;28(4):447-54. **Abstract**

Veronesi U et al. **A preliminary report of intraoperative radiotherapy (IORT) in limited-stage breast cancers that are conservatively treated.** *Eur J Cancer* 2001;37(17):2178-83. **Abstract**

Veronesi U et al. **Intraoperative radiation therapy for breast cancer: Technical notes.** *Breast J* 2003;9(2):106-12. **Abstract**

Willett CG. **Intraoperative radiation therapy.** *Int J Clin Oncol* 2001;6(5):209-14. **Abstract**

Gershon Locker, MD

Kellogg Scanlon Chair of Oncology,
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Edited comments by Dr Locker

Implications of the updated ATAC trial data

I saw the initial data a month before it was initially presented in San Antonio in 2001, and I was literally blown away. No one expected the trial to turn so positive so quickly. My takeaway, even after the initial data, was that a newly diagnosed, postmenopausal woman with hormone receptor-positive breast cancer should be offered anastrozole, at least as an alternative, if not the preferred treatment. In the year since, and with the updated data, my feelings have not changed at all. The 47-month follow-up was very reassuring, because the curves continue to separate. I would have been surprised if they didn't.

Everyone is waiting for survival data, but it is important to remember the disease-free survival is remarkably good — in the 88 to 90 percent range — in this group of women. Therefore, it will be a while before we can evaluate survival. However, it should be emphasized that in every adjuvant trial demonstrating a disease-free survival difference, a survival difference has eventually appeared.

I tell my patients that these data are preliminary, albeit with very strong statistical support for efficacy. Approximately 75 percent of my postmenopausal, ER-positive patients receive anastrozole instead of tamoxifen.

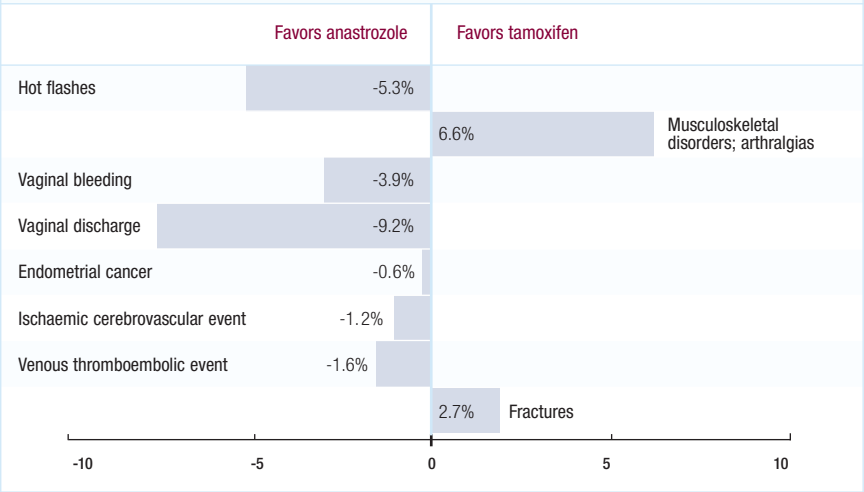
Anastrozole is a better hormonal adjuvant treatment than tamoxifen for ER-positive postmenopausal women, but there will always be a subset of women for whom tamoxifen may be preferred. For example, tamoxifen may be better for women with osteoporosis coming in with the diagnosis of breast cancer, particularly those already on bisphosphonates or calcitonin. In general, I believe anastrozole is the preferred treatment.

Risks and side effects of tamoxifen versus anastrozole

The biggest problem with tamoxifen is not the risk of thromboembolism or uterine cancer, but managing uterine bleeding. Any woman who has uterine

bleeding on tamoxifen goes through a panoply of tests, which causes a great deal of anxiety. A large percentage of women, sometime during their five years of therapy, undergo a gynecologic procedure. This is what's really unacceptable about tamoxifen. We over-investigate some of these symptoms. This may be due to our medical-legal milieu, but it contributes to a miserable lifestyle and a lot of anxiety for women on tamoxifen in the adjuvant and preventative settings.

