# Table of Contents



**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 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 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 4, 2003 of *Breast Cancer Update for Surgeons* consists of discussions with five research leaders on a variety of important topics including use of bisphosphonates, adjuvant endocrine therapy, management of hot flashes, sentinel lymph node biopsy and partial breast irradiation.

## SPECIFIC LEARNING OBJECTIVES FOR ISSUE 4

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

- Consider the absolute and relative contraindications to sentinel lymph node biopsy when deciding on optimal surgical management of the axilla.
- Evaluate the major cooperative group trials of sentinel lymph node biopsy in order to counsel patients regarding participation.
- Describe the ongoing clinical trials of systemic therapy for DCIS.
- Discuss the results of the ATAC trial and the implications of treating postmenopausal women with ER-positive breast cancer.
- Counsel breast cancer patients and survivors about nonestrogenic treatment alternatives for women with severe hot flashes.
- Consider the potential benefits and limitations of partial breast irradiation compared to whole breast radiation therapy.

## ACCREDITATION STATEMENT

NL Communications Inc is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

## CREDIT DESIGNATION STATEMENT

NL Communications Inc designates this educational activity for a maximum of 2.75 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

## FACULTY DISCLOSURES

As a provider accredited by the ACCME, it is the policy of NL Communications Inc to require the disclosure of any significant financial interest or any other relationship the sponsor or faculty members have with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

| | |
|---|---|
| **William C Wood, MD** | **Honorarium:** Aventis Pharmaceuticals Inc |
| **Norman Wolmark, MD** | No financial interests or affiliations to disclose |
| **Aman Buzdar, MD, FACP** | **Grants/Research Support:** AstraZeneca Pharmaceuticals LP, Eli Lilly & Company, Pfizer Inc, Genentech Inc, Bristol-Myers Squibb Company, Roche Laboratories Inc |
| **David N Krag, MD, FACS** | No financial interests or affiliations to disclose |
| **Charles Loprinzi, MD** | No financial interests or affiliations to disclose |

### Pharmaceutical agents discussed in this program

| GENERIC | TRADE | MANUFACTURER |
|---|---|---|
| anastrozole | Arimidex® | AstraZeneca Pharmaceuticals LP |
| capecitabine | Xeloda® | Roche Laboratories Inc |
| carboplatin | Paraplatin® | Bristol-Myers Squibb Company |
| citalopram HBr | Celexa® | Forest Pharmaceuticals Inc |
| clodronate | Various | Various |
| clonidine | Catapres® | Boehringer Ingelheim |
| docetaxel | Taxotere® | Aventis Pharmaceuticals Inc |
| exemestane | Aromasin® | Pfizer Inc |
| fluoxetine HCL | Prozac® | Eli Lilly & Company |
| gabapentin | Neurontin® | Pfizer Inc |
| goserelin | Zoladex® | AstraZeneca Pharmaceuticals LP |
| letrozole | Femara® | Novartis Pharmaceuticals Corporation |
| medroxyprogesterone acetate | Various | Various |
| megestrol acetate | Megace® | Bristol-Myers Squibb Company |
| pamidronate | Aredia® | Novartis Pharmaceuticals Corporation |
| paroxetine HCl | Paxil® | GlaxoSmithKline |
| raloxifene | Evista® | Eli Lilly & Company |
| tamoxifen citrate | Nolvadex® | AstraZeneca Pharmaceuticals LP |
| triptorelin | Various | Various |
| venlafaxine HCl | Effexor®XR | Wyeth Pharmaceuticals Inc |
| vinorelbine | Navelbine® | GlaxoSmithKline |
| zoledronic acid/zoledronate | Zometa® | Novartis Pharmaceuticals Corporation |

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. NL Communications Inc does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

## Editor's Note

### Half empty or half full?

We have to wait for the data from our NSABP-B-17 DCIS protocol to mature to determine if radiation therapy decreases the incidence of invasive recurrence. Meanwhile, our new DCIS protocol, B-24, just started a week ago and although we don't have the results from B-17, we had to select a control arm for B-24, which will be lumpectomy plus radiation. The B-24 trial will compare tamoxifen to placebo. The study is provocative, but I will pursue it with enthusiasm because I think, biologically, it is very interesting and will give us a great deal of very needed information. DCIS is being detected much more frequently, but we really don't know how to treat the disease. Our work is cut out for us, and we all look forward to the day when advances in molecular genetics and in the biochemistry of cancer will make today's discussion seem like a very primitive exercise.

*— Interview with Norman Wolmark, MD*
*Breast Cancer Update, May 1991*

During my monotonous drive up the Florida Turnpike from Miami to Orlando on the way to the June 2003 NSABP Annual Group Meeting, I decided to dust off and listen to an interview I conducted with Dr Norm Wolmark more than a decade ago. At that time, the NSABP had just launched three potentially paradigm-shifting trials: the high-dose adjuvant chemotherapy B-22 study, the preoperative chemotherapy B-18 trial and P-1, the "tamoxifen prevention study." By now, we all know the results of these studies. Like other high-dose chemo attempts, B-22 was a total bust; B-18 left perhaps a promissory note for the future and P-1 delivered. One out of three ain't bad when you're trying to shift paradigms, and I considered how other recent research advances would fit into the historical perspective of breast cancer management.

In this program, Dr David Krag reviews the NSABP sentinel node B-32 trial. While this procedure has greatly benefited patients by reducing operative morbidity, it is unlikely to impact mortality. Dr Krag also reviews his laboratory research on targeted cancer strategies. This discussion — like so many I hear from contemporary breast cancer research leaders — is fascinating biology, but one wonders when Dr Wolmark's 1991 wish will be fulfilled, and we will begin to see these approaches translated into patient-care advances.

Dr Wolmark's above comments on DCIS are also interesting in a historical perspective. B-17 eventually did demonstrate an advantage to radiation therapy, but skeptics such as previous *Breast Cancer Update* interviewee, Dr Mel Silverstein, still believe that many patients can be managed with lumpectomy alone. NSABP-B-24 demonstrated that tamoxifen reduced local recurrence and contralateral disease.

Our continuing medical education group is also interested in the issue of how clinical breast cancer research is translated into practice, and in that regard, for the second year, we conducted a national patterns of care telephone survey in July of this year. One hundred surgeons from our mail list were randomly surveyed on a variety of management issues, and the data are presented in this booklet starting on page 22.

The results of this survey provide a fascinating glimpse into current management patterns. With regard to DCIS, most patients are receiving tamoxifen, and Dr Wolmark discussed NSABP-B-35 that is comparing this agent to anastrozole in an attempt to verify that the advantages of this aromatase inhibitor demonstrated in invasive disease are also seen in noninvasive breast cancer. Our patterns of care survey demonstrates optimism that an advantage will be observed (see page 23).

The survey also reveals that sentinel node biopsy is now firmly entrenched in community care (see page 30) and that there is considerable heterogeneity in how surgeons approach clinical practice. Our group will utilize these findings as part of our needs assessment for upcoming education programs.

The NSABP meeting included what many will consider a bold step in breast cancer clinical research: a proposed preoperative trial that will focus on intratumoral markers of response in an attempt to accelerate the timetable for identifying effective adjuvant or neoadjuvant therapies (see figure below). At this same meeting, the group discussed plans for a new colorectal adjuvant trial that will include the anti-VEGF agent, bevacizumab, and Dr Wolmark told me that a similar trial may be considered in breast cancer in the future.

Is this news from the "frontline of the war on breast cancer" encouraging or discouraging? I would be interested in your point of view.

**—Neil Love, MD**
(NLove@ResearchtoPractice.net)

### Proposed NSABP-B-27 Replacement Trial

AC q 3w ↔ docetaxel q 3w → Surgery
AC q 3w ↔ docetaxel/capecitabine q 3w → Surgery
AC q 3w ↔ docetaxel/carboplatin q 3w → Surgery
AC q 3w ↔ docetaxel/vinorelbine q 3w → Surgery

↔ In this proposed 4 x 2 factorial design, some patients will receive AC followed by docetaxel or docetaxel combination regimens; in others, the sequence of administration will be reversed.

