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Breast Cancer™ UPDATE

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

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Breast Cancer Update for Surgeons
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer screening, diagnosis and treatment.
- Describe the current guidelines for, and ongoing clinical trials of, local and regional therapy for noninvasive and invasive breast cancer.
- Describe and implement an algorithm for HER2 and estrogen receptor testing in the primary breast cancer setting.
- Develop and explain a management strategy for local and systemic treatment of breast cancer in the adjuvant, neoadjuvant and recurrent disease settings.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors in the adjuvant and neoadjuvant settings.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.

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

The purpose of Issue 3 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Pierce, Robert, Ravdin and Margolese on the integration of emerging clinical research data into the management of breast cancer.

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Editor's Note

The issue is the tissue

Agree/Disagree? The single most important action a surgeon can take in the management of a patient with breast cancer is to do everything possible to ensure that the estrogen and progesterone receptor and HER2 assays are performed accurately.

When I finished my oncology fellowship in 1977, the most hotly debated topic in breast cancer management was mastectomy versus breast conservation. Over the next decade, patient advocates like Rose Kushner challenged surgeons to consider emerging randomized trial data and present lumpectomy as an option to patients for whom it was clinically appropriate. At that time, Bernie Fisher and other breast cancer surgery leaders — including Richard Margolese, who was interviewed for this issue — appeared to be in a constant state of umbrage due to the disappointingly low rates of breast conservation in the United States.

Clearly, lesser surgery for this disease is evolving rapidly. Sentinel node biopsy is now a widely accepted standard of care, and partial breast irradiation — as eloquently discussed by Lori Pierce in this issue — is allowing more women to choose breast conservation because the time commitment to radiation therapy is significantly reduced. When I first met Dr Margolese in 1986, he predicted that breast cancer would eventually be considered a nonsurgical disease. While that has not fully occurred, there has been a major shift in emphasis toward systemic treatment options. Specifically, breast cancer has become the model for targeted therapy. While most other solid tumors have no such treatment strategies, this disease has two.

The first approach was theorized by an English surgeon in the 1890s based on observations of lactating cows on his farm. It would be 70 years before laboratory scientists began to unravel the mysteries of endocrine therapy pioneered by Sir George Beatson. We have truly come a long way in our understanding of this complex mechanism. I can remember developing an educational video in 1985 that had a Pac-Man-like model of an estrogen molecule scurrying across the cell membrane to join up with the estrogen receptor — and then the dynamic duo meandered into the nucleus.

Today, even a rudimentary diagram of breast cancer growth pathways looks like a map of the London Underground with multiple types of ER, cofactors, PR, HER2 and other receptors and ligands. However, in the middle of this intricate system and fascinating science is a somewhat simple but crucial issue — women whose tumors are considered "ER-positive" receive endocrine therapy and the rest do not.

After decades of emphasis on chemotherapy, medical oncologists have finally figured out that the key to breast cancer control is the use of early endocrine treatment. Moreover, exciting new data from clinical trials is resulting in a shift away from tamoxifen and toward aromatase inhibitors for postmenopausal patients and ovarian suppression combined with tamoxifen for premenopausal patients. These relatively nontoxic strategies with hormonal therapy have halved recurrence rates and substantially reduced mortality.

The greatest challenge to Dr Beatson's legacy and a truly frightening public health concern is the likelihood that a substantial number of tumors are being incorrectly labeled as ER-negative. In the next issue of this series, Craig Allred will spin a horror story that suggests that up to 20 percent of patients are denied hormonal therapy because lower-volume community laboratories incorrectly classify their tumors. To say the least, this is not good.

We go from bad to worse when it comes to HER2. Oncologists utilize HER2 information for a number of decisions in the management of early breast cancer, including the selection of chemotherapy and hormonal therapy, establishing a prognosis and identifying women for participation in arguably the most important breast cancer clinical trials now being conducted — the paradigm-shifting adjuvant trastuzumab (Herceptin®) trials.

Moreover, when breast cancer relapse occurs, HER2 status determines whether an oncologist will recommend trastuzumab — breast cancer's second targeted therapy — which is highly efficacious and virtually without side effects. Like ER and PR, the usual initial test for HER2 is immunohistochemistry (IHC), which also suffers from frequent misclassification in lower-volume laboratories. A second assay — fluorescence in situ hybridization (FISH) — is used in equivocal cases but also has less than optimal quality control in the community.

