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 CD or tape, review the monograph and complete the post-test and evaluation form on page 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**.

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
exemestane	Aromasin®	Pharmacia Corporation
raloxifene	Evista®	Eli Lilly & Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
pamidronate	Aredia®	Novartis Pharmaceuticals Corporation

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 2, 2003, of Breast Cancer Update for Surgeons consists of discussions with four research leaders on a variety of important topics, including updated data from the ATAC trial, sentinel node biopsy, intraoperative radiation therapy, postmastectomy radiation and clinical trials of breast cancer chemoprevention.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 2

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

- Evaluate the risk/benefit profile of anastrozole as adjuvant hormonal therapy compared to tamoxifen and other third-generation aromatase inhibitors for postmenopausal patients with estrogen receptor-positive breast cancer in order to counsel patients on adjuvant therapy options.
- Determine which clinical trials are available to patients who are at high risk for developing breast cancer in order to counsel select patients who are interested in breast cancer chemoprevention.
- Evaluate the role of surgical resection of a primary lesion in the management of patients presenting *de novo* with metastatic breast cancer.
- Determine for which patients postmastectomy and/or intraoperative radiotherapy or enrollment in an ongoing clinical trial would be appropriate.

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

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Editor's Note

Equipoise in Clinical Trials

The current practice of breast cancer medicine — and for that matter, medical care in general — is dominated by the need for research-based evidence to support clinical decision-making. At the core of relevant clinical investigation is the randomized trial, and one of the great challenges in designing these critical studies is the requirement for randomization arms that physicians can ethically and comfortably discuss with their patients. Researchers often state that they must be "in equipoise with the options": all of the randomization arms are essentially equivalent, until proven otherwise.

In this issue, we follow up on a series of tumor panel discussions conducted at the 2003 Miami Breast Cancer Conference and interview two faculty participants, Drs Monica Morrow and Jay Harris. One of the fascinating aspects of the Miami meeting was the keypad polling related to a number of current randomized trials. We focused on some of the most controversial studies: RTOG-9915, which randomizes women with one to three positive axillary nodes to either postmastectomy radiation therapy or observation; American College of Surgeons ACOS-Z-11, which randomizes women with positive sentinel node biopsies to either axillary lymph node dissection or not; and IBIS-II, which randomizes high-risk postmenopausal women to either the aromatase inhibitor, anastrozole, or placebo.

During the Miami meeting, the attendees were asked what advice they would give to their own patients about participation in these studies. We were interested in this topic not only from a research perspective, but also to gain another view of what people consider standard of care. Both Drs Morrow and Harris support the postmastectomy radiation trial, but acknowledge how difficult this randomization is for both patients and physicians to accept. In this regard, they reflected on another study with a challenging randomization — the classic NSABP-B-06 trial — which randomized women to either lumpectomy or mastectomy.

Dr Morrow encourages patients to enter the ACOS sentinel node trial, but she has ethical reservations about IBIS-II because she finds the placebo arm problematic in the presence of NSABP data demonstrating a proven breast cancer risk reduction effect from tamoxifen. Another interviewee, Dr Michael Baum, staunchly defends IBIS-II because he feels the overall health benefit of tamoxifen in women who are at high risk of developing breast cancer is marginal or nonexistent.

The other speaker on this issue, Dr Bernard Fisher — who is widely viewed as the "father of breast cancer clinical research" — launched and championed NSABP-B-06 in a furor of controversy several decades ago. Dr Fisher supports trials evaluating aromatase inhibitors in women who are at high risk for developing breast cancer, but he is more interested in "paradigm-breaking" studies that will have a fundamental effect on our understanding of the disease.

These debates are relevant not only to the research community, but to all physicians providing care to breast cancer patients. The current Phase III randomized trials will set new standards for therapy over the next decade, and practitioners must be aware, in advance, of the issues and controversies likely to evolve as these trials mature. Perhaps of even greater relevance is that discussions about ongoing studies provide perspectives on how the most experienced breast cancer research leaders view the subtleties of the risks and benefits of current available interventions. Ultimately, the issue of equipoise with multiple treatment options is a daily part of breast cancer medicine. Through this series, we attempt to provide further perspectives on this challenging issue.

—Neil Love, MD

2003 Miami Breast Cancer Conference: Attendees' response to tumor panel cases

CASE 1: 63-year-old woman with atypical hyperplasia and a family history of breast cancer (mother at age 54, sister at age 58).

Outside a clinical trial, what intervention, if any, should be suggested?

None	8%
Bilateral prophylactic mastectomies	6%
Tamoxifen	76%
Other chemoprevention	6%
Other	3%

If this woman were eligible for the following trials, what advice should she be given regarding participation?