Sequential core biopsies will be performed before and after chemotherapy, and molecular biomarkers will be assessed.

*SOURCE:* NSABP Annual Meeting, Orlando, Florida, July 2003


### William C Wood, MD

Joseph Brown Whitehead Professor and Chairman, Department of Surgery, Emory University School of Medicine

Clinical Director, Winship Cancer Center

Chief of Surgery, Emory University Hospital

Section Head, General Surgery, The Emory Clinic


# Edited comments by Dr Wood

## Validation of sentinel lymph node biopsy

Data continue to be presented at our scientific meetings validating the efficacy of sentinel lymph node biopsy (SLNB). Individual institutional series demonstrate better technical ability of the surgeons performing SLNB. The change from peritumoral to subareolar injection of blue dye has made it virtually impossible not to identify a sentinel node. For those who perform numerous biopsies, there's probably no need to use anything other than blue dye. For those who do it less frequently, there's a great advantage to using a "double-dye technique" with technetium sulfur colloid. With two labels, it's even easier to identify the sentinel lymph node.

## Phase III trials evaluating SLNB

NSABP-B-32 is evaluating whether the abandonment of axillary node dissection in patients with negative nodes is detrimental. NSABP-B-04 was a very small study done years ago, which failed to demonstrate the virtue of axillary dissection. Despite the inadequate power of B-04, it is difficult to understand why the NSABP would address this issue in preselected lymph node-negative patients.

We participate, to a limited extent, in the American College of Surgeons' (ACOS) trial, which asks very different questions than B-32. The ACOS study aims to determine whether there is any advantage to removing nonpalpable involved lymph nodes. Clearly, radiation to the breast radiates the lower part of the axilla. Sentinel lymph node biopsy removes almost one-half of involved lymph nodes — so, even in the node-positive patients, only about one-half will have any other lymph nodes involved — and radiation probably sterilizes most of those. What do we gain by the additional dissection? This is a very important clinical question. I applaud the ACOS in undertaking this trial.

I am comfortable presenting the ACOS trial to a patient, but frankly, if

pressed, I don't have personal therapeutic equipoise about it. I would prefer to see a woman with a positive sentinel node have an axillary dissection. It gets a little tougher when the patient asks you that old question, "How would you want your sister treated?" I explain that, although I would choose axillary dissection, I have colleagues who would not, and I think either choice is legitimate. The only way to find out for our daughters' generation is to do the clinical trial.

Ironically, I would not be comfortable entering a patient or someone in my family in the NSABP trial. The data are entirely clear that patients with negative sentinel lymph nodes — if more than one node is examined — are so unlikely to have unidentified positive nodes that I don't believe the morbidity of axillary dissection, even in very good hands, is justified.

## Contraindications to SLNB

I see three contraindications for SLNB. For DCIS, if one is not doing mastectomy, I see no role for SLNB. Another contraindication would be in cases of invasive cancer with palpable nodes prior to a core biopsy, because the lymphatics may be blocked and dye can go off to uninvolved secondary nodes, making the sentinel node appear negative.

The third area in which we do not know how to perform the procedure is in the rare cases in which the tumor truly begins in the axilla. Radioisotope shines through, and blue dye runs in all directions. Even if you place the dye in the subareolar location, I'm not sure it goes to the same node that a metastasis from an axillary tail in the mid-axilla would go.

It is clear that SLNB can be done after induction chemotherapy, but it is not clear whether it is as effective. Studies purporting to demonstrate its effectiveness have a false-negative rate of eight percent to 12 percent. In a good series, the false-negative rate should be one percent to three percent. This suggests to me that SLNB is less effective after induction chemotherapy. Numerous studies will sort that out, but at present, we're doing SLNB prior to induction chemotherapy.

## Intraoperative radiation therapy

Intraoperative radiation therapy (IORT) can be administered in a variety of ways. Dr Veronesi performs IORT with a linear accelerator, pulling the breast together inside the wound with a couple of stitches and then radiating it. The dosimetry with this technique is very difficult because radiation is given right at the moment, and you can only try to reconstruct it after the fact. Other modes of administration include the intracavitary balloon radiation device or intraoperative radiation with catheters.

Intraoperative radiation therapy will likely help prevent local recurrence of DCIS or very small breast cancers within the first year to two years. However, over the next eight years, more than 50 percent of the recurrences are likely to occur at a considerable distance from the lumpectomy site. So,

the early results from IORT trials will likely be wonderfully positive, and a negative result won't emerge for five years to 10 years. By that time, the whole world will have begun using these intracavitary forms of radiation therapy. It is disconcerting that "the horse will be out of the barn" before we have real data to demonstrate the safety of these procedures.

## Nonprotocol role of ductal lavage for patients at high risk

Ductal lavage offers an interesting way of gathering material for research, but we do not have a clear clinical indication for this procedure. In performing ductal lavage as part of a study at Northwestern, Dr Seema Khan found that numerous breast cancers were lavage negative, while in many lavages with atypical cells, no abnormality could be found. Cells present within ducts may appear abnormal over time, and ductal smears often appear atypical with no associated clear abnormality. I definitely do not see a role for ductal lavage in a nonprotocol situation.

The advocates of ductal lavage have backed away from the idea that it is a diagnostic test and now suggest that its real role is in risk assessment. But, if the ductal lavage reveals no abnormality, are you going to tell a woman at high risk that she shouldn't consider an intervention with tamoxifen or entry into the STAR trial? I see no clinical basis for the use of ductal lavage.

## Integration of adjuvant endocrine therapy into surgical practice

Surgeons have enough to do without trying to take on the superb work done by our medical oncology colleagues with cytotoxic agents. However, the use of hormonal agents is so easily integrated into our ordinary care of patients, that I believe it will continue to be a part of the surgical oncologist's role today. In terms of surgeons' comfort in prescribing aromatase inhibitors, I have not seen a difference in women utilizing tamoxifen compared to an aromatase inhibitor. Women on both agents do well with few side effects.

The ATAC trial is a very exciting study. Dr Mike Baum is once again leading the pack with another class of agents in a massive trial. Should we now use anastrozole instead of tamoxifen for all our postmenopausal patients? That's a difficult question. The older the woman, the more satisfied I am using anastrozole. I still have concerns about the younger postmenopausal woman. There's no question that we can prevent the bone fractures that can occur in women on anastrozole with bisphosphonates. Surgeons need to be alert regarding this issue.

In the adjuvant setting, I'm not enthusiastic about using aromatase inhibitors other than anastrozole outside of a clinical trial. We really need Phase III data for the other aromatase inhibitors with sufficient follow-up.

## Anthracyclines, taxanes and dose-dense adjuvant chemotherapy

The last three years have brought about some very clear answers to three big questions. The first is: Do anthracyclines really make a big difference? And

yet another study shows that anthracyclines really are dramatically better than CMF-based therapy, not just a little bit. The second question is: Does the addition of taxanes add to the benefit seen with the anthracycline-based combinations? We now have two studies — the NSABP and breast Intergroup studies — each with over 3,000 women, clearly demonstrating that taxanes add benefit. The third answered question revolves around the benefit seen with the dose-dense approach to chemotherapy, which was recently demonstrated by CALGB-9741.