In this issue, medical oncologists Nicholas Robert and Peter Ravdin discuss their management strategies for patients based on ER, PR and HER2 results. Nick is also trained in pathology and expounds on the histological factors and the emerging role of the genetic tissue assays, such as the one discussed by Soon Paik in our last issue. What emerges from these interviews is essentially the fulfillment of Richard Margolese's 1986 prediction — breast cancer has become a complex medical disease. It seems clear that a continued decrease in breast cancer mortality will be a direct consequence of our ability to interrupt growth control mechanisms based on improved understanding of tumor cell biology.

The bottom line is that when a friend, family member or coworker asks me to refer them to a surgeon for a breast lesion, I am not thinking so much about surgical technique as much as an orientation toward overall management of this increasingly complex disease. Somewhere in that approach is the absolute insistence that the precious tissue being removed be directed to a laboratory that accepts the responsibility of performing an accurate evaluation of two tissue targets with potentially life-saving implications.

— Neil Love, MD

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Lori J Pierce, MD

EDITED COMMENTS

Clinical trials evaluating partial breast irradiation

Single-institution trials have shown that in highly selected patients, partial breast irradiation (PBI) to the area from which the tumor was removed appears to provide good results in terms of tumor control. Patients have generally been treated with brachytherapy techniques, but we also have limited experience with external beam radiation. In those investigators' hands, PBI appears to be a very promising technique for treating select patients.

However, the trials have been conducted at a limited number of institutions and in limited numbers of highly selected patients. For that reason, a large trial is being planned that will randomly assign women to either whole breast radiation therapy (WBT) or PBI. I strongly support that trial; otherwise we'll never know which patients will benefit from this type of technique.

Proposed NSABP/RTOG randomized trial comparing PBI to WBT

A proposed NSABP/RTOG trial will include women with DCIS or Stage I/II breast cancer and up to three positive nodes. The patients can have either invasive or noninvasive cancers, and their margins must be negative. At one time, it was discussed that only patients with infiltrating ductal carcinoma (not lobular carcinoma) would be included because many of the pilot studies did not include patients with lobular carcinoma. The NSABP wanted to include all patients, so those with lobular carcinoma and DCIS will also be enrolled.

The PBI techniques allowed in the proposed randomized trial include external beam radiation therapy and brachytherapy with either an implant or MammoSite®, which is an easier way to deliver brachytherapy. Although outcome data with MammoSite® are not yet available, the data demonstrate it to be a safe procedure.

When the trial opens for accrual, I predict external beam radiation will be used most frequently because most radiation oncologists use that technique. Few radiation oncologists in this country have continued using brachytherapy in the

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treatment of patients with breast cancer. As we gather more data about the use of external beam PBI, most radiation oncologists will probably gravitate toward that technique.

Techniques for delivering PBI

Brachytherapy is delivered through a catheter either with a template that guides the radioactive sources or by freehand. Doctors who are experienced in brachytherapy can do it freehand, but using a template is the kinder, simpler method because it forces the catheters in a certain direction. However, the template method may not provide as thorough coverage as the freehand method.

Placement of catheters is extremely important. Catheters placed too close to the chest wall may cause rib, localized lung or heart complications. Catheters placed in the deep part of the breast where the heart is close to the chest wall may cause cardiac problems. Catheters placed too close to the skin may cause severe fibrosis, telangiectasia and an adverse cosmetic result.

MammoSite® is like a glorified Foley catheter with high dose rate radiation. The balloon treats a spherical target area inside the breast. The FDA approved MammoSite® based on safety. We still need efficacy data, and studies are currently underway. MammoSite® has caught on dramatically with the radiation oncology community and surgeons. Radiation oncologists do the dosimetry, but surgeons are involved in the actual placement.

External beam radiation is the most "user friendly" of the three techniques. With external beam radiation, however, in order to treat the target area, a larger portion of the breast may be exposed to radiation than with brachytherapy. We don't want the external beam radiation technique for PBI to end up treating nearly the whole breast. To do PBI, we want to limit the doses administered and the area exposed to a high dose of radiation.