	STAR (tamoxifen vs raloxifene)	IBIS-II (anastrozole vs placebo)
Strongly encourage	58%	19%
Provide option, do not strongly encourage	35%	38%
Discourage	6%	7%
Discourage - don't like placebo	—	35%
Other	1%	1%

CASE 2: 37-year-old premenopausal patient with a 2.1-cm, ER-positive, HER2-positive breast cancer. Modified radical mastectomy with immediate implant reconstruction is performed, and axillary dissection reveals three positive nodes.

	YES	NO
Should regional radiation therapy generally be recommended?	36%	64%
If she were to receive regional radiation, should the tissue expander be removed prior to radiation treatment?	23%	77%

If she were eligible for Intergroup trial (SWOG-S9927; RTOG-9915) comparing radiation therapy to observation, what advice should she be given regarding participation?

Strongly encourage	35%
Provide option, do not strongly encourage	48%
Discourage	17%

Monica Morrow, MD

Professor of Surgery
Northwestern University Feinberg School of Medicine
Director, Lynn Sage Comprehensive Breast Program
Northwestern Memorial Hospital

Edited comments by Dr Morrow

The significance of micrometastatic disease

The increasing use of sentinel node biopsy has raised a whole new set of questions, including whether micrometastases detected by immunohistochemistry are clinically significant. This is a biologically interesting question, and I strongly agree with the College of American Pathologists' consensus statement that we do not yet understand the meaning of these micrometastases. The retrospective studies of micrometastases have been a "mixed bag," including patients who have large areas of missed tumor in their lymph nodes and patients with small numbers of cells in subcapsular sinuses that aren't even in the node parenchyma. It's not particularly surprising that some of these studies show no survival difference, some show small survival differences, and some show very big survival differences.

This is an area where both the NSABP-B-32 sentinel node study and the American College of Surgeons Z-10 study will provide us with very important information. Until that information is available, we use immunohistochemistry only if there's diagnostic uncertainty on the basis of something seen on an H&E stain. We do not routinely perform immunohistochemical staining of sentinel lymph nodes because we don't know what to tell the patients.

AJCC staging system revisions for lymph node micrometastases

"The sixth edition of the *AJCC Cancer Staging Manual*… records an additional descriptor (i) for 'immunohistochemical' in cases that are histologically negative by H&E for lymph node metastasis and in which IHC techniques were used. For example, the designation pN0(i+) would indicate a case that was H&E-negative but in which an isolated tumor cell deposit not greater than 0.2 mm in greatest dimension was identified by IHC. Likewise, the designation pN1mi(i+) would indicate a case that was H&E-negative but in which a micrometastasis greater than 0.2 mm but not greater than 2.0 mm in greatest dimension was identified by IHC."

SOURCE: Singletary SE et al. **Revision of the American Joint Committee on Cancer Staging System for Breast Cancer.** *J Clin Oncol* 2002;20:3628-36. Abstract

Clinical use of adjuvant aromatase inhibitors

The follow-up data with anastrozole from the ATAC trial look good and suggest that the bone problems may be reaching a plateau, which is encouraging. For women with low-risk, ER-positive, HER2-negative breast cancers with very favorable prognosis, we still use as much tamoxifen as anastrozole. For women with HER2-positive breast cancers, I favor an aromatase inhibitor because of the debate as to whether overexpression of HER2 predicts resistance to tamoxifen.

If the patient's prognosis is less favorable, I would be more likely to treat her with an aromatase inhibitor. There is clearly a greater benefit from anastrozole compared to tamoxifen in the short term. In a patient whose risk of relapse is quite high, the absolute difference between these two treatments is much larger. I would favor an aromatase inhibitor in this setting, and the data we have right now in the adjuvant setting is with anastrozole.

Aromatase inhibitors for chemoprevention and DCIS

The question about aromatase inhibitors as preventive agents is a very important one. I am concerned that the IBIS-II trial — comparing anastrozole to placebo — won't give us the answer we need. We'll know if anastrozole is better than a placebo but we won't know how SERMs compare to aromatase inhibitors or which is better in terms of overall health. We will not be able to extrapolate these answers from two completely different study populations, and this will leave us with another trial to do. In addition, I would not recommend this trial to a woman at very high risk. With tamoxifen on the market, proven to reduce breast cancer risk, I don't think taking a 50 percent chance of being randomized to a placebo is a good choice. IBIS-II also has a randomization for women with DCIS, but this compares anastrozole to tamoxifen. I agree that treating DCIS is prevention — it's a lesion that carries a significantly increased risk of invasive breast cancer. We tend to think of it differently because we treat it like cancer, but the question is the same. The NSABP-B-35 trial is asking the same question, randomizing women with DCIS to anastrozole versus tamoxifen. It is a very good trial, addressing a very important question, and I heartily support that study.