## Select publications

### *Partial breast irradiation*


Arthur DW et al. **Partial breast brachytherapy after lumpectomy: Low-dose-rate and high-dose-rate experience.** *Int J Radiat Oncol Biol Phys* 2003;56(3):681-9. **Abstract**

Edmundson GK et al. **Dosimetric characteristics of the MammoSite RTS, a new breast brachytherapy applicator.** *Int J Radiat Oncol Biol Phys* 2002;52(4):1132-9. **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**

Keisch M et al. **Initial clinical experience with the MammoSite breast brachytherapy applicator in women with early-stage breast cancer treated with breast-conserving therapy.** *Int J Radiat Oncol Biol Phys* 2003;55(2):289-93. **Abstract**

Lawenda BD et al. **Dose-volume analysis of radiotherapy for T1N0 invasive breast cancer treated by local excision and partial breast irradiation by low-dose-rate interstitial implant.** *Int J Radiat Oncol Biol Phys* 2003;56(3):671-80. **Abstract**

Polgar C et al. **Radiotherapy confined to the tumor bed following breast conserving surgery current status, controversies, and future projects.** *Strahlenther Onkol* 2002;178(11):597-606. **Abstract**

Polgar C et al. **Sole brachytherapy of the tumor bed after conservative surgery for T1 breast cancer: Five-year results of a phase I-II study and initial findings of a randomized phase III trial.** *J Surg Oncol* 2002;80(3):121-8; discussion 129. **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**

Resch A et al. **Long-term results (10 years) of intensive breast conserving therapy including a high-dose and large-volume interstitial brachytherapy boost (LDR/HDR) for T1/T2 breast cancer.** *Radiother Oncol* 2002;63(1):47-58. **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**

Van Limbergen E. **Indications and technical aspects of brachytherapy in breast conserving treatment of breast cancer.** *Cancer Radiother* 2003;7(2):107-20. **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.

Vicini FA et al. **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003;95(16):1205-10. **Abstract**

Vicini F et al. **The emerging role of brachytherapy in the management of patients with breast cancer.** *Semin Radiat Oncol* 2002;12(1):31-9. **Abstract**

Wazer DE et al. **Preliminary results of a phase I/II study of HDR brachytherapy alone for T1/T2 breast cancer.** *Int J Radiat Oncol Biol Phys* 2002;53(4):889-97. **Abstract**


**Norman Wolmark, MD**

Chairman, Department of Human Oncology, Allegheny General Hospital

Professor, Human Oncology, Drexel University College of Medicine

Chairman, National Surgical Adjuvant Breast and Bowel Project


# Edited comments by Dr Wolmark

## NSABP trial B-35: Anastrozole versus tamoxifen in DCIS

NSABP-B-35 is the next protocol in a generation of NSABP DCIS trials: B-17 compared radiotherapy to no treatment, B-24 added tamoxifen to lumpectomy and radiotherapy, and B-35, which opened in January 2003, compares anastrozole to tamoxifen for five years. We're hoping that anastrozole will be superior to tamoxifen, as it was in the ATAC trial; however, that trial was powered to detect small differences in efficacy.

We debated considerably whether ER positivity should be required for eligibility in B-35. Dr Craig Allred reanalyzed data from NSABP-B-24 and demonstrated benefit from tamoxifen only in those patients with ER-positive DCIS. Ultimately, we decided to limit eligibility for B-35 to patients with ER-positive DCIS. Only a small subset of women with DCIS — approximately 20 percent — is ER-negative. At the current time, I believe it is overly restrictive and authoritarian to dictate that the community standard require estrogen receptor assay prior to treating DCIS.

## NSABP-B-32: The value of axillary dissection in patients with negative sentinel lymph node biopsy

If we accepted the postulate that SLNB is accurate, then conducting NSABP-B-32 would be unconscionable, because women with negative axillary lymph nodes would be subjected to an unnecessary procedure with its associated morbidity. However, we did not accept that postulate.

I am astounded that we are succeeding in enrolling 5,400 women in a trial that randomizes patients to SLNB alone or SLNB followed by axillary dissection. This has been one of the NSABPs best-accruing protocols. I'm grateful to the individuals who participated in the study and for the commitment and persistence of Dr David Krag, who cajoled and convinced

us that the trial should be initiated. The response to NSABP-B-32 from the surgical community has been remarkable, and we will meet our target accrual this year.

## Proposed NSABP trial evaluating partial breast irradiation

We have proposed a Phase III randomized, prospective trial comparing traditional external beam to partial breast radiotherapy. The initial sample size estimate for this trial was 6,300 women to show a 1.4 risk of inferiority for interstitial radiotherapy.

We did not believe it was worth the investment, so we are re-evaluating the sample size necessary to demonstrate the risk of 1.5, which would likely be 3,000 patients. While the difference between a risk of 1.4 and 1.5 doesn't sound large, when the event rate is relatively small — six percent to eight percent over a 10-year period — and you alter the power, there's a significant difference in the overall number of patients required.

## Proposed NSABP trial evaluating systemic therapy for locoregional relapse

Ipsilateral breast tumor recurrence is a biologic event that increases the risk of disseminated extramammary disease. The NSABP has always been interested in launching a trial to evaluate systemic treatment for locoregional relapse, but we were uncertain whether we could complete such a trial. We've worked out a solution whereby we will conduct this trial in collaboration with the International Breast Cancer Study Group (IBCSG). The NSABP would be the North American principal for that trial, with CTSU participation.

## Select publications

### *NSABP experience with DCIS*


Fisher B et al. **Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17.** *J Clin Oncol* 1998;16(2):441-52. **Abstract**

Fisher B et al. **Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer.** *N Engl J Med* 1993;328:1581-86. **Abstract**

Fisher B et al. **Prevention of invasive breast cancer in women with ductal carcinoma in situ: An update of the National Surgical Adjuvant Breast and Bowel Project experience.** *Seminars in Oncology* 2001;28(4):400-418. **Abstract**

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**

Fisher ER et al. **Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17. Intraductal carcinoma.** *Cancer* 1999;86(3):429-38. **Abstract**


**Aman Buzdar, MD, FACP**

Professor of Medicine, Ashbel Smith Professor
and Deputy Chairman,
Department of Breast Medical Oncology,
University of Texas MD Anderson Cancer Center


# Edited comments by Dr Buzdar

## Updated data from the ATAC trial: 47-month follow-up

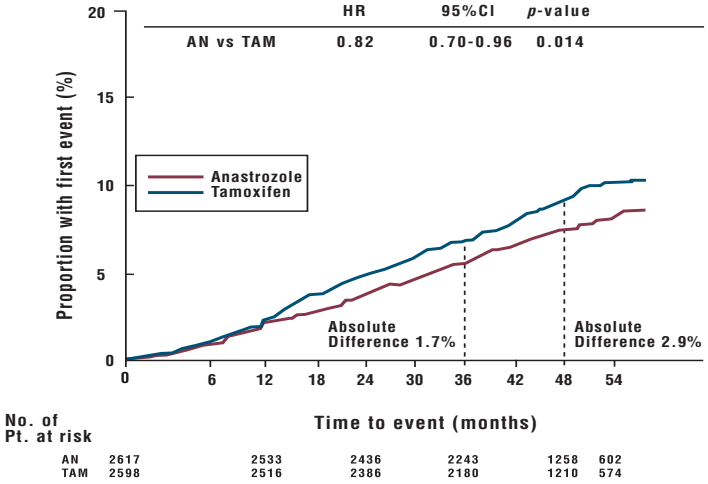
The initial publication of the ATAC results caused concern because the data represented only about two-and-a-half years of follow-up. Now the median follow-up is four years, there are no new safety concerns and the early efficacy advantages have persisted — in fact, the absolute differences are increasing with time. I believe the data provide strong support for the adjuvant use of anastrozole in postmenopausal patients with hormone receptor-positive, early-stage breast cancer.

The divergence of the curves is not unique to the ATAC trial. The Oxford overview of chemotherapy data or ovarian ablation demonstrates a persistent divergence of the curves with time. I believe this is what happens with a successful adjuvant therapy. Basically, there is a reduction in events and, in a fraction of patients, micrometastases are eliminated by the systemic therapy. It takes time for the patients receiving the alternate therapy to show evidence of recurring disease, and when that happens, you see this pattern of divergence.