Select Publications

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**

Shah NM et al. **Early toxicity and cosmesis with MammoSite compared with interstitial brachytherapy for accelerated partial breast irradiation.** *Breast Cancer Res Treat* 2003;**Abstract 1052**.

Suh WW et al. **Comparing the cost of partial versus whole breast irradiation following breast conserving surgery for early-stage breast cancer.** *Breast Cancer Res Treat* 2003;**Abstract 1043**.

Vaidya JS et al. **Intraoperative radiotherapy for breast cancer.** *Lancet Oncol* 2004;5(3):165-73. **Abstract**

Vicini F. **Partial breast irradiation: current status.** *Breast Cancer Res Treat* 2003;**Abstract MS2-1**.

Whelan T et al. **Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer.** *J Natl Cancer Inst* 2002;94(15):1143-50. **Abstract**

Nicholas J Robert, MD

EDITED COMMENTS

Implications of the ATAC trial data

The ATAC data make a strong case to use an aromatase inhibitor in the adjuvant setting. In this trial of more than 9,000 patients, anastrozole demonstrated approximately a 20 percent proportional improvement in disease-free survival compared to tamoxifen, and had a more favorable toxicity profile. Anastrozole is associated with less risk of thromboembolic disease and uterine cancer. While the loss of bone density is greater with anastrozole, even postmenopausal women on tamoxifen are at risk for bone loss and osteoporosis. I believe the oncology community is becoming more aggressive in evaluating and treating this toxicity and, fortunately, we have agents to manage bone loss.

Aromatase inhibitors versus tamoxifen in the adjuvant setting

Over the past couple of decades, tamoxifen has had a huge impact on the management of breast cancer, but its use in the adjuvant setting may be declining. Several studies have demonstrated the superiority of aromatase inhibitors over tamoxifen, including the ATAC trial, the NCIC-CAN-MA17 trial in which women received letrozole after five years of tamoxifen, and two trials in which women were switched to an aromatase inhibitor after two or three years of tamoxifen. The Intergroup study utilizing exemestane and Boccardo's trial utilizing anastrozole demonstrated an advantage to switching early from tamoxifen to the aromatase inhibitor.

When I use endocrine therapy in newly diagnosed patients, I use anastrozole. If I'm going to switch therapy after two or three years of tamoxifen, I use exemestane, but after five years of tamoxifen, I choose letrozole.

Risk of recurrence after five years of adjuvant tamoxifen

In an article published in the *Journal of Clinical Oncology* in 1996, Dr Saphner et al reviewed trials from the ECOG database to determine annual hazard rates of recurrence for breast cancer after primary therapy (Figure 1.1). Patients with four or more positive nodes had a higher risk of recurrence in all time intervals.

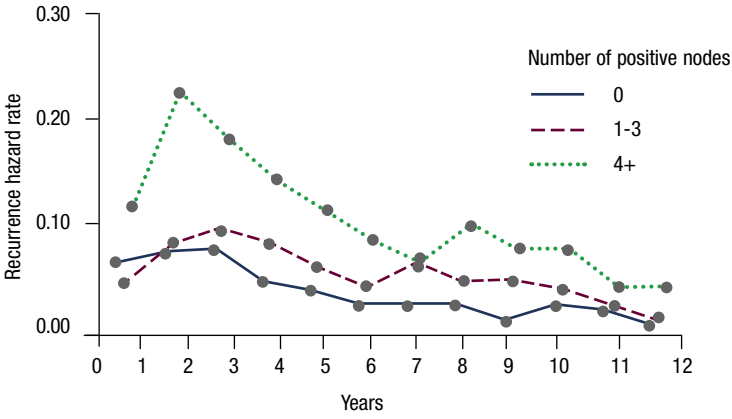
Dr Robert is Chairman of the Research Committee at the Cancer Center of the Inova Fairfax Hospital and Chair of the Breast Cancer Committee of the US Oncology Research Network in Fairfax, Virginia.

I believe nodal involvement is key to the risk of recurrence after the first five years. Letrozole is appropriate in a patient with node-positive breast cancer who completed five years of tamoxifen a year or two ago, but if four or five years have passed and the patient had a small tumor and node-negative disease, the benefit of letrozole would be marginal.

