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Breast Cancer™ UPDATE

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

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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 4 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Vicini, Tripathy, Edge and Allred on the integration of emerging clinical research data into the management of breast cancer.

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Pharmaceutical agents discussed in this program

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doxorubicin	Adriamycin® Rubex®	Pfizer Inc Bristol-Myers Squibb Company
exemestane	Aromasin®	Pfizer Inc
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Editor's Note

Scary, scary stuff

Craig Allred is one of the nicest people in our field, and it is ironic that every time I chat with him, I feel awful. My instantaneous bad humor has nothing to do with Craig personally, but rather the human implications of his work. Most specifically, it is his continued demonstration that many women with breast cancer are being denied an effective, relatively nontoxic intervention because of poor quality control in the performance and interpretation of estrogen- and progesterone-receptor assays.

Almost every medical oncologist and breast surgeon has heard about Craig's presentation at the 2002 San Antonio Breast Cancer Symposium, which demonstrated that women with ER-negative DCIS do not benefit from tamoxifen. Far fewer physicians, though, are aware that many women's tumors that are determined to be ER-negative by community-based laboratories would be considered ER-positive in Craig's laboratory. A ton of time, money and effort has gone into the development of the first truly targeted therapy for breast cancer, and it is pitiful that many women will not reap the potentially substantial benefits of this treatment because we can't get their ER status right.

This compelling issue has been on the table for a decade without much reaction. Craig, in his gentle manner, finds this "a little disheartening." A little disheartening? If I'm a person whose disease has relapsed without having been given the option of receiving adjuvant endocrine therapy based on a false-negative result, I'm profoundly disheartened. In fact, I'm angry as hell.

While the "powers that be" muddle over resolving this mess, it is imperative that individual physicians and patients approach tumors labeled as "ER-negative" with considerable skepticism. Sure, some breast cancers do not express ER, but many more may have lower-level positive values that correlate with benefit from endocrine therapy. Consequently, oncologists must consider a second pathology opinion for any woman whose tumor is labeled as ER-negative. As discussed by Craig on this program, perhaps one out of four of these tumors might be reclassified as ER-positive.

The same issues might be said about quality control in HER2 testing, although the implications are perhaps less in the adjuvant setting. That said, in a recent case-based CME conference I moderated, an oncologist presented the case of an 87-year-old woman with bone and lung metastases and a previous HER2 assay result that scored zero on immunohistochemistry (IHC). The treating physician

was suspicious of the rapid progression of this woman's cancer and had the original tumor retested by fluorescence *in situ* hybridization (FISH). This proved to be positive for HER2 amplification and, fortunately, the woman did well for some years on trastuzumab-based therapy.

Patients should not need to rely on astute physicians to be rescued from outdated pathology or pathologists. We must demand better quality from our laboratory colleagues.

— Neil Love, MD
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Related comments from this program

False negatives in ER analysis

In my practice, I consult on several hundred difficult cases each year. Many of these are sent for repeat ER testing and the conversion rate from negative to positive is 20 to 30 percent. The reasons for false negatives have been studied in detail in invasive cancer and the same errors probably occur when assessing the ER status in patients with DCIS.

The single biggest contributor is the antigen retrieval, which is an artsy part of the assay in which we try to reverse the cross-linking between the proteins caused by the initial formalin fixation. Another major problem is the antibody selected. Dozens of antibodies are available and they are not equivalent in sensitivity and specificity.

Another significant error is setting the cut point for positivity too high. It is usually set arbitrarily rather than based on clinical studies, and averages 10 or even 20 percent across the country. In invasive disease the cut point is much lower; almost so low that if it's measurable, there's probably a good chance the tumor will respond to hormonal therapy. The cut point we use — one percent — is based on clinical trials involving invasive breast cancer, but when applied to the B-24 DCIS study, the results were reasonable.

It's worrisome that many community labs simply report the ER status as positive or negative. A comprehensive report provides an impression as to positivity or negativity of the specimen, a percent or proportion of positive cells, and may footnote relevant clinical trials.