## Recurrence and mortality data from the ATAC trial

Patients on anastrozole had fewer local and distant recurrences and fewer second primary breast cancers, but more follow-up is required. When there are more than 704 distant recurrences between the two arms, we should be able to determine the effect of the therapies on systemic recurrences. The numeric differences already favor anastrozole, both with an intent-to-treat analysis and when looking at ER-positive patients, and I expect that overall survival will parallel the disease-free survival pattern. Currently, there are very few deaths, but when there are more than 704 deaths between the two monotherapy arms, the survival data will also be unblinded.

Probability of first event in receptor-positive population in the ATAC trial




*DERIVED FROM:* Buzdar A. Presentation, 2002 San Antonio Breast Cancer Symposium

## Implications of the ATAC trial in clinical practice

As an academic and a practicing clinician, my role is to be candid with my patients and let them be an active participant in their treatment decisions. Since the initial results of the ATAC trial were reported, I have discussed them with my patients, including the benefits of anastrozole and the effects on bone. In my practice, about nine out of 10 women choose anastrozole over tamoxifen.

I believe the ASCO Technology Assessment is very conservative, and I respectfully disagree with their recommendations. The data favoring anastrozole is very strong and is already impacting clinical practice and research. There is a very large Canadian trial taking place in which the control arm is anastrozole rather than tamoxifen.

## Use of other aromatase inhibitors in the adjuvant setting

Currently, I do not recommend the use of aromatase inhibitors other than anastrozole in the adjuvant setting. I recently published a review in *Cancer* demonstrating differences in the pharmacology and pharmacokinetics among the newer generation of aromatase inhibitors — anastrozole, letrozole and exemestane. Until we have long-term safety and efficacy data on letrozole and exemestane, I don't recommend their use outside of a clinical trial.

Experimental data in mice show possible benefits of exemestane on the bone, but this still needs to be proven in patients. In addition, exemestane is a steroidal molecule that, because of its agonistic effect, may have safety issues

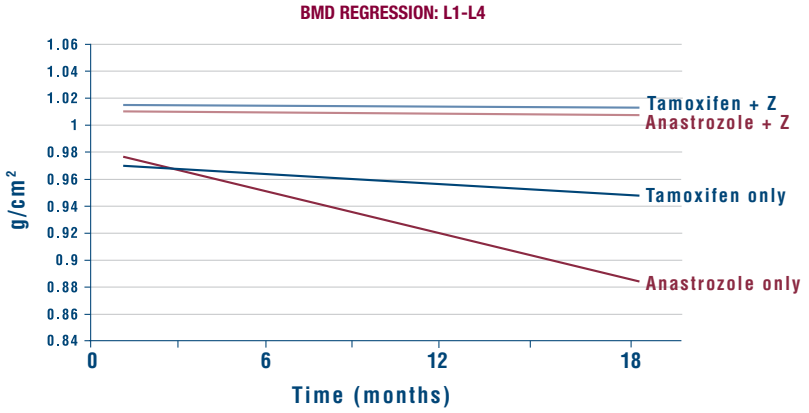
similar to tamoxifen. We don't have enough in long-term safety or efficacy data, even in metastatic disease, to know whether these androgenic effects will be beneficial or detrimental when exemstane is given to patients for a long period of time.

## Use of bisphosphonates in patients on estrogen deprivation therapy

An Austrian group evaluated the effect of bisphosphonates in premenopausal patients who received LHRH agonists and tamoxifen or anastrozole. Significant prevention of the bone loss and bone-related events was seen in the patients who received the bisphosphonate.

For patients on anastrozole, the key is to evaluate baseline bone density and then follow these patients. If and when there is a change, effective therapies can be implemented to prevent further bone loss. A number of effective bisphosphonates are available. The EORTC is comparing exemestane to tamoxifen, and we are participating in the bone subprotocol. In this study, patients have a bone density evaluation up front and at regular intervals to monitor changes in bone.

Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronic acid) as adjuvant treatment for hormone receptor-positive, premenopausal breast cancer: Results of a randomized multicenter trial (ABCSG-12).




Z = Zoledronic Acid

*SOURCE:* Gnant M. Presentation, 2002 San Antonio Breast Cancer Symposium

## Adjuvant endocrine therapy in premenopausal women

The majority of premenopausal patients go into premature ovarian failure after chemotherapy; however, in a small fraction of those who are young, ovarian function remains intact. At this time, the evidence is very weak for

utilizing LHRH agonists with tamoxifen in that setting; however, there are several large, multinational studies taking place that will provide that answer in the next few years. Even if a premenopausal patient becomes amenorrheic, one should not assume she is postmenopausal, because patients can experience transient amenorrhea. LH, FSH and estradiol levels should be measured and unless they all fall in the postmenopausal range, it is not appropriate to use an aromatase inhibitor. Women who become amenorrheic but maintain borderline levels may still regain ovarian function.

An ongoing trial is examining whether the aromatase inhibitors (with ovarian ablation or suppression) will have a favorable impact on the disease-free and overall survival in hormone-receptive, premenopausal patients. Until we have that answer, we will all make different treatment decisions in an effort to select the best therapy for our patients without definitive data to guide us. My general, nonprotocol approach to an ER-positive, premenopausal woman with multiple positive nodes is to offer tamoxifen in addition to chemotherapy.

### Ongoing Trials of Adjuvant Endocrine Therapy in Premenopausal Patients

| Study | Entry Criteria | Intervention | Target Accrual |
|---|---|---|---|
| ABCSG-AU12 | Stage I, II | Tamoxifen + goserelin ± zoledronate<br>Anastrozole + goserelin ± zoledronate | 1,250 |
| IBCSG-24-02 | T1-T3, pN0-N2 | Tamoxifen<br>Ovarian suppression + tamoxifen<br>Ovarian suppression + exemestane | 3,000 |
| IBCSG-25-02 | T1-T3, pN0-N2 | Triptorelin + tamoxifen<br>Triptorelin + exemestane | 1,845 |
| IBCSG-26-02 | T1-T3, pN0-N2 | Ovarian suppression + tamoxifen or exemestane<br>Ovarian suppression + chemotherapy + tamoxifen or exemestane after chemotherapy | 1,750 |

*DERIVED FROM:* NCI Physician Data Query and ASCO Technology Assessment, September 2003: **Aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer.**

## Select publications

### *Publications discussed by Dr Buzdar*


Buzdar AU et al. **An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane.** Cancer 2002;95(9):2006-16. **Abstract**

Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial.** Breast Cancer Res Treat 2002:**Abstract 12**.

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.** San Antonio Breast Cancer Symposium 2002:**Poster 633**.


### *Use of bisphosphonates in breast cancer*


Body JJ, Mancini I. **Bisphosphonates for cancer patients: Why, how, and when?** *Support Care Cancer* 2002;10(5):399-407. **Abstract**

Brown JE, Coleman RE. **The present and future role of bisphosphonates in the management of patients with breast cancer.** *Breast Cancer Res* 2002;4(1):24-9. **Abstract**

Chlebowski RT. **Factors influencing the role of bisphosphonates in breast cancer management.** *Semin Oncol* 2001;28(4 Suppl 11):42-8. **Abstract**

Coleman RE. **Efficacy of zoledronic acid and pamidronate in breast cancer patients: A comparative analysis of randomized phase III trials.** *Am J Clin Oncol* 2002;25(6 Suppl 1):S25-31. **Abstract**

Gasser JA et al. **Intravenous administration of zoledronic acid offers long-term protection against bone loss in rats induced as a consequence of estrogen deprivation.** *Breast Cancer Res Treat* 2002:**Abstract 274**.

Gralow JR. **The role of bisphosphonates as adjuvant therapy for breast cancer.** *Curr Oncol Rep* 2001;3(6):506-15. **Abstract**

Paterson AH. **Bisphosphonates: Biological response modifiers in breast cancer.** *Clin Breast Cancer* 2002;3(3):206-16; discussion 217-8. **Abstract**

Pavlakis N, Stockler M. **Bisphosphonates for breast cancer.** *Cochrane Database Syst Rev* 2002;(1):CD003474. **Abstract**

Pickering LM et al. **The bisphosphonate zoledronic acid downregulates signalling through Ras effector pathways in human breast cancer cell lines.** *Breast Cancer Res Treat* 2002:**Abstract 356**.