Aromatase inhibitors for chemoprevention and DCIS

Protocol ID	Eligibility	Randomization	Accrual target
IBIS-II	DCIS High risk	Anastrozole versus tamoxifen Anastrozole versus placebo	4,000 6,000
NSABP-B-35	DCIS	Anastrozole versus tamoxifen	3,000

Management of the primary breast lesion in women presenting with metastatic disease

I have traditionally thought that we should only treat the primary tumor if it was progressing and causing local problems; however, last year my colleague Seema Kahn and I published a study in the *Journal of Surgery* of 15,000 women who presented with metastatic disease from the National Cancer Database of the American College of Surgeons.

We looked at differences in survival based on surgical treatment of the primary lesion versus no surgery. This was based on tumor registry data. We controlled for a number of documented metastatic sites and visceral versus soft tissue, and we found a very consistent pattern wherein surgical treatment of the primary lesion was associated with improved survival. While there may be selection bias to some extent, the differences were seen in all subgroups.

This study raises some questions as we develop more effective systemic therapy and keep people alive longer: Does it make sense to reduce the tumor burden maximally so there are fewer places the treatment has to work? We see this in renal cell carcinoma for example, where removal of the primary tumor results in survival differences. I think it's an open question. However, removal of the primary lesion is a reasonable option to try to maintain local control and prevent morbidity, even if it doesn't improve survival. If the patient is clinically node-negative, I don't see that there's a lot to be gained by dissecting the axilla.

Impact of local therapy and margin status on survival in patients with metastatic disease: A review of 16,023 patients

	3-year survival	5-year survival	Median survival
No surgery	17.3%	6.7%	11.9 months
Clear margins			
Partial mastectomy	34.7%	16.6%	22.9 months
Total mastectomy	35.7%	18.4%	25.3 months
Involved margins			
Partial mastectomy	26.4%	11.3%	17.6 months
Total mastectomy	26.1%	11.5%	20.0 months

DERIVED FROM: Khan SA et al. **Does aggressive local therapy improve survival in metastatic breast cancer?** *Surgery* 2002;132(4):620-7. Abstract

Emerging evidence of benefit from local control of the primary tumor in patients with metastatic disease

"…there is an emerging body of data that challenges the previously held assumption that local control of a primary tumor is irrelevant in the setting of metastatic disease. This spans different organ sites (kidney, breast, stomach, colon), and although much of this information comes from retrospective, uncontrolled studies, there is a sufficient degree of consistency to justify a prospective randomized trial dealing with this issue."

SOURCE: Khan SA et al. **Does aggressive local therapy improve survival in metastatic breast cancer?** *Surgery* 2002;132(4):620-7. Abstract

2003 Miami Breast Cancer Conference: Attendees' response to tumor panel cases (cont)

CASE 3: 58-year-old postmenopausal patient presented four years ago with a 4-cm, ER-positive, HER-negative breast cancer. Bone scan revealed multiple lesions in the ribs, skull and spine. Chest X-ray and CT scan demonstrated multiple bilateral pulmonary nodules. The patient was treated with pamidronate and FAC. After six cycles of chemotherapy, the breast mass decreased to 1 cm, the pulmonary nodules decreased in size, and bone pain resolved. Chemotherapy was stopped, and the patient was switched to tamoxifen.

What should be the suggested management of the breast lesion at this time?

No specific therapy at this time	25%
Excision	23%
Excision and local radiation	24%
Excision, axillary dissection +/- local radiation	11%
Mastectomy +/- axillary dissection +/- local radiation	17%

CASE 4: 58-year-old with a 1-cm palpable lesion, which on core biopsy proved to be an ER-positive, HER2-positive breast cancer. The patient has been on hormone replacement therapy for six years for severe vasomotor symptoms unresponsive to other interventions.

Outside of a clinical trial, what intervention should be suggested regarding HRT?

Continue	0%
Stop immediately	72%
Gradually taper down and stop over several weeks	24%
Gradually taper down and stop over several months	4%

Patient is treated with a lumpectomy and SLNB is negative. If she were eligible for NSABP-B-32, comparing axillary dissection to no further surgery, what advice should she be given regarding participation?

Strongly encourage	33%
Provide option, do not strongly encourage	39%
Discourage	28%

What endocrine therapy, if any, should be suggested?