— D Craig Allred, MD

Quality control of ER assays

Quality assurance is an important issue in ER testing — the stain needs to be nuclear, the pathologist's experience is important, and we've learned that even a small amount of ER staining confers clinical sensitivity to hormone therapy. Even if only five percent of the cells stain, the entire tumor mass may respond to hormonal therapy and this may be due to a cell cycle-specific phenomena or

the biology may be such that we achieve a cytostatic effect, or even an apoptotic effect, when only a fraction of the cells express ER.

We need to reassess how we define ER status. Some proponents of a revised scaling contend that even five percent of tumor cells with 1+ staining would qualify as ER-positive. A qualitative reading alone is no longer acceptable; more labs are reporting intensity and some provide a histoscore, which is a composite based on the percentage of positively staining cells and the intensity of staining. Hormonal therapy has the single greatest impact on outcome, so it's important that tumors are classified accurately.

— Debu Tripathy, MD

Accuracy in HER2 testing

In HER2 testing, we see false positives and false negatives. One reason for this is that tissue preservation can destroy protein epitope and with the standard antibody assay, we may not obtain an accurate representation. In false negatives, the protein is present, but the fixation technique can make the protein less immunoreactive. In false positives, for whatever reason, the antibody assay stains nonspecifically.

In certain cases, DNA testing with FISH is important because DNA is more stable than protein. Experience has taught us that a very high level of protein staining, meaning 3+ with the standard IHC, truly represents a lot of protein; however at the 2+ level, approximately 25 to 50 percent will be positive by gene testing, which is why it's important to verify a 2+ with FISH. The zeros and ones are rarely positive by FISH, and remain controversial. Some clinicians also perform FISH in cases with aggressive features of either the markers or the clinical history.

I believe it's appropriate to perform HER2 testing on every primary breast cancer tumor specimen because the information may become important at some point in the future. Data from the cooperative groups show that 10 to 20 percent of the time, IHC scores are reclassified when central lab testing is compared to community labs. The NCCTG published a small pilot study showing the same discordance rate with FISH. It appears that the throughput of the lab is the single most predictive factor in accuracy, and labs that perform more than 300 or 400 tests per year have better accuracy rates.

— Debu Tripathy, MD

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002;81(Suppl 1);**Abstract 30**.

Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer.** *J Clin Oncol* 1999;17(5):1474-81. **Abstract**

Paik S et al. **Real-world performance of HER2 testing — National Surgical Adjuvant Breast and Bowel Project experience.** *J Natl Cancer Inst* 2002;94(11):852-4. **Abstract**

Roche PC et al. **Concordance between local and central laboratory HER2 testing in the breast intergroup trial N9831.** *J Natl Cancer Inst* 2002;94(11):855-7. **Abstract**

Interstitial brachytherapy

At William Beaumont Hospital, we matched 199 patients treated with interstitial brachytherapy with 199 patients who received conventional external beam radiotherapy. With a median follow-up for surviving patients of 65 months, we found the endpoints to be equivalent, including local control rates, regional failure rates and cause-specific survival (1.1). In the past 10 years of published data, the collective experience with interstitial brachytherapy consists of approximately 500 to 600 patients, compared to tens of thousands of women treated with whole breast radiation therapy. With brachytherapy, we have only small numbers of highly selected patients treated at single institutions. We don't really know what the efficacy will be in larger patient populations with less restrictive criteria.

1.1 Five-Year Actuarial Treatment Outcomes from Matched-Pair Analysis of Patients Treated with Whole Breast versus Limited-Field Radiation Therapy

Outcome	Whole breast % (95% CI)	Limited-field % (95% CI)	*p*-value
Ipsilateral recurrence	1 (0-2.4)	1 (0-2.8)	0.65
Regional failure*	1 (0-1.5)	1 (0.1-2.1)	0.54
Distant metastasis	5 (2.2-8.4)	3 (0.5-5.9)	0.17
Disease-free survival	91 (86.5-94.7)	87 (81.5-92.1)	0.30
Overall survival	93 (89.7-96.7)	87 (82.1-92.7)	0.23
Cause-specific survival	97 (95.0-99.8)	97 (93.8-99.9)	0.34
Contralateral breast failure	4 (1.0-6.4)	1 (0-2.4)	0.03

*Regional failure = recurrence of cancer in a regional nodal site before or simultaneously with the diagnosis of local recurrence or distant metastasis.