Pickering LM, Mansi JL. **The role of bisphosphonates in breast cancer management: Review article.** *Curr Med Res Opin* 2002;18(5):284-95. **Abstract**

Plunkett TA, Rubens RD. **Bisphosphonate therapy for patients with breast carcinoma.** *Cancer* 2003;97(3 Suppl):854-8. **Abstract**

Reinholz GG et al. **Distinct mechanisms of bisphosphonate action between osteoblasts and breast cancer cells: Identity of a potent new bisphosphonate analogue.** *Breast Cancer Res Treat* 2002;71(3):257-68. **Abstract**

Saarto T et al. **The effect of clodronate and antioestrogens on bone loss associated with oestrogen withdrawal in postmenopausal women with breast cancer.** Br J Cancer 2001;20;84(8):1047-51. **Abstract**

Senaratne SG, Colston KW. **Direct effects of bisphosphonates on breast cancer cells.** *Breast Cancer Res* 2002;4(1):18-23. **Abstract**

Theriault RL, Hortobagyi GN. **The evolving role of bisphosphonates.** *Semin Oncol* 2001;28(3):284-90. **Abstract**

Van Poznak C. **How are bisphosphonates used today in breast cancer clinical practice?** *Semin Oncol* 2001;28(4 Suppl 11):69-74. **Abstract**

Van Poznak CH. **The use of bisphosphonates in patients with breast cancer.** *Cancer Control* 2002;9(6):480-9. **Abstract**

Vehmanen et al. **Long-term impact of chemotherapy-induced ovarian failure on bone mineral density (BMD) in premenopausal breast cancer patients. The effect of adjuvant clodronate treatment.** *Eur J Cancer* 2001;37(18):2373-8. **Abstract**

**David N Krag, MD, FACS**

SD Ireland Professor of Surgery,
Department of Surgery,
University of Vermont College of Medicine

# Edited comments by Dr Krag

## Rationale for axillary lymph node dissection (ALND)

The rationale for performing ALND is threefold: regional control, staging and prognosis, and the possibility of improving survival. Most people regard staging as the primary value derived from ALND; but in fact, we also use it because of presumed therapeutic benefit. Data from a variety of sources document the accuracy of SLNB for staging the axilla. If staging were our primary concern, then we could simply utilize SLNB, but regional control and survival must be considered.

We don't have any data on long-term regional control rates for SLNB, but we know that ALND achieves nearly 100 percent control in the axillary region, and radiation has a similar control rate. Abandoning these procedures, which we know work very well therapeutically, would be a big step because the mortality associated with regional recurrence is approximately 50 percent.

It's somewhat heretical to say this, but there may be a survival benefit from controlling the axilla. I make this point because not many studies have excluded ALND. In addition, in the few NSABP studies in which ALND was not performed, hundreds — not thousands — of patients were randomized. Although the data in these studies demonstrated no survival differences between ALND and SLNB, these trials did not have the statistical power to detect survival differences of five percent or less.

I do not believe we have enough data to justify SLNB in a nonprotocol setting, and I've personally never performed SLNB in a breast cancer patient outside of a clinical trial.

## Methodologies in performing SLNB

SLNB is not a quick "get-in and get-out" surgery. Occasionally, the node is easy to find, and you're done in about 10 minutes. However, in about one-third of

cases, the node is not obvious, and the procedure is time-consuming — often more so than ALND. SLNB is a delicate surgery, and I believe that lack of patience is one of the most common mistakes made while performing it.

In the United States, there are limited methods to perform SLNB. There are dye-based methods, including blue dye and isosulfan blue (Lymphazurin™), and radioactive tracers — typically, technetium sulfur colloid. The other important methodological factor is the location of the injection. The injection can be deep — either into or around the tumor — or superficial into the skin that overlies the tumor or the skin adjacent to the areola complex.

Each method has advantages and disadvantages. If you want to capture the lymphatic ducts leading from a tumor, it is logical to inject the dye or tracer around the tumor; however, data show that injections into the skin or an alternate location also produce good results.

Confirmatory ALNDs performed on large numbers of patients — collectively, thousands of patients using different injection locations — have measured both SLNB success rates and whether the correct node was located. We've collated this data and found high success rates — from 90 percent to 98 percent — in all categories. The rates of finding pathologically positive nodes with any given technique differ. The positivity rate is about 35 percent when the injection is intradermal over the tumor or intra- or peritumoral, which is consistent with our expectations. However, in the subareolar category, the rate is approximately 27 percent. I hope that this nearly 10 percent difference reflects patient selection and a limited data set, but the results are from more than 500 patients. At the very least, questions have been raised regarding use of the technique in this location.

## SLNB with neoadjuvant systemic therapy

Data suggests SLNB works quite well in the neoadjuvant setting. There is also information that suggests it could be used reasonably in patients with multiple tumors throughout the breast. I also believe that it would not be harmful to perform SLNB in conjunction with ALND in patients with locally advanced disease because it can guide the pathologist to nodes more likely to contain cancer and may assist in detecting additional axillary nodes that would be important to resect.

## Replacement study for NSABP-B-32

We're working on a correlative pathology study that is conceptually linked to B-32 but is not really a sentinel node study. We're attempting to incorporate the most current technologies in a prospective manner to evaluate bone marrow aspirates and peripheral blood samples. We also want to perform genomic studies on the primary tumor. To minimize patient discomfort, we would perform the bone marrow aspiration and collect peripheral blood procedures at the time of surgery.

# Select publications

## *Recent publications on SLNB*


Bevilacqua JL et al. **A selection algorithm for internal mammary sentinel lymph node biopsy in breast cancer.** *Eur J Surg Oncol* 2002;28(6):603-14. **Abstract**

Blanchard DK et al. **Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer.** *Arch Surg* 2003;138(5):482-7;discussion 487-8. **Abstract**

Blessing WD et al. **A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping.** *Am J Surg* 2002;184(4):341-5. **Abstract**

Chua B et al. **Outcomes of sentinel node biopsy for breast cancer in British Columbia, 1996 to 2001.** *Am J Surg* 2003;185(2):118-26. **Abstract**

den Bakker MA et al. **Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; too early to abandon axillary clearance.** *J Clin Pathol* 2002;55(12):932-5. **Abstract**

Fant JS et al. **Preliminary outcome analysis in patients with breast cancer and a positive sentinel lymph node who declined axillary dissection.** *Ann Surg Oncol* 2003;10(2):126-30. **Abstract**

Guenther JM et al. **Axillary dissection is not required for all patients with breast cancer and positive sentinel nodes.** *Arch Surg* 2003;138(1):52-6. **Abstract**

Jakub JW et al. **Current status of sentinel lymph node mapping and biopsy: Facts and controversies.** *Oncologist* 2003;8(1):59-68. **Abstract**

Mamounas EP. **Sentinel lymph node biopsy after neoadjuvant systemic therapy.** *Surg Clin North Am* 2003;83(4):931-42. **Abstract**

Moonka R et al. **A comparison of rates of lymph node metastases between patients undergoing sentinel and axillary lymphadenectomy.** *Am J Surg* 2002;183(5):558-61. **Abstract**

Reitsamer R et al. **Sentinel lymph node biopsy alone without axillary lymph node dissection — follow up of sentinel lymph node negative breast cancer patients.** *Eur J Surg Oncol* 2003;29(3):221-3. **Abstract**

Sanidas EE et al. **How many cases are enough for accreditation in sentinel lymph node biopsy in breast cancer?** *Am J Surg* 2003;185(3):202-10. **Abstract**

Schijven MP et al. **Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy.** *Eur J Surg Oncol* 2003;29(4):341-50. **Abstract**

Schwartz GF et al. **Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast April 19 to 22, 2001, Philadelphia, Pennsylvania.** *Hum Pathol* 2002;33(6):579-89. **Abstract**