None	1%
Tamoxifen	37%
Anastrozole	60%
Other aromatase inhibitor	2%

Select publications

Lymph node micrometastases

Liang WC et al. **Is a completion axillary dissection indicated for micrometastases in the sentinel lymph node?** *Am J Surg* 2001;182(4):365-8. **Abstract**

Noguchi M. **Therapeutic relevance of breast cancer micrometastases in sentinel lymph nodes.** *Br J Surg* 2002;89(12):1505-15. **Abstract**

Tan LK et al. **Occult/micrometastases in axillary lymph nodes of breast cancer patients are significant: A retrospective study with long-term follow-up.** *Proc ASCO* 2002;**Abstract 146.**

Tjan-Heijnen VC et al. **Micro-metastases in axillary lymph nodes: An increasing classification and treatment dilemma in breast cancer due to the introduction of the sentinel lymph node procedure.** *Breast Cancer Res Treat* 2001;70(2):81-8. **Abstract**

Jay R Harris, MD

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Edited comments by Dr Harris

Accrual to RTOG-9915/SWOG-S9927: Postmastectomy radiation therapy versus observation in women with one to three positive nodes

It's pretty clear that women with four or more positive nodes should receive postmastectomy radiation therapy, and women with negative nodes — unless the margins are positive — should not receive radiation therapy. The uncertainty is in women with one to three positive nodes. Unfortunately, accrual to the trial addressing this issue has been extremely slow.

We participated in the trial but found it very hard to do in Boston. I think it suggests that patients and their physicians feel strongly that they should or should not receive radiation. Unlike a trial comparing a medication to a placebo, in which patients don't know what they are receiving, patients know when they're being treated with radiation. This trial might actually close without an answer, which would be very unfortunate.

Outside of participating in a clinical trial, we try to use other factors to sway us one way or the other regarding the administration of radiotherapy. The most obvious factor is whether the woman has three positive nodes or one. We are also convinced that lymphatic vessel invasion, tumor size, closeness to the margins of resection and young patient age are important prognostic factors with regard to local recurrence.

Potential risks of postmastectomy radiation therapy

Long-term cardiac toxicity is the biggest concern we've had over the years, particularly for tumors in the left breast. Fortunately, technology has come to our aid, and radiation treatment is now planned and simulated by CT scan, allowing us to contour the heart and devise beams to minimize treating the heart. Use of CT simulation is rapidly becoming standard across the country. Patients and physicians should ask for this as a part of their treatment planning.

The other significant issue is increased risk of arm edema. If an axillary dissection has been performed, the risk of edema is in the range of 10 to 15 percent. This risk may increase with radiotherapy, depending on how the radiotherapy is done. It is critical whether or not the radiation is applied to the dissected area or to the adjacent nodal areas. You can double the risk of arm edema if you add radiation after a fairly thorough dissection; however, if it's a more limited dissection and radiation stays away from that area, the increase in arm edema is quite modest.

Phase III Randomized Study of Radiotherapy after Mastectomy and Adjuvant Chemotherapy and/or Hormonal Therapy in Women with Stage II Breast Cancer with One to Three Positive Nodes Open Protocol

Protocol IDs: SWOG-S9927, ACOSOG-S9927, CAN-NCIC-SWOG-S9927, CLB-49910, E-S9927, NCCTG-S9927, NSABP-SWOG-S9927, RTOG-9915, GUMC-00223

Expected Accrual: 2,500 patients

Eligibility: Patients with Stage II breast cancer ≤ 5 cm, with one to three positive nodes, who have undergone modified radical mastectomy with a level I and II axillary dissection and ≥ 10 nodes examined within the past 8 months; negative surgical margins; and no gross extracapsular disease or residual disease to the axilla.

ARM 1: Radiotherapy 5 days a week x 5 weeks

ARM 2: Observation

Study Contacts

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SOURCE: NCI Physician Database Query, April 2003.

Postmastectomy radiation therapy and breast reconstruction

There is a negative interaction between postmastectomy radiation therapy and implants. There is a significant problem with cosmetic results, and the chances for encapsulation and fat necrosis are significantly increased with irradiation of implants. We tell our patients that there is a 50 percent chance that they will need to remove the implant. In addition, it is difficult to contemplate putting an implant in after radiation. Although we're still learning in this area, a common belief is that these patients should have flap reconstruction. Most plastic surgeons would rather bring in fresh tissue with a fresh blood supply. Our preliminary findings suggest that radiation therapy in a patient with a flap has a much more modest effect on the cosmetic result than radiation therapy in a patient with an implant.