ATAC Trial: Significant differences in pre-defined adverse events between anastrozole and tamoxifen



DERIVED FROM: Sainsbury R on behalf of the ATAC Trialists' Group. **Beneficial side-effect profile of anastrozole compared with tamoxifen confirmed by additional 7 months of exposure data: A safety update from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Breast Cancer Res Treat* 2002;**Abstract 633**.

Rates of breast-conserving surgery in the ATAC trial

There was a striking difference in breast conservation rates in the ATAC trial between the two largest countries accruing patients — the United Kingdom and the United States. In a large, multivariate analysis taking every other factor into account, being an American woman increases your likelihood of having a mastectomy by 44 percent, compared to being a British woman. There is something about American patients or surgeons that seems to favor mastectomy compared to what is done in the United Kingdom.

One potential explanation is that, although we have guidelines set by the National Cancer Institute, American medicine is still individualized — the surgeon and patient make the final decision. Guidelines tend not to be as significant a factor in decision-making. Another issue is our American view that more is better. We have data, however, that this is not true in the mastectomy versus lumpectomy decision. Psychological factors also play a role for some women, in whom the thought of having a "cancerous breast," even if the cancer

is removed, is not acceptable. It is also conceivable that geography is a significant issue for some women. In England, no woman is more than 50 or 60 miles from a major city. A woman in Montana may be hundreds of miles from a center where she can receive radiation therapy.

We need to better educate surgeons and patients that there is no survival difference between these two methods of treating early-stage breast cancer, and the preferred approach, when possible, is lumpectomy and radiation, for aesthetic, psychological and a number of other reasons.

Clinical trials of aromatase inhibitors for risk reduction

Aromatase inhibitors have potential as chemopreventive agents. The data from ATAC show that anastrozole is more effective in preventing contralateral breast cancers than tamoxifen. It's a natural transition to move anastrozole into the preventative research setting. I would have preferred that the European IBIS-II prevention trial compare anastrozole to tamoxifen rather than to placebo. Because it doesn't, this trial would never fly in the United States, but I'm glad the NSABP-B-35 DCIS trial is making the correct comparison of anastrozole versus tamoxifen.

Select publications

Anastrozole, Tamoxifen, Alone or in Combination (ATAC Trial)

ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131-2139. **Abstract**

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal patients: Factors influencing the success of patient recruitment.** *Eur J Cancer* 2002;38:1984–1986. **Abstract**

Buzdar A. **Anastrozole as Adjuvant Therapy for Early-Stage Breast Cancer: Implications of the ATAC Trial.** *Clin Breast Cancer* 2003;4 Suppl 1:S42-8. **Abstract**

Buzdar A et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer — Updated efficacy results based on a median follow-up of 47 months.** *Breast Cancer Res Treat* 2002; **Abstract 13**.

Chung CT, Carlson RW. **The role of aromatase inhibitors in early breast cancer.** *Curr Treat Options Oncol* 2003;4(2):133-40. **Abstract**

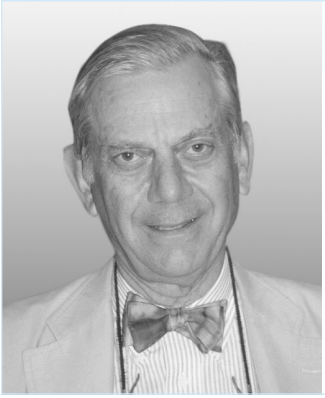
Klijn J, for the ATAC Trialists' Group. **The ATAC (anastrozole, Tamoxifen, Alone or in Combination) trial: An efficacy update, focusing on breast cancer (BC) events, based on a median follow-up of 47 months.** *Proc ASCO* 2003:**Abstract 338**.

Ligibel JA, Winer EP. **Clinical differences among the aromatase inhibitors.** *Clin Cancer Res* 2003;9(1 Pt 2):473S-9S. **Abstract**

Locker GY et al. **The time course of bone fractures observed in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003:**Abstract 98**.

Sainsbury R on behalf of the ATAC Trialists' Group. **Beneficial side-effect profile of anastrozole compared with tamoxifen confirmed by additional 7 months of exposure data: A safety update from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Breast Cancer Res Treat* 2002;**Abstract 633**.