One issue raised by the MA17 and ATAC trials is the selection of endpoints in adjuvant studies. These trials included contralateral tumors and local and regional recurrences. In the future, I suspect we'll be more interested in the distant disease recurrence endpoint. If we had used that as the endpoint in the MA17 trial, the study would probably still be open and we may have obtained additional information.

Figure 1.1

Annual Hazard Rates of Recurrence for Breast Cancer after Primary Therapy



SOURCE: Adapted with permission from Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14(10):2738-46. **Abstract**

Assessment of HER2 status and choice of therapy

To determine a patient's HER2 status, FISH is currently the best method we have in terms of linking outcome with intervention. I believe ascertaining the HER2 status in patients with metastatic breast cancer is mandatory. One can use the primary tissue; however, whenever feasible, one should biopsy metastatic lesions and re-evaluate the HER2 and hormone receptors.

In the adjuvant setting, establishing the patient's HER2 status is important for several reasons. Circumstantial evidence suggests anthracycline-containing regimens are more effective than non-anthracycline regimens in treating HER2-positive tumors. The HER2 status may also affect one's choice of endocrine agents, but again, this may become academic as the enthusiasm for aromatase

inhibitors increases. Another reason to evaluate the HER2 status is its prognostic value. Most oncologists believe HER2-positive disease is more aggressive and the patients may have a greater risk of recurrence.

Clinical trials evaluating adjuvant trastuzumab

Four adjuvant trastuzumab trials have been initiated to test three different principles (Figure 1.2). Two ongoing studies — the NSABP and Intergroup trials — basically compare the gold standard, doxorubicin/cyclophosphamide followed by a taxane, with or without trastuzumab. This is a reasonable "next-step" type of protocol. In the completed BCIRG-006 trial, two arms were similar to these trials, but the third arm — docetaxel/carboplatin/trastuzumab — was based on exciting preclinical and clinical work that showed the addition of carboplatin improved outcome. The HERA trial is evaluating the duration of adjuvant trastuzumab, randomly assigning some patients to one or two years of therapy. In the other three trials trastuzumab is given for one year, but no data exist to suggest that's the optimal duration. The results will be interesting because if we use trastuzumab like we use endocrine agents, we may be looking at very prolonged usage.

Figure 1.2

Randomized Clinical Trials of Adjuvant Trastuzumab

Trial (target accrual)	Eligibility	Randomization
NSABP-B-31 (2,700 patients)	Node positive IHC 3+ or FISH positive	AC x 4 → paclitaxel x 4 AC x 4 → paclitaxel x 4 + H qwk x 1 year
Intergroup N9831 (3,300 patients)	Node positive IHC 3+ or FISH positive	AC x 4 → paclitaxel qwk x 12 AC x 4 → paclitaxel qwk x 12 → H qwk x 1 year AC x 4 → (paclitaxel + H) qwk x 12 H qwk x 40 wk
BCIRG-006 (3,150 patients)	Node positive FISH positive	AC x 4 → docetaxel x 4 AC x 4 → docetaxel x 4 + H (qwk x 12 wk) → H (qwk x 40 wk) (Docetaxel + C) x 6 + H (qwk x 18 wk) → H (qwk x 34 wk)
BIG-01-01 HERA (4,482 patients)	Node positive and negative IHC 3+ or FISH positive	H q3wk x 1 year H q3wk x 2 years No H

H = trastuzumab; C = cisplatin or carboplatin; AC = doxorubicin + cyclophosphamide

SOURCE: NCI Physician Data Query, June 2004.

Treatment of patients with HER2-positive, ER-positive metastases

HER2-positive Stage IV disease encompasses a heterogeneous group of patients who have different rates of progression. In a patient with relatively indolent HER2-positive, ER-positive disease who has received tamoxifen, I believe it's appropriate to consider another endocrine intervention. However, in a patient

whose disease is more life-threatening, I believe it's reasonable to consider an endocrine intervention plus trastuzumab.

A trial evaluating anastrozole with or without trastuzumab is nearing completion, but we don't have the data yet. HER2-positive tumors may respond better to aromatase inhibitors than to tamoxifen, which I believe relates to some interaction downstream from the estrogen receptor. Tamoxifen binds the estrogen receptor, but HER2-positive tumors have an alternate pathway by which the receptor can be activated. Aromatase inhibitors basically eliminate estrogen and thus avoid its activation.