We don't know the optimal timing of radiation therapy with respect to the flap; however, based on anecdotal information, the preference is to do the radiation first and then perform flap reconstruction. Within our medical community, if there's a hint that the patient might need radiation, they'll be told to hold off on reconstruction. Sentinel lymph node biopsy is helpful in that we are obtaining some indication about the nodal status earlier on, which facilitates decision-making.

Status of research on partial breast irradiation

I sometimes joke that McDonald's is one of America's great contributions to world civilization — fast is good. There's an interest in finding a way to do radiation in less than six weeks. One method of partial breast irradiation involves the surgeon putting a balloon into the biopsy cavity soon after the resection and using high-dose-rate radiation on an outpatient basis twice a day for five days to deliver radiation to a local area.

We have very limited information about this procedure, but there is a great deal of interest from patients. It has received FDA approval based on short-term Phase I data, and many people around the country are already certified or trained. The NSABP is considering looking at partial breast irradiation in a randomized trial, which would be wonderful. We are finalizing our own Phase I study at Dana-Farber and Brigham and Women's Hospital in a low-risk group of older node-negative patients who do not have an extensive intraductal component or lymphatic vessel invasion. Our view as a group is that right now, based on the available data, we will only use this approach as part of a protocol and carefully follow those patients.
The biggest surgical issue seems to be the proximity to the skin, because if there isn't much distance from the balloon to the skin, the skin may receive a substantial dose of radiation that could result in cosmetic problems. This would defeat the purpose of this technology: to attain local control and a cosmetic result as good as that of six weeks of external beam radiation.

Select publications

Partial breast irradiation

Baglan KL et al. **Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT).** *Int J Radiat Oncol Biol Phys* 2003;55(2):302-11. **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**

Krishnan L et al. **Breast conservation therapy with tumor bed irradiation alone in a selected group of patients with stage I breast cancer.** *Breast J* 2001;7(2):91-6. **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**

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**

Vicini FA et al. **Accelerated treatment of breast cancer.** *J Clin Oncol* 2001;19(7):1993-2001. **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**

Michael Baum, MD, ChM, FRCS, FRCR

Professor Emeritus of Surgery
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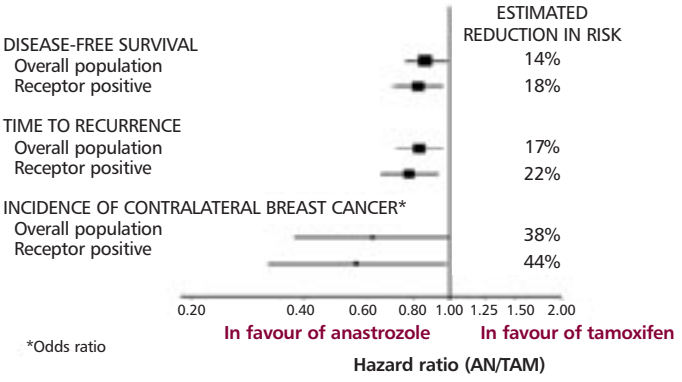
Edited comments by Professor Baum

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

The new ATAC trial data gives me comfort and a sense of vindication that we waited a year before starting to make therapeutic recommendations. Last year I needed persuasion to use adjuvant anastrozole. It was a nice option if tamoxifen could not be tolerated or was contraindicated.

This year, however, with the updated efficacy and safety data, my position has changed. Now my default therapy for postmenopausal women with estrogen receptor-positive tumors is anastrozole, unless contraindicated. We have another year of follow-up in the ATAC trial, and I am impressed by the separation of the curves. The safety update is also comforting. The fracture rate isn't racing away, the relative risks are stable, and the other safety profile issues continue to strongly favor anastrozole.

ATAC trial 47-month updated efficacy data



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

ATAC trial 47-month updated safety data

Adverse events	Anastrozole (A) N=3092	Tamoxifen (T) N=3093	Relative risk A/T
Endometrial cancer	3 (0.1%)	15 (0.7%)	0.20
Vaginal bleeding	147 (4.8%)	270 (8.7%)	0.54
Vaginal discharge	94 (3.0%)	378 (12.2%)	0.25
Cerebrovascular events	34 (1.1%)	70 (2.3%)	0.49
Thromboembolic events	68 (2.2%)	116 (3.8%)	0.59
Hot flashes	1082 (35.0%)	1246 (40.3%)	0.87
Musculoskeletal disorders	936 (30.3%)	732 (23.7%)	1.28
Fractures	219 (7.1%)	137 (4.4%)	1.60

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.