Simmons R et al. **Methylene blue dye as an alternative to isosulfan blue dye for sentinel lymph node localization.** *Ann Surg Oncol* 2003;10(3):242-7. **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**

Swenson KK et al. **Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer.** *Ann Surg Oncol* 2002;9(8):745-53. **Abstract**

Veronesi U et al. **A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.** *N Engl J Med* 2003;349(6):546-53. **Abstract**

Wilke LG, Giuliano A. **Sentinel lymph node biopsy in patients with early-stage breast cancer: Status of the National Clinical Trials.** *Surg Clin North Am* 2003;83(4):901-10. **Abstract**

Wong SL et al. **Optimal use of sentinel lymph node biopsy versus axillary lymph node dissection in patients with breast carcinoma: A decision analysis.** *Cancer* 2002;95(3):478-87. **Abstract**

**Charles Loprinzi, MD**

Professor of Oncology,
Mayo Clinic

# Edited comments by Dr Loprinzi

## Management of vasomotor symptoms in breast cancer survivors

Hot flashes are a major problem for many women during menopause, but they can be even more of a problem in women with breast cancer for a number of reasons. We may induce premature menopause with chemotherapy or exacerbate hot flashes with tamoxifen, and we deny the woman estrogen. While there are fewer hot flashes with the aromatase inhibitors than with tamoxifen, some women on aromatase inhibitors experience hot flashes.

We started looking at the management of hot flashes over a decade ago, and have found a number of effective therapies. Clonidine was one of the earliest agents studied, and while placebo decreases hot flashes by about 25 percent from baseline, clonidine decreases them by another 15 percent to 20 percent. There are, however, a number of side effects, and many patients did not like clonidine. Vitamin E has a small effect, decreasing symptoms by approximately one hot flash per person per day. Megestrol acetate reduces hot flashes by approximately 80 percent, a reduction comparable to that achieved by administration of estrogen. However, some people are as concerned about giving progesterone to a breast cancer survivor as they are about giving estrogen.

These observations led us to look at the newer antidepressants. We conducted a dose-finding, placebo-controlled trial of venlafaxine, wherein we saw that a placebo decreased hot flashes by 27 percent. A dose of 37.5 mg per day of venlafaxine in a sustained-release preparation decreased hot flashes by 40 percent from baseline, and a 75 mg dose decreased hot flashes by about 60 percent from baseline. Raising the dose to 150 mg did not result in additional improvement. These are relatively low doses, compared to the 150 mg and 225 mg generally used to treat depression.

We are also looking at a number of newer antidepressants. In addition to studying venlafaxine, we published a trial with fluoxetine, demonstrating a

significant reduction in hot flashes — though not quite the magnitude of effect we saw with venlafaxine. We didn't, however, look at multiple doses like we did with venlafaxine. Other pilot trials suggest that other antidepressants like citalopram, paroxetine and other newer antidepressants have a similar effect.

We are also studying the antiseizure medication gabapentin, which demonstrated a 60 percent reduction in hot flashes in a pilot study. Some people experience lightheadedness, dizziness, some fatigue during the day and some edema while taking gabapentin, but for many patients, it is well-tolerated.

Usually patients will have tried Vitamin E before they see me. It is nontoxic, well-tolerated, inexpensive, readily available and it results in a slightly greater reduction in hot flashes than the placebo effect. After first trying Vitamin E, I move on to venlafaxine, starting at 37.5 mg and increasing to 75 mg if necessary. This is usually effective for 40 percent of patients. I have been using gabapentin next in practice. This helps another 20 percent of women. My next intervention is generally medroxyprogesterone acetate 500 mg IM every 14 days for three doses. I do tell my patients that at the current time we don't know the effect of progesterone on breast cancer.

## Select publications

### *Publications discussed by Dr Loprinzi*


Barton D et al. **Hot flashes: Aetiology and management.** *Drugs Aging* 2001;18(8):597-606. **Abstract**

Carpenter JS. **The Hot Flash Related Daily Interference Scale: A tool for assessing the impact of hot flashes on quality of life following breast cancer.** *J Pain Symptom Manage* 2001;22(6):979-89. **Abstract**

Jacobson JS et al. **Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer.** *J Clin Oncol* 2001;19(10):2739-45. **Abstract**

Loprinzi CL et al. **Phase III evaluation of fluoxetine for treatment of hot flashes.** *J Clin Oncol* 2002;20(6):1578-83. **Abstract**

Loprinzi CL et al. **Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors.** *J Clin Oncol* 1998;16(7):2377-81. **Abstract**

Loprinzi CL et al. **Tamoxifen-induced hot flashes.** *Clin Breast Cancer* 2000;1(1):52-6. **Abstract**

Loprinzi CL et al. **Venlafaxine in management of hot flashes in survivors of breast cancer: A randomised controlled trial.** *Lancet* 2000;356(9247):2059-63. **Abstract**

Morant R et al. **St. John's Wort extract relieves hot flashes in women with breast cancer — Preliminary results of a phase II study.** *Proc ASCO* 2003;**Abstract 3178**.

Quella SK et al. **Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: A North Central Cancer Treatment Group Trial.** *J Clin Oncol* 2000;18(5):1068-74. **Abstract**

Stearns V et al. **A pilot trial assessing the efficacy of paroxetine hydrochloride (Paxil) in controlling hot flashes in breast cancer survivors.** *Ann Oncol* 2000;11(1):17-22. **Abstract**

Stearns V et al. **Paroxetine is an effective therapy for hot flashes: Results from a prospective randomized clinical trial.** *Proc ASCO* 2003;**Abstract 2940**.

Van Patten CL et al. **Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: A randomized, controlled clinical trial.** *J Clin Oncol* 2002;20(6):1449-55. **Abstract**

## Ductal Carcinoma In Situ

### What percentage of your patients with DCIS do you treat with the following:

| | |
|---|---|
| Mastectomy | 15% |
| Lumpectomy with radiation (XRT) | 68% |
| Lumpectomy without XRT | 17% |

### What percentage of your patients with DCIS receive tamoxifen?

| | |
|---|---|
| Receive tamoxifen | 75% |
| Do not receive tamoxifen | 25% |

### Patient is a 61-year-old woman with a 1.8-cm DCIS (intermediate grade, comedo histology, ER-positive) excised with a minimum of **1-cm margins** (patient had a prior hysterectomy).

#### Should this patient receive XRT?

| | |
|---|---|
| Yes | 69% |
| It is an option, but not necessary | 26% |
| No | 5% |

#### Would you prescribe endocrine therapy to this patient?

| | |
|---|---|
| Yes | 47% |
| No | 10% |
| Defer decision to medical oncologist | 43% |

#### Should this patient receive tamoxifen?

| | |
|---|---|
| Yes | 86% |
| It is an option, but not necessary | 12% |
| No | 2% |

Patient is a 61-year-old woman with a 1.8-cm DCIS (intermediate grade, comedo histology, ER-positive) excised with a minimum of **1-mm margins** (patient had a prior hysterectomy).

Should she receive XRT?

| | |
|---|---|
| Yes | 84% |
| It is an option, but not necessary | 7% |
| No | 9% |

Would you prescribe endocrine therapy to this patient?

| | |
|---|---|
| Yes | 50% |
| No | 7% |
| Defer decision to medical oncologist | 43% |

Should she receive tamoxifen?

| | |
|---|---|
| Yes | 91% |
| It is an option, but not necessary | 5% |
| No | 4% |

What results would you expect from a trial comparing tamoxifen to anastrozole in postmenopausal women with DCIS?

**Regarding Toxicity**

| | |
|---|---|
| Less toxicity with anastrozole | 62% |
| No significant difference | 21% |
| Less toxicity with tamoxifen | 9% |
| Don't know | 8% |

**Regarding Efficacy**

| | |
|---|---|
| Greater benefits with anastrozole | 46% |
| No significant difference | 39% |
| Greater benefits with tamoxifen | 6% |
| Don't know | 9% |

The patient has a 0.8-cm noncomedo DCIS in the upper outer quadrant, excised with **1-cm margins**, treated with excision, XRT and tamoxifen. One year later, a nodule in the suture line is excised and found to be **recurrent DCIS**.