Winer EP et al. **American Society of Clinical Oncology Technology Assessment Working Group Update: Use of aromatase inhibitors in the adjuvant setting.** *J Clin Oncol* 2003;21(13). **Abstract**



Blake Cady, MD, FACS

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Edited comments by Dr Cady

Relationship between local tumor control and survival

Strong evidence in breast and other cancers shows that no matter how radical the local treatment — surgery or surgery plus radiation therapy — cure rates are not decreased by high local recurrence rates. Local recurrence is an indicator of the biology of the tumor, not a governor of the outcome.

In the NSABP-B-06 trial, there was more than a 40 percent local recurrence rate in the group treated with lumpectomy alone, but for the three groups — mastectomy, lumpectomy and radiation or lumpectomy alone — there was no statistical difference in survival.

Until the two recent trials from Denmark and British Columbia, the data have been totally consistent — no matter what measures were taken for local control, it did not change survival. The Danish trials comparing mastectomy, adjuvant CMF and axillary dissection with or without radiation therapy seem to contradict all others, but are seriously flawed. There was a 45 percent rate of axillary recurrence after axillary dissection that has never been seen before. Because they took out only six or seven nodes when they did the axillary dissection, there are serious concerns about improper staging in the Danish trial. The Danish trial is different in that all the patients received adjuvant CMF. In the era of routine adjuvant chemotherapy, therefore, it's possible that the standard assumption in surgical oncology may have to be looked at more carefully.

In the trial by Veronesi comparing quadrantectomy to quadrantectomy plus radiation therapy, there was no difference in overall survival for the patients with negative nodes. The patients with positive nodes all received chemotherapy, and at about five years, the two arms split showing an advantage for the group treated with radiation therapy. That's consistent with data from the Danish trials.

The breast cancer trials comparing mastectomy to lumpectomy plus radiation have shown no difference in survival, and yet there are tremendously higher

local recurrence rates. The data is consistent. Some small cancers can be treated with local excision alone and no radiation. I'm still convinced that the "radicalness" of local treatment governs local recurrence, but not survival.

I tell breast cancer patients that no woman pays with her life for saving a breast. A woman, even with marginal indications for lumpectomy, won't pay with her life but will pay with a higher local recurrence rate. She might need a mastectomy later on, but it's not going to negatively affect her survival.

Radiation therapy in women with DCIS

In our unit, we've designed some protocols based on the Van Nuys Prognostic Index. We only radiate 20 percent of our DCIS patients. Due to the extensive nature of their disease or patient choice, 30 percent of our patients require mastectomy. Another 30 percent are treated by local excision alone with re-excision to achieve a one-centimeter margin — Mel Silverstein's criteria.

DCIS is not a homogeneous disease; there are a variety of biological patterns and manifestations. The median diameter of the average DCIS detected today by mammography is only eight or nine millimeters, and those patients should not be treated with radiation therapy.

Revised American Joint Committee on Cancer (AJCC) staging

Nodes are no longer just nodes, because there are micrometastases and submicrometastases. It is distressing that many oncologists are treating patients systemically for submicrometastases, which is why the new AJCC staging system is so important.

Cells found in a node that are less than 0.2-mm, largely by IHC, should not be used for therapeutic decisions. Those are considered N0 in breast cancer. That type of information should not be used to make therapeutic decisions — either for axillary dissection, chemotherapy or radiotherapy. We don't know what those things mean.

Select publications

Fisher B et al. **Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer.** *N Engl J Med* 1995;333(22):1456-61.

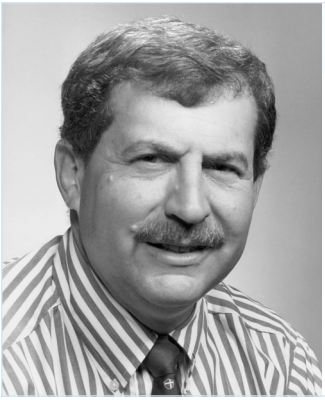
Overgaard M et al. **Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy.** *N Engl J Med* 1997;337:949-955. **Abstract**