Role of the surgeon in requesting tumor markers

Generally the surgeon is involved in the initial diagnosis, but often today it's the radiologist who performs a stereotactic biopsy, and the specimen is sent to the pathologist. The pathologists must not only evaluate the histology, but also evaluate hormone receptors and HER2 status. These studies are probably even more important than studies of the proliferation index, because we can usually capture that with grade. So the pathologist has a very important role.

It is frustrating to be involved in a case in which the surgeon never requested these studies. When you see the patient two or three weeks after surgery, you have to wait another one to two weeks for that information before you can provide some intelligent advice about their treatment options.

It's important for these studies to be performed up front. Breast cancer care is a multidisciplinary process. It's not necessary to have a breast cancer center, but you certainly should have the treatment team interacting and have some general principles about how to evaluate patients.

Select publications

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10. **Abstract**

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 3**.

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

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

Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14(10):2738-46. **Abstract**

Peter M Ravdin, MD, PhD

EDITED COMMENTS

ADJUVANT! computer program for predicting risk of breast cancer recurrence and mortality

The ADJUVANT! computer program (available at: **www.adjuvantonline.com**) is based on about a decade of work that originated with information from the San Antonio database. Originally the underpinnings of ADJUVANT! were based on the Surveillance, Epidemiology and End Results (SEER) database, a large population-based database with some great strengths. I believe it is a relevant database, and it's certainly more population-based than the clinical trials in which only about three percent of patients participate. However, some approximations about the impact of adjuvant therapy in different groups must be made because information about them is not included in SEER.

ADJUVANT! focuses on the baseline data for untreated patients and incorporates the Oxford overview data about the efficacy of different adjuvant therapies. The Oxford overview approximates the absolute benefit by multiplying baseline estimates and proportional risk reductions. One of the strengths of ADJUVANT! is its extensive help files which describe the assumptions that underlie some of the estimates. Like the Oxford overview, the assumptions in ADJUVANT! are based as much as possible on global composite information.

Because all of the parameters used in ADJUVANT! and how they were reached are discussed in the help files, if someone disagrees with the proportional risk reductions that were assigned to a particular therapy, their own estimate can be entered.

Information about competing natural causes of mortality is also incorporated into ADJUVANT!. In many of our older patients with node-negative disease, competing causes of mortality may be more important than their risk from breast cancer. To some extent, the urge to treat every patient is predicated on the concept that breast cancer is the only issue for the patient. For many patients with breast cancer, particularly the older ones, the competing causes of mortality reduce the actual benefit and the number of patients with a chance for long-term benefit.

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Clinical trial results of adjuvant aromatase inhibitors

Several recent reports offer important data from trials of aromatase inhibitors in postmenopausal women with early breast cancer. The first is the ATAC trial. As first-line adjuvant therapy, anastrozole is about 20 percent better than tamoxifen. In the first public presentation of data from the trial comparing letrozole to placebo after five years of adjuvant tamoxifen, patients receiving letrozole were reported to have a 40 percent proportional risk reduction in relapse events. Like the ATAC trial, the results were presented early because they were extremely positive.

An Italian trial also presented at the 2003 San Antonio Breast Cancer Symposium was very provocative. In that trial, patients received a total of five years of adjuvant endocrine therapy. They all received two to three years of adjuvant tamoxifen and were then randomly assigned to complete their therapy with tamoxifen or anastrozole. The patients who switched to anastrozole had a 60 percent proportional reduction in the risk of relapse, which was greater than expected (Figure 2.1).

Figure 2.1

Anastrozole (A) versus Tamoxifen (T) in Women Already Receiving Adjuvant Tamoxifen (Median Follow-Up 24 Months)

Treatment	Event-free survival		Progression-free survival	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Tamoxifen (n=225)	1.0	0.0004	1.0	0.002
Anastrozole (n=223)	0.36 (95%CI 0.21-0.63)		0.35 (95%CI 0.18-0.69)	

"Conclusion: These findings confirm the role of A in the treatment of early breast cancer. Furthermore the findings show that switching patients on adjuvant T to treatment with adjuvant A appears to decrease their risk of relapse and death. A was found to be more effective and induce less serious adverse effects than T in women already on treatment with this antiestrogen."