What local therapy are you most likely to recommend for each of the following women?

| | 43-year-old | 65-year-old | 78-year-old |
|---|---|---|---|
| Re-excision | 37% | 48% | 62% |
| Mastectomy | 63% | 52% | 38% |

What endocrine therapy are you most likely to recommend for each of the following women?

| | 43-year-old | 65-year-old | 78-year-old |
|---|---|---|---|
| Continue tamoxifen | 5% | 5% | 9% |
| Discontinue tamoxifen and start aromatase inhibitor (with or without ovarian ablation) | 13% | 19% | 25% |
| Refer to an oncologist for an endocrine therapy decision | 82% | 76% | 59% |
| Don't know | — | — | 7% |

Patient is a 43-year-old woman with a 0.8-cm noncomedo DCIS in the upper outer quadrant, excised with **1-cm margins**, treated with excision, XRT and tamoxifen. **One year later**, a nodule in the suture line is excised and found to be **invasive cancer**.

What local therapy are you most likely to recommend?

| | |
|---|---|
| Re-excision | 28% |
| Mastectomy | 72% |

What endocrine therapy are you likely to recommend?

| | |
|---|---|
| Continue tamoxifen | 5% |
| Discontinue tamoxifen and start aromatase inhibitor (with or without ovarian ablation) | 8% |
| Refer to an oncologist for an endocrine therapy decision | 87% |

Patient is a 43-year-old woman with a 0.8-cm noncomedo DCIS in the upper outer quadrant, excised with 1-cm margins, treated with excision, XRT and tamoxifen. **Three years later**, a nodule in the suture line is excised and found to be recurrent DCIS.

What local therapy are you most likely to recommend?

| | |
|---|---|
| Re-excision | 59% |
| Mastectomy | 41% |

What endocrine therapy are you likely to recommend?

| | |
|---|---|
| Continue tamoxifen | 10% |
| Discontinue tamoxifen and start aromatase inhibitor (with or without ovarian ablation) | 3% |
| Discontinue tamoxifen and start aromatase inhibitor alone | 7% |
| Refer to an oncologist for an endocrine therapy decision | 80% |

## Adjuvant Endocrine Therapy

How familiar are you with the ATAC trial?

| | |
|---|---|
| I am not aware of the ATAC trial | 22% |
| I have heard of it, but I am unfamiliar with the results | 33% |
| I am familiar with it, but I would not be comfortable counseling a patient about the results | 31% |
| I am familiar enough with it to counsel patients on the results | 14% |

In the future, if anastrozole generally replaces tamoxifen as adjuvant endocrine therapy for postmenopausal women with ER-positive breast cancer, how likely is it that you will prescribe anastrozole?

| | |
|---|---|
| Very likely | 43% |
| Likely | 18% |
| Somewhat likely | 18% |
| Very unlikely | 21% |

## When you use an aromatase inhibitor in the adjuvant setting, what percentage of this use is for each of the following agents?

| | |
|---|---|
| Anastrozole | 92% |
| Letrozole | 6% |
| Exemestane | 2% |

## Have you prescribed adjuvant aromatase inhibitors in premenopausal women*?

| | |
|---|---|
| Yes | 8% |
| No | 92% |

*Aromatase inhibitors should not be utilized in premenopausal women.

## In how many patients have you switched from adjuvant tamoxifen to an aromatase inhibitor because the patient had difficulty tolerating tamoxifen?

| | |
|---|---|
| Mean | 5 |

## How do you generally counsel the following postmenopausal patients about endocrine therapy?

| | Higher-risk, node-positive | Lower-risk, node-negative |
|---|---|---|
| Generally recommend tamoxifen, and don't discuss aromatase inhibitors as an option | 19% | 27% |
| Generally recommend tamoxifen, but discuss aromatase inhibitors as an option | 22% | 25% |
| Generally discuss tamoxifen and aromatase inhibitors as equal options | 15% | 16% |
| Generally recommend an aromatase inhibitor, but discuss tamoxifen as an option | 8% | 5% |
| Generally recommend an aromatase inhibitor, and don't discuss tamoxifen as an option | 1% | 1% |
| Generally do not counsel these patients about adjuvant endocrine therapy, rather, I defer this discussion to the medical oncologist | 35% | 26% |

# Pathology

## How do you define ER positivity?

| | |
|---|---|
| Any staining | 17% |
| Staining above lab cutoff | 67% |
| Staining above your own cutoff | 1% |
| Some other criteria | 7% |
| Don't know/refused | 8% |

## Do you generally request ER status for DCIS?

| | |
|---|---|
| Yes | 71% |
| No | 29% |

## Do you order IHC on sentinel node specimens?

| | |
|---|---|
| Yes | 55% |
| No | 45% |

## In general, which of the following best describes your ordering of HER2 tests when you first submit specimens from newly diagnosed breast cancer patients with local disease?

| | |
|---|---|
| Don't order HER2 tests when I first submit specimens | 12% |
| Order IHC only when I first submit specimens | 9% |
| Order FISH only when I first submit specimens | 1% |
| Initially order both IHC and FISH | 12% |
| I do not specify the HER2 test, rather just that HER2 testing be done | 66% |

# Risk Assessment and Chemoprevention

## Do you use the Gail model to assess breast cancer risk in women with no prior history of breast cancer?

| | |
|---|---|
| Never | 26% |
| Occasionally | 36% |
| Commonly | 23% |
| Routinely on all patients with breast concerns | 15% |

## Do you use ductal lavage in your practice?

| | |
|---|---|
| No | 84% |
| Occasionally | 16% |

## Do you use tamoxifen for chemoprevention?

| | |
|---|---|
| Yes | 39% |
| No | 61% |

## (Of physicians utilizing tamoxifen) How many women have you started on tamoxifen for chemoprevention in the past year?

| | |
|---|---|
| Mean | 8 |

## What percent of women to whom you offer tamoxifen for chemoprevention accept it?

| | |
|---|---|
| Accept tamoxifen | 73% |
| Do not accept tamoxifen | 27% |

## Which of the following best describes your understanding of the results from the ATAC trial related to the incidence of contralateral breast cancer?

| | |
|---|---|
| Anastrozole reduces the incidence of contralateral breast cancer more than tamoxifen | 31% |
| No difference between anastrozole and tamoxifen | 22% |
| Tamoxifen reduces the incidence of contralateral breast cancer more than anastrozole | 1% |
| Not familiar with these specific results | 46% |

## Which of the following results would you expect from a trial comparing tamoxifen to anastrozole in postmenopausal women at high risk?

### Regarding Toxicity

| | |
|---|---|
| Less toxicity with anastrozole | 62% |
| No significant difference | 25% |
| Less toxicity with tamoxifen | 8% |
| Don't know | 5% |

### Regarding Efficacy

| | |
|---|---|
| Greater benefits with anastrozole | 53% |
| No significant difference | 39% |
| Greater benefits with tamoxifen | 4% |
| Don't know | 4% |

## Have you used anastrozole or another aromatase inhibitor in the prevention setting in a postmenopausal woman at high risk with no previous history of breast cancer*?

| | |
|---|---|
| Yes | 6% |
| No | 94% |

*Aromatase inhibitors are not indicated for breast cancer risk reduction.