SOURCE: Vicini FA et al. **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003;95(16):1205-11. **Abstract**

Dr Vicini is Chief of Oncology Services in Oncology Services Administration at William Beaumont Hospital in Royal Oak, Michigan.

Partial breast irradiation

One of the advantages of partial breast irradiation (PBI) is that it can be completed quickly before systemic therapy is initiated. Our surgeons are progressive in this field. William Beaumont is one of the few institutions that offers interstitial brachytherapy, MammoSite® and conformal external beam radiation therapy. Each technique has its advantages and none of them are applicable to all clinical scenarios. Treatment must be individualized based on factors such as the patient's access to a radiation facility and the location of the lesion within the breast.

At our institution, of the patients who receive PBI, approximately 60 percent are treated with the MammoSite®, 30 percent with conformal external beam radiotherapy and a small percentage with interstitial brachytherapy. Some physicians question whether it's worthwhile to study PBI given the high efficacy and low toxicity achieved with breast conservation using whole breast radiation therapy. However, in the United States a large proportion of women do not undergo breast-conserving therapy. A recent study showed that the distance to a radiation facility still factors into a woman's decision-making. In addition, some people fear radiation. Reducing the amount of time required and the amount of toxicity associated with radiation therapy may increase the rate of breast conservation. I believe that an additional 10 to 20 percent of women making this decision would select breast-conserving therapy if PBI was an option.

Proposed NSABP-RTOG trial comparing whole breast radiation versus PBI

The NSABP and RTOG plan to conduct a joint study that will randomly assign 3,000 patients to conventional whole breast radiation therapy versus one of three PBI techniques — interstitial brachytherapy, MammoSite®, or 3-D conformal external beam radiation. The eligibility will be broad, with no age restrictions. It will include patients with DCIS, infiltrating lobular histology and up to three positive nodes. Patients with four or more positive nodes will be excluded because they are candidates for regional nodal radiation therapy. Randomization will occur after surgery to ensure the pathology criteria are met.

Partial breast irradiation for DCIS

The American Brachytherapy Society (ABS) has developed recommendations for the off-protocol use of brachytherapy. Based on the data currently available, the ideal patients are those with tumors less than three centimeters, negative lymph nodes, negative margins and no extensive intraductal component. They exclude patients with DCIS because only a small number of such patients have been treated with this technique. I suspect that this will change in the next few years. Considering the applications for PBI, I believe patients with DCIS are ideal for testing this concept because the issue of a survival disadvantage is no longer arguable. The only difference between whole breast irradiation and PBI is that the latter targets the tissues that most likely need it. I consider PBI a reasonable compromise between no radiation and six and a half weeks of radiation, which is probably overkill in the majority of these patients.

MammoSite® placement

The MammoSite® can be placed either during or after surgery. There are more than 1,000 patients on the MammoSite® registry, and the device was placed intraoperatively in approximately 50 percent. However, it appears the more experienced institutions prefer to place it postoperatively. I prefer the postoperative, closed-cavity technique because it allows me to obtain the pathology results and determine the technical feasibility of any PBI procedure before I discuss it with the patient. It's distressing for a patient to learn she is not a candidate for PBI after a device or needles have been placed.

A patient may be ineligible based on pathologic factors such as positive margins, large tumors, lobular histology, DCIS or positive nodes. A CAT scan is performed postoperatively to rule out technical difficulties. In placing the MammoSite® it is important to keep the surface of the balloon at least five to seven millimeters away from the skin surface to avoid excessive radiation to the skin. In the registry data, 94 percent of patients treated with adequate spacing achieved good to excellent cosmetic results. We only have one to two years of follow-up, but early cosmetic results generally predict late results and I doubt we'll see any unusual late cosmetic effects.

Off-protocol use of the MammoSite®

The MammoSite® is easier for surgeons to use and patients to accept, but some physicians are concerned that it's being disseminated to the community before it's been fully tested in randomized trials. Many argue that we cannot extrapolate the interstitial experience to the MammoSite®, and experience with the interstitial approach itself is very limited with only five years of follow-up. Some worry that because it's hyperfractionated radiation, we'll encounter very late deterioration in cosmetic results not seen in the five-year data.