Clinical trials of anastrozole in the prevention setting

Some might argue that the reduction of contralateral breast cancers in ATAC looks less promising with the updated data than with the original data — it has gone from about a 60 percent relative reduction to about a 50 percent relative reduction in contralateral breast cancer in the estrogen receptor-positive group. We had the same experience early on with tamoxifen. The extremely dramatic difference seen at three years was reduced over the next few years.

This suggests that these endocrine agents don't prevent cancer, but rather delay the appearance of cancer. Perhaps anastrozole delays the appearance of breast cancer longer than tamoxifen. I am confident that anastrozole will reduce the risk of estrogen receptor-positive breast cancers — the adjuvant setting will predict the preventive setting. The issue to me is the trade-off and harm/benefit ratio.

Breast conservation rates in the ATAC trial

Gershon Locker presented breast conservation rates in the ATAC trial at the 2002 San Antonio Breast Cancer Symposium. The dramatic finding is that breast conservation is much less common in the United States than in the United Kingdom and other countries. This study shows the beauty of this incredible international database, which allows us to explore cultural differences. It is fascinating that the two countries with the highest rates of breast conservation were France — which is not unexpected — and Brazil. Brazilians are obsessed with the "body beautiful," but in addition, most Brazilian radiotherapists are trained in France, so we see an interesting cultural issue.

In fairness to the Americans, we should not overinterpret these data. The United Kingdom is a small country in which everyone lives within 100 miles of a radiotherapy center. In contrast, parts of the United States are thousands of miles from a radiotherapy center. Radiation therapy consists of six weeks of treatment. I can sympathize with women for whom it is just impractical to have breast-conserving surgery.

Intraoperative radiation therapy

This technology, in theory, could allow us to give all radiotherapy at the time of surgery with a portable machine in a community hospital. We have a neatly packaged mobile electron generator that delivers X-rays at the tip of the probe. You can remove the tumor, apply a spherical applicator to the tumor bed cavity, wrap the tumor bed around this applicator and deliver radiotherapy to the index quadrant. The whole process adds only one-half an hour to the operating time.

This technique gives the biological equivalent dose of 50 Gy to the tumor bed. The geometry is better than conventional radiotherapy. Traditional conformal radiotherapy conforms to an uncertain shape. With this method, we conform the cavity to the radiotherapy source, so I think we'll do better than with conventional external beam radiation therapy.

We did a Phase II study in 40 patients, and although I distrust Phase II studies, it appears extremely safe and has excellent cosmetic results. Only one woman developed ulcerated skin, which ultimately healed. In this series, over the maximum four or five years of follow-up, we have not had a single local recurrence.

We have opened an exciting trial, randomizing patients to conventional postoperative radiotherapy versus intraoperative radiotherapy. We're hoping to enroll 2,000 patients in the study, so we need to "spread our wings." There is enormous interest, and we have started randomization. We have groups in Australia, North America and Germany.

Select publications

Use of aromatase inhibitors in the adjuvant setting

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(9324):2131-9. **Abstract**

Buzdar AU. **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**.

Locker G et al. **Breast surgery in the ATAC trial: Women from the United States are more likely to have mastectomy.** *Breast Cancer Res Treat* 2002;**Abstract 27**.

Vaidya JS et al. **Targeted intraoperative radiotherapy (TARGIT) for breast cancer: An international trial.** *Breast Cancer Res Treat* 2002;**Abstract 452**.

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

Bernard Fisher, MD

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University of Pittsburgh
Past Chairman and Scientific Director
National Surgical Adjuvant Breast and Bowel Project
(NSABP)

Edited comments by Dr Fisher

Preoperative systemic therapy

Most of the early NSABP trials — the so-called "paradigm-shifting" trials — arose from research in my laboratory. We evaluated what we now call translational research — transferring laboratory research data into clinical practice. The concept of preoperative chemotherapy started in my laboratory in the 1980s.

Animal studies showed that the tumor kinetics are different when you remove the tumor compared to treating it before surgery with radiation therapy, tamoxifen or cytotoxic agents. These observations resulted in the concept of preoperative therapy.

The NSABP-B-18 trial was the first well-designed, randomized clinical trial that evaluated the importance of the timing of chemotherapy. Early studies of preoperative chemotherapy suggested that it doesn't really matter whether you give therapy before or after surgery in terms of distant disease-free and overall survival.

However, the use of preoperative therapy may be of value as a biological tool. The most important issue is whether or not you can use preoperative therapy as a surrogate for determining who will benefit from systemic therapy. Essentially, the question is, "Can we determine, based on how patients respond to therapy in the first 63 days, who will benefit in terms of disease-free and overall survival?"

The next question to be addressed is, "Would more effective tumor reduction translate into more complete responders, and, if so, would that therapy be more likely to have a beneficial effect on distant disease?" If not, then use of some other systemic therapy should be considered.