SOURCES: Boccardo F. Presentation, San Antonio Breast Cancer Symposium, 2003.

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 3**.

Time course for breast cancer recurrences

Because two-thirds of the recurrences occurring within the first 10 years happen in the first five years, the greatest risk of recurrence is during the first five years. There are two potential strategies for adjuvant therapy. The first is to always use the best drugs first because the patients are at the highest risk. The converse would be to use the best drugs later because the impact of stopping tamoxifen is proportionally larger, and that strategy would take a bigger bite out of the late recurrences.

I believe both strategies have a lot of uncertainties, but they may end up being fairly equivalent at 10 years. However, applying the general principle of adjuvant therapy that more benefit may be derived when the best drugs are used first, it appears that starting with an aromatase inhibitor would be the best path.

Use of up-front adjuvant aromatase inhibitors in postmenopausal women

In the nonprotocol setting we inform patients of the continued uncertainties, but we have started treating most postmenopausal women with up-front adjuvant aromatase inhibitors. I don't feel uncomfortable accommodating patients who don't want an adjuvant aromatase inhibitor, because the letrozole study and the Italian study found that switching from tamoxifen doesn't abrogate the positive impact of an aromatase inhibitor. Currently, however, most of my postmenopausal patients with ER-positive disease are treated up front with anastrozole.

Role of the aromatase inhibitors following five years of adjuvant tamoxifen

All patients with Stage II or Stage III disease who have recently completed a five-year course of adjuvant tamoxifen should receive an aromatase inhibitor. Whether patients with Stage I disease should receive an aromatase inhibitor is an open question because they have a relatively small amount of residual risk. The aromatase inhibitors can be quite expensive for a fairly marginal benefit in patients with very low-risk disease. Additional costs are associated with monitoring bone mineral density or treating with a bisphosphonate. I would like to see more data in Stage I patients.

Although we don't yet have any data for patients who have finished their five-year course of adjuvant tamoxifen one or two years ago, we will have some data from the patients in the letrozole trial who were taking placebo and then switched to letrozole. In patients who finished a five-year course of adjuvant tamoxifen one year ago, an aromatase inhibitor is strongly justified. On the other hand, for patients who finished a five-year course of adjuvant tamoxifen five years ago, I don't believe an aromatase inhibitor is justified, and gray area exists for those patients who finished a five-year course of adjuvant tamoxifen between one and five years ago.

Select Publications

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 42**.

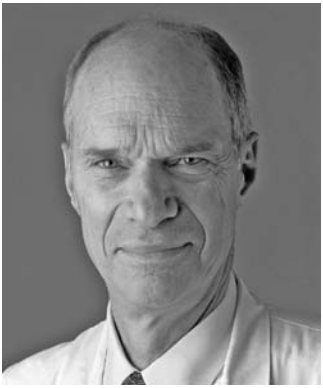
Hilner BE et al; American Society of Clinical Oncology. **American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer.** *J Clin Oncol* 2003;21(21):4042-57. **Abstract**

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91. **Abstract**

Richard G Margolese, MD

EDITED COMMENTS

Surgery for DCIS



In managing DCIS, I think the most common question is: Who needs a mastectomy after breast-conserving surgery without clear margins? In my opinion, too many mastectomies are performed. In extensive cases of DCIS, mastectomies are necessary, but you can actually remove two-thirds of the breast with excellent cosmesis as long as the tumor is in the upper part of the breast. We still try to conserve a lot of the breast in patients with extensive tumors.

Role of sentinel lymph node biopsy in DCIS

Performing sentinel lymph node biopsy in patients with DCIS does not make sense. The way DCIS is currently processed, pathologically, is much improved compared to previous methods. The pathologists are performing step sections at small intervals, and it's unlikely that we'll miss invasive cancer. We know there's a one percent mortality rate from DCIS, even though the most current statistics we have are from around 1990. The incidence of detecting a positive sentinel node is approximately 10 percent, but a lot of that is by immunohistochemistry. We're not sure what that means. If you find cancer cells in the lymph nodes, you can't dismiss it, but I'm not sure it's going to make a big difference in DCIS.