While I favor enrolling patients in randomized trials, data from the current trials won't be mature and analyzed for at least eight years after accrual is completed. I was involved in writing the ABS recommendations and we stated that with informed consent and in selected patients, it is reasonable to offer the MammoSite® off protocol. Most new concepts in medicine are not proven in Phase III trials before they're used in clinical practice, as seen with sentinel node biopsy. I believe it's more reasonable to give recommendations on the optimal use of this technique than to blatantly oppose its use off protocol.

Select Publications

Arthur DW et al. **Accelerated partial breast irradiation: An updated report from the American Brachytherapy Society.** *Brachytherapy* 2002;1(4):184-90. **Abstract**

Kuerer HM et al. **Accelerated partial breast irradiation after conservative surgery for breast cancer.** *Ann Surg* 2004;239(3):338-51. **Abstract**

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

Vicini FA et al. **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003;95(16):1205-11. **Abstract**

Adjuvant aromatase inhibitors

Hormonal therapy is the single most important and effective therapy we have for breast cancer, so any advance in that area will improve patient outcome. The current aromatase inhibitor trials in postmenopausal women demonstrate approximately a 25 to 50 percent relative reduction in the risk of recurrence compared to tamoxifen, which translates into a two to five percent absolute difference in overall events, including local and distant recurrences and new contralateral cancers.

In postmenopausal patients, when using an aromatase inhibitor, I base my selection on the current clinical research data. For example, in a patient presenting for initial adjuvant hormone therapy, I use anastrozole based on the ATAC trial, but if the patient has completed five years of adjuvant tamoxifen, I select letrozole based on the data from Goss and colleagues' MA17 trial. In patients who have completed only two or three years of tamoxifen, I choose exemestane based on the Intergroup exemestane study, but one could also use anastrozole based on Boccardo's data.

It's ideal to have several choices for tolerability, but I believe in time we'll find the aromatase inhibitors are interchangeable. I've definitely seen cases in which patients with musculoskeletal complaints have noted improvement when switched to a different agent. I also believe it's reasonable to use an aromatase inhibitor in patients who have been off adjuvant tamoxifen for a couple of years. We don't have data on this, but we have to extrapolate from what we know, and the bottom line is that these patients are still at risk for recurrent breast cancer.

Tolerability of aromatase inhibitors versus tamoxifen in the adjuvant setting

All of the studies comparing adjuvant aromatase inhibitors to tamoxifen are reporting compositely better tolerability with the aromatase inhibitors. The side effects of vaginal discharge, vaginal bleeding, hot flashes and uterine cancer are more common with tamoxifen, while arthralgias and myalgias are more common with aromatase inhibitors. As women become older — late sixties, seventies, and

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eighties — the risk of deep-vein thrombosis and stroke in women on tamoxifen becomes significant, and this is clearly not observed with aromatase inhibitors.

Osteoporosis and fractures are a concern with aromatase inhibitors, and I recommend using bisphosphonates, as we would in patients not taking these agents. I believe it's important to obtain a baseline bone mineral density, more for long-term management rather than to make an initial decision. I counsel patients with very low bone mineral density differently based on their age, but by the early seventies the cardiovascular risk with tamoxifen is significant, and some risk of osteoporosis might be acceptable.

None of the current trials are giving patients calcium supplementation. I believe we can reduce the bone density concern by recommending calcium and vitamin E for all patients, and using bisphosphonates a little earlier than we might in patients not on aromatase inhibitors.

Clinical trials of adjuvant trastuzumab

Approximately 20 percent of women with breast cancer have HER-positive tumors by gene amplification. Trastuzumab is a proven, active agent in this population. In metastatic disease, trastuzumab has clearly shown a benefit in survival and response rates in patients with HER2-positive tumors. Adding trastuzumab to chemotherapy — particularly the taxanes although probably other agents as well — improves outcome. The adjuvant studies are the next logical step, and I predict we will see a five to seven percent reduction in recurrence at five years and an impact on disease-free survival in the adjuvant setting.