Overgaard M et al. **Postoperative radiotherapy in high-risk postmenopausal breast cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial.** *Lancet* 1999;353:1641-1648. **Abstract**

Ragaz J et al. **Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer.** *N Engl J Med* 1997;337:956-962. **Abstract**

Singletary SE et al. **Revision of the American Joint Committee on Cancer staging system for breast cancer.** *J Clin Oncol* 2002;20(17):3628-36. **Abstract**

Veronesi U et al. **Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer.** *N Engl J Med* 2002;347(16):1227-32. **Abstract**



Hyman Muss, MD

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Edited comments by Dr Muss

Defining ER positivity

We are in an era when every pathology laboratory should report the percentage of cells staining positive for estrogen receptors, rather than just reporting "positive" or "negative." Negative should be defined as tumors with virtually no cells staining positively — truly "stone cold zero." Data from women whose tumors have just a few percent of cells expressing estrogen receptors show that these women derive benefit from endocrine therapy.

A common standard in the United States is for laboratories to report less than 10 percent of cells staining as negative. When invasive breast cancer is reported to be ER-negative, you should call your pathologist and verify the numbers. It's not just academic anymore, it's very important in treating patients.

Estrogen receptor status and DCIS

Craig Allred reported very provocative data from the NSABP-B-24 trial on estrogen receptor assays in women with DCIS at the 2002 San Antonio Breast Cancer Symposium. In this trial, women with DCIS received lumpectomy and breast radiation and then were randomized to receive five years of tamoxifen or not.

A central slide review in the NSABP laboratories found that only women with ER- or PR-positive DCIS derived benefit from tamoxifen in preventing ipsilateral breast tumor recurrence and new contralateral primary tumors. They also found a great deal of disparity in reporting the estrogen receptor data, especially in community centers.

Based on this data and Dr Allred's recommendations, it is appropriate to test for estrogen and progesterone receptors in patients with DCIS. Fifteen to 20 percent of patients in B-24 had ER-negative DCIS, therefore, the actual benefit

from tamoxifen may be even greater than was reported in that trial, and more careful selection of patients for tamoxifen will probably result in a higher benefit-to-risk ratio for the drug.

Updated results of the ATAC trial

The ATAC trial is a superb study of more than 9,000 patients. An update of the data was presented by Dr Aman Buzdar in San Antonio and showed that at four years follow-up, anastrozole was superior to tamoxifen with respect to disease-free survival and event rates. In addition, anastrozole is a less toxic drug, without the risks of endometrial cancer or thromboembolic disease. Anastrozole was associated with an increased risk of fractures, which is important because fractures are a cause of mortality in the United States; we need a lot more information with regard to bone. This statistically powerful trial gives us another option for adjuvant therapy in estrogen receptor-positive postmenopausal patients, and I discuss both tamoxifen and anastrozole with patients.

Communication with oncologists about axillary status

There are two goals of axillary surgery: one is to decrease the risk of local recurrence; the other is for prognosis. Axillary dissection is performed to help the medical oncologist make treatment decisions. Axillary nodal status remains the best prognostic indicator we have for predicting recurrence.

Radiation and medical oncologists should be involved early to help determine whether or not axillary surgery should be performed. I like multidisciplinary clinics because the surgeon can ask the radiation or medical oncologist whether knowing the axillary status will help guide treatment decisions. For most patients, this information will help, but not always — especially in women with coexisting illnesses in whom we may not want to use chemotherapy. In some cases, knowing the precise number of positive lymph nodes will not change treatment decisions. It's much easier to decide on adjuvant endocrine therapy, which is probably less toxic than aspirin.