When a mastectomy is performed for DCIS, one to three lymph nodes will likely be present in the specimen — unless you assiduously avoid those lymph nodes in the tail of the breast. Is there a concern that these are not from the sentinel node? Is it necessary to inject a tracer to make certain you have the sentinel node? I don't think that's a very important question these days.

DCIS and radiation therapy

Selecting patients with DCIS who require radiation therapy seems to be a debate that's out of proportion to the problem. If you examine the retrospective studies all the way back to Lagios and Silverstein, you can identify patients who have tumors with such favorable prognostic features that they don't need radiation. We see

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them in invasive cancer and 100 percent in tubular cancers. They're probably not going to need radiation therapy.

In the NSABP prospective study, every group benefited to some extent from radiation therapy, but patients with the smallest tumors and the best nuclear grade had only a small benefit from radiation therapy. The annual hazard rate went from approximately 1.85 down to 1.1, which is not large, but it is a difference. If you think radiation therapy is problematic or toxic, maybe you would withhold it from such patients. If you think it's not such a problem, you would probably give it to everybody.

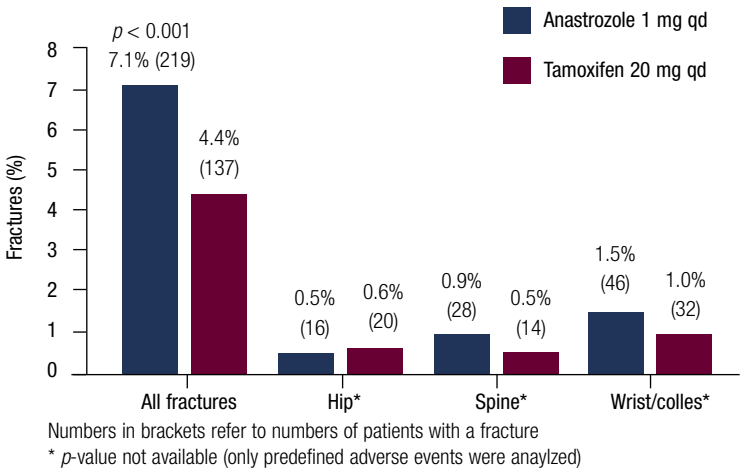
Comparison of the side-effect profiles of anastrozole and tamoxifen

Anastrozole seems to be a well-tolerated and safe drug. It certainly does not carry the risk of uterine cancer, and thromboembolic events occur less than with tamoxifen. Most women receiving anastrozole do not report any problems, although hot flashes are frequently mentioned. I haven't heard complaints about arthralgias.

In terms of bone mineral density and the potential threat of fractures, tamoxifen results in a significant reduction in hip and wrist fractures and a slight reduction in compression fractures of the spine (Figure 3.1). The aromatase inhibitors will produce more fractures, but we don't know if this is a serious problem or not. We don't know the long-term effects of estrogen deprivation, and we don't have long-term data for patients on aromatase inhibitors. It will be important for the ATAC investigators to gather long-term toxicity data.

Figure 3.1

Bone Fracture Adverse Events at the Updated Safety Analysis



Numbers in brackets refer to numbers of patients with a fracture

* *p*-value not available (only predefined adverse events were anaylzed)

SOURCE: Locker G. Poster presentation, Lynn Sage Breast Cancer Symposium, 2003.

Time Course of Bone Fractures in the ATAC Trial

"Six-monthly fracture rates… remained fairly constant for both A (range 0.93 to 1.57) and T (0.58 to 1.37), with the greatest difference between A and T seen at 18 and 24 mths. After 24 mths, the 6-monthly fracture rates seen with A reached a plateau. Overall osteoporotic fractures, encompassing sites of hip + spine + wrist, showed similar patterns. Anastrozole leads to an increased fracture incidence compared with T, a drug known to have a positive effect on bone. Importantly, the fracture rate in the A-treated group appeared to have stabilized after reaching a peak at 2 years."

A = anastrozole; T = tamoxifen

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

NSABP-B-35: Anastrozole versus tamoxifen in postmenopausal women with DCIS

NSABP-B-35 was designed shortly before the ATAC study was publicized, so data from ATAC and MA17 were not available to us. It was initiated because of the growing body of evidence that aromatase inhibitors appear to be effective in settings where tamoxifen is efficacious. Indeed, two large studies in advanced disease showed drugs like anastrozole were either equivalent to or even slightly better than tamoxifen. While we didn't have the ATAC data at the time, the dramatic reduction in second or contralateral breast cancers in women who received anastrozole versus tamoxifen is very exciting and emphasizes the importance of our trial.