The ongoing adjuvant trastuzumab trials are limited to patients with node-positive or high-risk, node-negative disease because the expected benefit must outweigh the known three to five percent short-term risk of cardiotoxicity associated with trastuzumab. The most common design is doxorubicin combined with cyclophosphamide followed by a taxane with or without trastuzumab.

One study also includes a carboplatin in combination with docetaxel arm because of the synergy seen in vitro and the possibility that omitting the anthracycline may mitigate cardiotoxicity. These studies have approximately 3,000 to 5,000 patients and are designed to detect small variations in outcome — approximately a five percent difference in recurrence and possibly a two percent survival benefit.

The adjuvant trials are evaluating one year of trastuzumab therapy, except for the European HERA study that randomly assigns patients to observation, one year or two years of trastuzumab. The natural history of breast cancer suggests that longer-term biological therapy is more beneficial, so I believe more than one year of trastuzumab will be necessary for optimal effect.

Adjuvant trastuzumab off protocol

I don't believe adjuvant trastuzumab should be used off protocol because we don't know that the benefit will outweigh short- and long-term toxicities; however, in some situations, a well-informed patient could be offered trastuzumab after extensive discussion.

On the other hand, off-protocol neoadjuvant trastuzumab may be appropriate in patients with locally advanced disease or borderline resectable disease. The FDA indicates it's reasonable to use trastuzumab in unresectable disease that is unresponsive to other therapies, so it then becomes a matter of judgment. Is this tumor resectable? Is it localized? Can I achieve negative margins? If the disease is extensive enough that the margins might be a problem and the patient is not responding to AC/paclitaxel, using trastuzumab with paclitaxel might be reasonable. We know the odds of recurrence are higher in such a patient, so the potential benefit is greater.

Response from neoadjuvant trastuzumab

Neoadjuvant studies are attractive because we can look at both clinical and tissue markers of response. In a study conducted at Baylor, patients received weekly trastuzumab for three weeks, followed by trastuzumab and docetaxel for 12 weeks prior to surgery. Interestingly, every patient experienced a reduction in tumor size after just three weeks of trastuzumab alone, and biopsies performed before and after single-agent trastuzumab showed apoptosis, which seemed to be a marker of clinical response.

We have always known patients respond better in the neoadjuvant setting than in the metastatic setting. Neoadjuvant chemotherapy response rates of 80 percent are common, whereas response rates of only 30 to 40 percent are seen in the metastatic setting, so it's no surprise to see clinical responses to preoperative, single-agent trastuzumab. Still, it's a little surprising to see the responses occur so quickly.

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;83(Suppl 1):6;**Abstract 3**.

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**

Chang JC et al. **Induction of apoptosis without change in cell proliferation in primary breast cancers with neoadjuvant trastuzumab.** *Proc SABCS* 2003;**Abstract 24**.

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**

Geyer, Jr CE et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus Herceptin in patients (Pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** *Proc SABCS* 2003;**Abstract 23**.

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

Pegram MD et al. **Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER2-positive advanced breast cancer.** *J Natl Cancer Inst* 2004;96(10):759-69. **Abstract**

Tan AR, Swain SM. **Ongoing adjuvant trials with trastuzumab in breast cancer.** *Semin Oncol* 2003;30(5 Suppl 16):54-64. **Abstract**

Clinical implications of abnormal mammograms

In a mature screening population, two or three breast cancers a year are diagnosed per 1,000 screening mammograms performed. To make the diagnosis, however, a fair number of biopsies must be performed. The best evidence suggests that approximately one-third of patients undergoing a biopsy for a mammogram-detected lesion will have breast cancer. In a very mature, well-audited mammography practice, that number may be as high as 40 percent.

In the United States the average is about 20 percent. We analyzed western New York claims data by surgeons, radiologists and medical centers and found the rate of breast cancer detected by mammogram ranged from seven to 40 percent (2.1). Interestingly, rates of biopsy-confirmed breast cancer were not correlated with the volume of mammograms performed.