Biologic tumor markers and neoadjuvant therapy

"Clinical and pathological response are, at best, crude and late indicators of overall outcome. The key potential of neoadjuvant therapy is to identify and validate biological markers during therapy that may predict early for long-term outcome. These may be biomarkers that are predictive of overall response, predictive of chemoresistance or predictive of response to particular agents. Breast cancer presents an ideal model for this research because of the ease of access to tumour tissue by fine-needle or core biopsy. Several biological markers have been studied in this setting including proliferation with Ki-67, apoptosis, proliferating fraction, ER, PgR, c-erbB2, bcl-2 and p53."

SOURCE: Shannon C, Smith I. **Is there still a role for neoadjuvant therapy in breast cancer?** *Crit Rev Oncol/Hematol* 2003;45:77-90. Abstract

Mastectomy versus breast-conserving surgery

One of my agendas associated with preoperative chemotherapy was to eliminate the need for most mastectomies by the year 2000. Mastectomy should not be used as a primary locoregional therapeutic approach in most patients. If a patient has a tumor too large to perform a lumpectomy, then that patient should receive preoperative chemotherapy before considering mastectomy. Some patients may still require mastectomy, but currently we are seeing complete clinical disappearance of tumors in 50 to 60 percent of patients. This improvement in our approach to breast cancer is another step that we've taken in going from radical to modified to simple mastectomy, to quadrantectomy to lumpectomy and finally to preoperative reduction allowing for lumpectomy.

A commentary on the 20-year results evaluating mastectomy versus breast-conserving surgery

"What proportion of women with breast cancer should receive breast-conserving therapy? The answer depends on the particular population of women, but a reasonable goal is that every woman should be informed of the availability of breast-conserving therapy and of the suitability of the procedure in her particular case. In a study of 231 women with breast cancer who were seen for a second opinion between 1996 and 1999, Clauson et al reported that 29 percent of the women had been offered only the option of a mastectomy during the initial consultation. ...

"Efforts to expand eligibility for breast-conserving therapy and to reduce the associated morbidity are well under way. Preoperative chemotherapy and endocrine therapy have been shown to be safe and effective ways to shrink tumors that are too large for a lumpectomy with a good cosmetic result. Accelerated fractionation schedules and brachytherapy are being studied as alternatives to six weeks of external-beam irradiation. However, if we do not apply what we have learned from the pioneering work of Fisher and Veronesi and their colleagues to the treatment of the women with breast cancer we see today, we will have made little or no progress over the past 20 years in the search for a rational approach to the local treatment of breast cancer. It is time to declare the case against breast-conserving therapy closed and focus our efforts on new strategies for the prevention and cure of breast cancer."

SOURCE: Morrow M. **Rational local therapy for breast cancer.** *N Engl J Med* 2002;347(16):1270-71.

Chemoprevention of breast cancer

NSABP-P-1 demonstrated a proof of principle. Tamoxifen prevented the clinical expression of breast cancers in about 50 percent of high-risk women. Epidemiologists question whether this is true prevention or whether we're simply treating early at the level of phenotypic expression. That's possible, but I'm certain that there will be other candidates for prevention, such as the aromatase inhibitors. These agents have less toxicity, which will make them ideal candidates for testing in the prevention setting.

As the mechanisms for detecting breast cancer improve, we are going to detect more lesions that are "preventable." The prognosis for these women is so good that we don't see why we should treat them. However, in the prevention mode we are treating these women and are very happy to reduce their risk of breast cancer by 50 percent. We are in a conundrum, "Should we treat them or not?"

Select publications

Preoperative (neoadjuvant) systemic therapy

Anderson TJ et al. **Effect of neoadjuvant treatment with anastrozole on tumour histology in postmenopausal women with large operable breast cancer.** *Br J Cancer* 2002;87(3):334-8. **Abstract**

Burstein HJ et al. **Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: A pilot study.** *J Clin Oncol* 2003;21(1):46-53. **Abstract**

Dixon JM et al. **Neoadjuvant endocrine therapy of breast cancer: A surgical perspective.** *Eur J Cancer* 2002;38(17):2214-21. **Abstract**

Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16. **Abstract**

Geisler J et al. **Influence of neoadjuvant anastrozole (Arimidex) on intratumoral estrogen levels and proliferation markers in patients with locally advanced breast cancer.** *Clin Cancer Res* 2001;7(5):1230-6. **Abstract**

Heys SD et al. **Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial.** *Clin Breast Cancer* 2002;3 Suppl 2:S69-74. **Abstract**