Select publications

Axillary lymph node status

Cummings MC et al. **Occult axillary lymph node metastases in breast cancer do matter: Results of 10-year survival analysis.** *Am J Surg Pathol* 2002;26(10):1286-95. **Abstract**

Millis RR et al. **Occult axillary lymph node metastases are of no prognostic significance in breast cancer.** *Br J Cancer* 2002;86(3):396-401. **Abstract**

Rouzier R et al. **Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes.** *J Clin Oncol* 2002;20(5):1304-10. **Abstract**

Weir L et al. **Prognostic significance of the number of axillary lymph nodes removed in patients with node-negative breast cancer.** *J Clin Oncol* 2002;20(7):1793-9. **Abstract**

Post-test: Breast Cancer Update for Surgeons, Issue 3, 2003

Conversations with Clinical Research Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Based on the work of pathologist Roland Holland, there is compelling evidence that DCIS is not a precursor lesion to invasive breast cancer.**
   a. True
   b. False

2. **In the treatment of DCIS, radiation therapy following excision:**
   a. Reduces local recurrences
   b. Improves survival
   c. Both a and b
   d. None of the above

3. **One rationale for the use of brachytherapy in the treatment of DCIS is that 80 or 90 percent of local recurrences occur at or near the primary site of disease.**
   a. True
   b. False

4. **Results of the ATAC trial show that the incidence of vaginal bleeding was less for women taking anastrozole compared to tamoxifen:**
   a. True
   b. False

5. **Results of the Canadian National Breast Screening Study-1 reported in 2002 showed that, in women younger than 50 years of age, screening mammography:**
   a. Reduced breast cancer mortality
   b. Did not reduce breast cancer mortality

6. **Clinical trials have demonstrated that the aromatase inhibitors anastrozole, letrozole and exemestane have the same side effects and efficacy rates and are interchangeable in the adjuvant setting.**
   a. True
   b. False

7. **A reduced incidence of invasive and noninvasive contralateral breast cancers for patients taking anastrozole compared to tamoxifen in the ATAC trial indicates that aromatase inhibitors have potential as chemopreventive agents.**
   a. True
   b. False

8. **In comparing the efficacy of mastectomy to breast conservation in the treatment of early breast cancer:**
   a. Mastectomy has superior survival rates
   b. Breast conservation has superior survival rates
   c. Both modalities have equivalent survival rates

9. **The 25-year results of NSABP-B-06 showed no difference in mortality between women treated with mastectomy versus lumpectomy with radiation therapy.**
   a. True
   b. False

10. **Accurate reporting of estrogen receptor positivity is critical because data showing that women whose tumors have just a few percent of cells expressing receptors derive benefit from endocrine therapy.**
    a. True
    b. False

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

Evaluation Form: Breast Cancer Update for Surgeons, Issue 3, 2003

NL Communications Inc respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of our completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

GLOBAL LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Critically evaluate the clinical implications of emerging clinical trial data in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer 5 4 3 2 1
- Counsel postmenopausal patients with estrogen receptor-positive tumors about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant setting 5 4 3 2 1
- Describe the current guidelines for, and ongoing clinical trials of, local and regional therapy for noninvasive and invasive breast cancer 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 3

Upon completion of this activity, participants should be able to:

- Distinguish subsets of patients with DCIS for whom radiation therapy may not be necessary 5 4 3 2 1
- Determine the role of estrogen receptor testing for patients with DCIS 5 4 3 2 1
- Counsel patients about the controversies regarding the value of screening mammography 5 4 3 2 1
- Describe the results of the ATAC trial and implications in treating postmenopausal women with ER-positive breast cancer 5 4 3 2 1
- Describe ongoing clinical trials of aromatase inhibitors for DCIS and chemoprevention; counsel appropriate patients about participation 5 4 3 2 1
- Counsel patients about the risks and benefits of mastectomy versus breast-conserving surgery 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Melvin Silverstein, MD	5 4 3 2 1	5 4 3 2 1
Gershon Locker, MD	5 4 3 2 1	5 4 3 2 1
Blake Cady, MD, FACS	5 4 3 2 1	5 4 3 2 1
Hyman Muss, 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
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Evaluation Form: Breast Cancer Update for Surgeons, Issue 3, 2003

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___Yes ___No

If Yes, please describe any change(s) you plan to make in your practice as a result of this activity.

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What other topics would you like to see addressed in future educational programs?

_____

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What other faculty would you like to hear interviewed in future educational programs?

_____

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Degree:

☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____

To obtain a certificate of completion and receive credit for this activity, please complete the exam, fill out the evaluation form and mail or fax both to: NL Communications Inc, 400 SE Second Avenue, Suite 401, Miami, FL 33131-2117, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.