# Sentinel Lymph Node Biopsy

## Do you perform sentinel node biopsy in your practice?

| | |
|---|---|
| Yes | 86% |
| No | 14% |

## Which of the following techniques do you generally utilize in performing sentinel lymph node biopsy?

| | |
|---|---|
| Dye | 12% |
| Radioisotope | 9% |
| Both | 79% |

## Do you believe sentinel node biopsy is currently the standard of care for patients with clinical T1N0 disease?

| | |
|---|---|
| Yes | 89% |
| No | 11% |

## Is sentinel node biopsy useful after neoadjuvant chemotherapy?

| | |
|---|---|
| Yes | 60% |
| No | 30% |
| Not sure | 10% |

## Have you done sentinel node biopsy in a woman with DCIS?

| | |
|---|---|
| Yes | 53% |
| No | 47% |

## If you have done sentinel node biopsy in a woman with DCIS, is it routine practice?

| | |
|---|---|
| Yes | 13% |
| No | 87% |

Do you believe sentinel node biopsy is a good option for a woman with two lesions in different quadrants of the breast?

| | |
|---|---|
| Yes | 68% |
| No | 32% |

Do you believe sentinel node biopsy is a good option for a woman with a 2-cm lesion high in the upper-outer quadrant of the tail of Spence?

| | |
|---|---|
| Yes | 67% |
| No | 33% |

## Surgical Issues

Have you performed skin-sparing mastectomy?

| | |
|---|---|
| Yes | 54% |
| No | 46% |

Have you performed modified radical mastectomy on an outpatient basis?

| | |
|---|---|
| Yes | 26% |
| No | 74% |

What percentage of eligible patients in your practice, in each of the following ages, undergo breast conservation therapy?

| | |
|---|---|
| 43-year-old | 87% |
| 65-year-old | 63% |
| 77-year-old | 46% |

In what percentage of your patients is accessibility or travel to radiation therapy a deterrent for choosing breast-conserving surgery?

| | |
|---|---|
| Is a deterrent | 22% |
| Is not a deterrent | 78% |

Have you ever used partial breast irradiation, for example, MammoSite®?

| | |
|---|---|
| Yes | 8% |
| No | 92% |

Patient is a 43-year-old woman with a 2-cm ER-negative, poorly differentiated, infiltrating ductal carcinoma. The patient wishes to have mastectomy and reconstruction.

Which type of reconstruction would you generally recommend?

| | |
|---|---|
| Implants | 38% |
| Latissimus dorsi flap | 4% |
| TRAM flap | 50% |
| Don't know | 8% |

When would you generally recommend the reconstruction be performed?

| | |
|---|---|
| Immediate | 62% |
| 3 to 6 months | 12% |
| After 6 months | 26% |

If the same patient had a prior hysterectomy with a horizontal incision, which type of reconstruction would you generally recommend?

| | |
|---|---|
| Implants | 44% |
| Latissimus dorsi flap | 20% |
| TRAM flap | 28% |
| Don't know | 8% |

When would you generally recommend the reconstruction be performed?

| | |
|---|---|
| Immediate | 61% |
| 3 to 6 months | 14% |
| After 6 months | 25% |

If the same patient was 62 years old with no prior hysterectomy, which type of reconstruction would you generally recommend?

| | |
|---|---|
| Implants | 48% |
| Latissimus dorsi flap | 10% |
| TRAM flap | 32% |
| Don't know | 10% |

When would you generally recommend the reconstruction be performed?

| | |
|---|---|
| Immediate | 58% |
| 3 to 6 months | 14% |
| After 6 months | 24% |
| Don't know | 4% |

## Postmastectomy Radiation

For each of the following women with 3-cm primary tumors, would you recommend postmastectomy radiation therapy?

| | Yes |
|---|---|
| 43-year-old with negative nodes | 10% |
| 43-year-old with 1+ node | 24% |
| 43-year-old with 3+ nodes | 70% |
| 43-year-old with 5+ nodes | 84% |
| 65-year-old with negative nodes | 8% |
| 65-year-old with 1+ node | 26% |
| 65-year-old with 3+ nodes | 50% |
| 65-year-old with 5+ nodes | 82% |
| 78-year-old with negative nodes | 4% |
| 78-year-old with 1+ node | 14% |
| 78-year-old with 3+ nodes | 32% |
| 78-year-old with 5+ nodes | 66% |

# Post-test: Breast Cancer Update for Surgeons, Issue 4, 2003

## Conversations with Clinical Research Leaders

*Bridging the Gap between Research and Patient Care*

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The NSABP is planning a Phase III randomized, prospective trial comparing traditional external beam radiotherapy to partial breast radiotherapy.**
   a. True
   b. False

2. **The efficacy data from the 47-month follow-up of the ATAC trial favors which arm of the study?**
   a. Anastrozole
   b. Tamoxifen
   c. Anastrozole/tamoxifen combination
   d. The efficacy data is equivalent in all three arms

3. **The preliminary analysis of ABCSG-12 demonstrates that zoledronate counteracts bone mineral density deterioration in premenopausal patients with hormone receptor-positive breast cancers treated with goserelin and tamoxifen or anastrozole.**
   a. True
   b. False

4. **If a premenopausal patient experiences amenorrhea following chemotherapy, FSH, LH and estradiol levels should be performed to confirm ovarian failure before considering treatment with aromatase inhibitors.**
   a. True
   b. False

5. **The antidepressant medication venlafaxine is effective in reducing hot flashes in breast cancer survivors.**
   a. True
   b. False

6. **Which of the following agents have been studied for the management of hot flashes?**
   a. Clonidine
   b. Vitamin E
   c. Venlafaxine
   d. Gabapentin
   e. All of the above

7. **Locoregional recurrence is associated with an increased risk of distant metastases.**
   a. True
   b. False

8. **Most surgeons consider SLNB standard of care for TINO breast cancer.**
   a. True
   b. False

9. **NSABP-B-32 randomizes women to undergo SLNB or ALND.**
   a. True
   b. False

10. **In a 2003 nationwide survey of surgical oncologists, a majority considered adjuvant anastrozole to have:**
    a. greater toxicity and less efficacy than tamoxifen
    b. less toxicity but less efficacy than tamoxifen
    c. less toxicity and greater efficacy than tamoxifen

11. **In a 2003 nationwide survey of surgical oncologists, the majority reportedly requested ER status for DCIS.**
    a. True
    b. False

*Post-test Answer Key: 1a, 2a, 3a, 4a, 5a, 6e, 7a, 8a, 9a, 10c, 11a*

# Evaluation Form: Breast Cancer Update for Surgeons, Issue 4, 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 your 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 4

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

- Consider the absolute and relative contraindications of sentinel lymph node biopsy when deciding on optimal surgical management of the axilla ..... 5 4 3 2 1
- Evaluate the major cooperative group trials of sentinel lymph node biopsy in order to counsel patients regarding participation ..... 5 4 3 2 1
- Describe the ongoing clinical trials of systemic therapy for DCIS ..... 5 4 3 2 1
- Discuss the results of the ATAC trial and the implications of treating postmenopausal women with ER-positive breast cancer ..... 5 4 3 2 1
- Counsel breast cancer patients and survivors about nonestrogenic treatment alternatives for women with severe hot flashes ..... 5 4 3 2 1
- Consider the potential benefits and limitations of partial breast irradiation compared to whole breast radiation therapy ..... 5 4 3 2 1

## EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

| Faculty | Knowledge of Subject Matter | Effectiveness as an Educator |
|---|---|---|
| William C Wood, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Norman Wolmark, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Aman Buzdar, MD, FACP | 5 4 3 2 1 | 5 4 3 2 1 |
| David N Krag, MD, FACS | 5 4 3 2 1 | 5 4 3 2 1 |
| Charles Loprinzi, 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 4, 2003

*Please Print Clearly*

Name: _____

Specialty: _____ ME#: _____ Last 4 digits of SS# (required): _____

Street Address: _____ Box/Suite: _____

City: _____ State: _____ Zip Code: _____

Phone Number: _____ Fax Number: _____Email: _____

NL Communications Inc designates this educational activity for a maximum of 2.75 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

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

Signature: _____

**Will the information presented cause you to make any changes in your practice?**

___Yes ___No

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

_____

_____

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

_____

_____

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

_____

_____

**Degree:**

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

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: NL Communications Inc, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.