Newman LA et al. **A prospective trial of preoperative chemotherapy in resectable breast cancer: Predictors of breast-conservation therapy feasibility.** *Ann Surg Oncol* 2002;9(3):228-34. **Abstract**

NSABP. **The effect on primary tumor response of adding sequential Taxotere to Adriamycin and cyclophosphamide: Preliminary results from NSABP Protocol B-27.** *Breast Cancer Res Treat* 2001;**Abstract 5.**

Paciucci PA et al. **Neo-adjuvant therapy with dose-dense docetaxel plus short-term filgrastim rescue for locally advanced breast cancer.** *Anticancer Drugs* 2002;13(8):791-5. **Abstract**

Smith IC et al. **Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel.** *J Clin Oncol* 2002;20(6):1456-66. **Abstract**

van der Hage JA et al. **Preoperative chemotherapy in primary operable breast cancer: Results from the European Organization for Research and Treatment of Cancer trial 10902.** *J Clin Oncol* 2001;19(22):4224-37. **Abstract**

von Minckwitz G et al. **Dose-dense doxorubicin, docetaxel, and granulocyte colony-stimulating factor support with or without tamoxifen as preoperative therapy in patients with operable carcinoma of the breast: A randomized, controlled, open phase IIb study.** *J Clin Oncol* 2001;19(15):3506-15. **Abstract**

Wolmark N et al. **Preoperative chemotherapy in patients with operable breast cancer: Nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18.** *J Natl Cancer Inst Monogr* 2001;(30):96-102. **Abstract**

Post-test: Breast Cancer Update for Surgeons, Issue 2, 2003

Conversations with Clinical Research Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. NSABP-B-35 randomizes patients with DCIS to tamoxifen or _____.
- a. Exemestane
- b. Anastrozole
- c. Letrozole
- d. Fulvestrant

2. The IBIS-II chemoprevention trial evaluates anastrozole versus placebo in high-risk women.
- a. True
- b. False

3. Khan, Morrow et al demonstrated that, compared to no surgery, resection of the primary tumor in patients presenting *de novo* with metastatic disease result in:
- a. Inferior overall survival
- b. Equivalent overall survival
- c. Improvement in overall survival

4. SWOG-S9927 randomizes patients with one to three positive nodes to either postmastectomy radiotherapy or observation.
- a. True
- b. False

5. The rate of arm edema after axillary dissection without radiation therapy is approximately:
- a. 10 to 15 percent
- b. 25 to 30 percent
- c. 40 to 50 percent

6. According to Dr Harris, radiation therapy after placement of implants results in implant removal in:
- a. <10 percent of patients
- b. 25-35 percent of patients
- c. >50 percent of patients

7. TRAM flap reconstruction is often preferred in patients who will need to undergo radiation therapy.
- a. True
- b. False

8. Partial breast irradiation may be completed in approximately:
- a. one week
- b. two weeks
- c. three weeks
- d. four weeks
- e. five weeks

9. In the ATAC trial (with 47-month follow-up), anastrozole resulted in a _____ relative reduction in contralateral breast cancers relative to tamoxifen.
- a. 10 percent
- b. 28 percent
- c. 44 percent
- d. 90 percent

10. In the ATAC trial (with 47-month follow-up), anastrozole was superior to tamoxifen in terms of disease-free survival.
- a. True
- b. False

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

Evaluation Form: Breast Cancer Update for Surgeons, Issue 2, 2003

NL Communications 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 only 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 2

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

- Evaluate the risk/benefit profile of anastrozole as adjuvant hormonal therapy compared to tamoxifen and other third-generation aromatase inhibitors for postmenopausal patients with estrogen receptor-positive breast cancer in order to counsel patients on adjuvant therapy options 5 4 3 2 1
- Determine which clinical trials are available to patients who are at high risk for developing breast cancer in order to counsel select patients who are interested in breast cancer chemoprevention 5 4 3 2 1
- Evaluate the role of surgical resection of a primary lesion in the management of patients presenting *de novo* with metastatic breast cancer 5 4 3 2 1
- Determine for which patients postmastectomy and/or intraoperative radiotherapy or enrollment on an ongoing clinical trial would be appropriate 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Monica Morrow, MD	5 4 3 2 1	5 4 3 2 1
Jay R Harris, MD	5 4 3 2 1	5 4 3 2 1
Michael Baum, MD, ChM, FRCS, FRCR	5 4 3 2 1	5 4 3 2 1
Bernard Fisher, 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 2, 2003

Please Print Clearly

Name: _____

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Street Address: _____ Box/Suite: _____

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Phone Number: _____ Fax Number: _____Email: _____

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 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.