2.1 Practice Volume is Not a Surrogate in the Diagnosis of Breast Cancer

"There is wide variation in diagnosis and treatment outcomes for patients with mammogram-detected breast carcinoma. Overall, practice volume was correlated with the use of BCS [breast-conserving surgery] but not with the rate of positive biopsy. A wide variation in the positive biopsy rate among high-volume providers and medical centers suggests that volume of practice is not a surrogate for quality in the diagnosis of breast carcinoma."

SOURCE: McKee MD et al. **Provider case volume and outcome in the evaluation and treatment of patients with mammogram-detected breast carcinoma.** *Cancer* 2002;95:704-12. **Abstract**

Another issue is the potential overuse of biopsy for mammograms that are so-called "probably benign," or BIRADS-3 mammograms. Abnormal mammograms are a source of enormous consternation and emotional distress for women, and the medical system isn't well set up to provide counseling and support for those women. They go to a mammography center, have an abnormal mammogram, are

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set up for a stereotactic needle biopsy and are sent to a surgeon whom they've never met. No support is available for them.

We need better mechanisms to inform patients about what we're looking for in mammograms and what the appropriate evaluation would be for them. Patients need to understand that time is not of the essence, and they can take time to ensure that they are appropriately evaluated and receive all the opinions they need.

We also need better mechanisms to reassure women when we recommend short-term follow-up as opposed to biopsy. My office is filled every week with women who have been told they need a short-term follow-up and are petrified that they might have breast cancer. They ask, "Why would I wait six months to find out if I've got breast cancer?" And yet, if we performed a biopsy on every woman who had a BIRADS-3 mammogram, they'd be lined up out the door and would undergo a lot of unnecessary morbidity.

Radiotherapy in the management of patients with DCIS

We have an unresolved dilemma between the high-level evidence from randomized clinical trials and anecdotal evidence, suggesting that large subsets of patients with *in situ* carcinoma do not need radiation therapy. The very best evidence suggests radiation therapy does not affect survival. A high percentage of local failures are *in situ* and most that are invasive are effectively treated. A very small percentage of individuals with *in situ* carcinoma will ultimately die of breast cancer whether we give them radiation therapy after breast-conserving surgery or not.

The NCCN guidelines recommend radiation therapy for almost all women with DCIS. The guidelines state the use of radiation therapy may be considered optional for individuals with lesions that are less than one-half centimeter and low grade, but I think many surgeons and many radiation oncologists extend that size limit well above one centimeter.

Sequencing and switching hormonal therapy

The aromatase inhibitors appear to be equivalent or even more effective than tamoxifen up front. My only hesitation is the lack of long-term follow-up in patients receiving aromatase inhibitors for a significant period of time.

I think many, if not most, oncologists have switched their practice and are exclusively using aromatase inhibitors in their postmenopausal patients. I think many of them are also using aromatase inhibitors quite broadly after five years of tamoxifen. Many of us in the NCCN and certainly in my cancer center are a little more skeptical about that approach, particularly in women in whom breast cancer is detected very early.

Many of my patients who had very small tumors are on hormonal therapy alone, so my practice is skewed to patients with node-negative, ER-positive, T1B breast cancer who are now in their mid-seventies. Should they be switched to letrozole after five years of tamoxifen? Their risk of recurrence after five years with an eight-millimeter Grade II cancer is one to three percent.

Letrozole may reduce that from three to 2.7 percent with a therapy that may impact bone health and result in fractures, and certainly will entail a cost to patients. Many of my older patients do not have prescription coverage. I do not think the blanket use of these drugs after five years of tamoxifen is necessarily the right answer.

In patients at higher risk, I'd be more likely to switch from tamoxifen to an aromatase inhibitor. These women have a substantial risk of distant recurrence after five years. In women with very high-risk disease, I have recommended continuing tamoxifen after completing five years. There's a theoretical chance that we might select resistant cells, but I think many medical oncologists have left people on tamoxifen in that situation. Currently, I would not hesitate to put women at higher risk on an aromatase inhibitor.