NSABP-B-24, which showed a reduction in invasive cancer in the patients with DCIS who were randomly assigned to adjuvant tamoxifen versus placebo, also played a role in the development of B-35. Reducing the risk of invasive cancer is key, and while a recurrence of DCIS is unfortunate and perturbing, it is not life-threatening. We found that tamoxifen reduced this risk to just under two percent, and we had to decide just how much room there was for improvement and whether B-35 was worthwhile. It should be noted that two percent was for the entire group and to determine if women with a higher risk for invasive recurrence have a greater absolute benefit, we would need to study them separately.

Select Publications

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

Silverstein MJ. **An argument against routine use of radiotherapy for ductal carcinoma in situ.** *Oncology* (*Huntingt*) 2003;17(11):1511-33; discussion 1533-4, 1539, 1542. **Abstract**

Post-test:
Breast Cancer Update for Surgeons — Issue 3, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Partial breast irradiation (PBI) was found to be better than whole breast radiation therapy in a large, multi-institutional Phase III randomized trial.**
   a. True
   b. False

2. **One of the benefits associated with PBI is a much shorter course of therapy.**
   a. True
   b. False

3. **Which of the following techniques have been used to deliver PBI?**
   a. External beam radiation
   b. Brachytherapy
   c. MammoSite®
   d. a and b
   e. a, b and c

4. **The FDA approved MammoSite® based upon:**
   a. Safety data
   b. Short-term efficacy data
   c. Long-term efficacy data
   d. All of the above
   e. None of the above

5. **In the HERA trial, which evaluates the duration of adjuvant trastuzumab, three years is the maximum duration of trastuzumab.**
   a. True
   b. False

6. **In terms of endocrine therapy, evidence shows that HER2-positive tumors may respond better to which of the following:**
   a. Aromatase inhibitors
   b. Tamoxifen

7. **The ADJUVANT! computer program is:**
   a. Available online
   b. Based on the SEER database
   c. Used to predict the reduction in risk of breast cancer recurrence and mortality associated with various adjuvant systemic therapies
   d. All of the above
   e. None of the above

8. **The ATAC trial evaluated which of the following aromatase inhibitors as up-front therapy in the adjuvant setting:**
   a. Exemestane
   b. Anastrozole
   c. Letrozole
   d. All of the above
   e. None of the above

9. **The Italian trial presented at the 2003 San Antonio Breast Cancer Symposium evaluated which of the following aromatase inhibitors after two to three years of adjuvant tamoxifen compared to continuing tamoxifen:**
   a. Exemestane
   b. Anastrozole
   c. Letrozole
   d. All of the above
   e. None of the above

10. **The mortality rate from DCIS is approximately:**
    a. One percent
    b. Five percent
    c. 10 percent
    d. 25 percent

11. **In the most recent safety update of the ATAC trial, the fracture rate associated with anastrozole stabilized after reaching a peak after two years.**
    a. True
    b. False

12. **The rate of hip, spine and wrist/colles fractures was much higher in patients receiving anastrozole compared to tamoxifen in the ATAC trial.**
    a. True
    b. False

Post-test Answer Key: 1b, 2a, 3e, 4a, 5b, 6a, 7d, 8b, 9b, 10a, 11a, 12b

Evaluation Form:
Breast Cancer Update for Surgeons — Issue 3, 2004

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Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer screening, diagnosis and treatment . . . . . 5 4 3 2 1 N/A
- 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 N/A
- Describe and implement an algorithm for HER2 and estrogen receptor testing in the primary breast cancer setting. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for local and systemic treatment of breast cancer in the adjuvant, neoadjuvant and recurrent disease settings . . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors in the adjuvant and neoadjuvant settings . . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer . . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Lori J Pierce, MD	5 4 3 2 1	5 4 3 2 1
Nicholas J Robert, MD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
Richard G Margolese, MD	5 4 3 2 1	5 4 3 2 1

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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

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As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

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Breast Cancer™ UPDATE

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Breast Cancer™

UPDATE

This program is supported by education grants from
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