Contraindications to sentinel lymph node biopsy

I do not perform a needle biopsy for patients with an obviously positive node, rather I perform an axillary lymph node dissection. I can't remember a patient in whom I dissected axillary lymph nodes and they turned out to have negative nodes. I have not performed sentinel node biopsy with neoadjuvant chemotherapy because we are generally doing neoadjuvant chemotherapy for large breast cancers with high rates of node involvement. When one truly has locally advanced breast cancer, I think you're beyond the issue of cosmetics and concerns about lymphedema. Locally advanced breast cancer is a horrible, life-threatening and mutilating disease. Local failures in breast cancer are disasters that occur in only a small minority of our patients, so I've not regretted performing axillary node dissections in patients with locally advanced breast cancer.

This year we've modified the NCCN guidelines to allow consideration of sentinel node biopsy before neoadjuvant therapy and then omission of axillary node dissection. One of the premises behind that change is that neoadjuvant chemotherapy and hormonal therapy are being utilized with smaller cancers than in the past. It wouldn't seem right to deny a patient a sentinel node biopsy because we put them on a neoadjuvant hormonal trial.

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;83(Suppl 1):6;**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**

McKee MD et al. **Provider case volume and outcome in the evaluation and treatment of patients with mammogram-detected breast carcinoma.** *Cancer* 2002;95(4):704-12. **Abstract**

D Craig Allred, MD

EDITED COMMENTS

The Genomic Health multigene assay

The Genomic Health assay, a 21-gene prognostic profile, was put to the test in NSABP-B-14, the Phase III comparison of adjuvant tamoxifen versus placebo in patients with node-negative, ER-positive breast cancer. Analysis of the tamoxifen arm showed the assay to be a superior prognosticator when compared to the standard biomarkers and independent predictors. I believe the relative risk was three- or fourfold more powerful than the next factor, which was the patient's age.

While the assay performed surprisingly well, it's still a work in progress. It was validated in a select group of patients not representative of the entire target population, but work is being done to refine it. Some experts feel it's premature to market the assay, but I believe it's provocative enough to utilize in some individual cases. I believe its real value at this time is its potential contribution to clinical research. For example, patients for whom the assay suggests tamoxifen resistance could be randomly assigned to tamoxifen or an aromatase inhibitor.

Estrogen receptor status and tamoxifen efficacy in DCIS

NSABP-B-24 compared adjuvant tamoxifen to placebo in patients with DCIS. After four or five years of follow-up, the tamoxifen arm showed a 30 percent benefit, but we didn't understand the relationship of this response rate to the tumor's hormone receptor status. When the trial was initiated, assessing hormone receptors wasn't required, but tumors were banked to conduct biological studies.

In a central laboratory, we later measured the estrogen and progesterone receptors by IHC on approximately 600 paraffin blocks distributed between the two arms of the study. The data convincingly showed that the benefit from tamoxifen was entirely restricted to the ER-positive cohort; no evidence of benefit was seen in the ER-negative cohort. We know that approximately 25 percent of DCIS cases are truly ER-negative.

Approximately two-thirds of the cases we analyzed had hormone receptors previously evaluated in their community hospitals and, using the central lab as the standard, the community error rate was approximately 30 percent — mostly false negatives. In the patients with ER-negative tumors, as defined by community

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labs, the relative risk for benefit from tamoxifen was approximately 0.5, which is biologically unbelievable.

Assessing the same patients in the central lab, the relative risk was 0.99, indicating no benefit, as we would expect. Clearly, the cohort of cases identified as ER-negative in the community was contaminated with false negatives. We can conclude from our data that tamoxifen does not reduce the recurrence rate in patients with ER-negative DCIS assessed in a reliable lab.

Effect of phenotype on benefit in the ATAC trial

The analysis of phenotypes and response to therapy using the ATAC data was fascinating. Anastrozole had an approximately 20 percent additional benefit over tamoxifen in the ER-/PR-positive and ER-negative, PR-positive subsets. In the ER-/PR-negative phenotype, the relative risk was close to one, but surprisingly in the ER-positive, PR-negative subset, the relative risk was 0.48.

We don't know why the latter phenotype behaves so differently, but Dowsett and Osborne have formulated a hypothesis that involves contrasting the effect of tamoxifen versus anastrozole on the classical nuclear versus nonclassical membrane ER pathways. When the nuclear pathway is intact, estrogen activates the estrogen receptor, which induces the synthesis of the progesterone receptor; however, we can hypothesize that the pathway is not functioning in ER-positive, PR-negative tumors. If the membrane pathway is activated, it can lead to the activation of growth factor receptors and induce cell growth.

Tamoxifen is an antagonist in the nuclear pathway (hypothetically the nonfunctioning pathway in the ER-positive, PR-negative subset) and it's an agonist in the membrane pathway, which may result in stimulating growth factors and tumor growth. On the other hand, aromatase inhibitors reduce estrogen levels to nearly zero and are antagonists on both pathways. This may explain the striking additional benefit for anastrozole seen in the ER-positive, PR-negative subset, which is the phenotype for 20 percent of breast cancer patients.

Select Publications

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002;**Abstract 30**.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;83(Suppl 1):7;**Abstract 4**.

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**

Paik S et al. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** *Breast Cancer Res Treat* 2003;82(Suppl 1):10;**Abstract 16**.

Perez EA et al. **HER2 testing in patients with breast cancer: Poor correlation between weak positivity by immunohistochemistry and gene amplification by fluorescence in situ hybridization.** *Mayo Clin Proc* 2002;77(2):148-54. **Abstract**

Post-test:
Breast Cancer Update for Surgeons — Issue 4, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the William Beaumont Hospital study matching 199 patients treated with interstitial brachytherapy and 199 patients who received conventional external beam radiotherapy, which of the following endpoints were equivalent at five years?**
   a. Local control rates
   b. Regional failure rates
   c. Disease-specific survival
   d. All of the above

2. **The proposed NSABP-RTOG trial will randomly assign patients to conventional whole breast radiation therapy versus PBI using which of the following PBI techniques:**
   a. Interstitial brachytherapy
   b. MammoSite®
   c. 3-D conformal external beam radiation
   d. All of the above

3. **The American Brachytherapy Society's indications for the off-protocol use of brachytherapy include ductal carcinoma *in situ*.**
   a. True
   b. False

4. **It is important in placing the MammoSite® to keep the surface of the balloon at least five to seven millimeters away from the skin surface to avoid excessive radiation to the skin.**
   a. True
   b. False

5. **RTOG is evaluating tamoxifen with or without radiotherapy in patients with tumors less than two and a half centimeters with low and intermediate grade lesions and a margin of three millimeters or greater.**
   a. True
   b. False

6. **The NCCN guidelines discourage the use of sentinel node biopsy in all patients who will undergo neoadjuvant therapy.**
   a. True
   b. False

7. **In NSABP-B-14, the Genomic Health assay was shown to be a superior prognosticator when compared to standard biomarkers and independent predictors in patients who had received adjuvant tamoxifen for node-negative, ER-positive breast cancer.**
   a. True
   b. False

8. **In the analysis of outcome according to estrogen and progesterone receptor status in the ATAC trial, patients with which phenotype had the greatest benefit from anastrozole compared to tamoxifen?**
   a. ER-positive, PR-positive
   b. ER-positive, PR-negative
   c. ER-negative, PR-negative
   d. ER-negative, PR-positive

9. **The most common design of the ongoing adjuvant trastuzumab trials is doxorubicin combined with cyclophosphamide followed by a taxane with or without trastuzumab.**
   a. True
   b. False

10. **The adjuvant trial presented by Boccardo at the 2003 San Antonio Breast Cancer Symposium randomly assigned patients who had received at least two years of tamoxifen to:**
    a. Anastrozole or placebo
    b. Anastrozole or continued tamoxifen
    c. Letrozole or placebo
    d. Letrozole or tamoxifen

11. **In the three large randomized trials comparing adjuvant aromatase inhibitors to tamoxifen, which of the following toxicities occurs less frequently with the aromatase inhibitors?**
    a. Hot flashes
    b. Vaginal discharge and bleeding
    c. Deep vein thrombosis and stroke
    d. Musculoskeletal disorders, arthralgias
    e. a, b and c

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

Evaluation Form:
Breast Cancer Update for Surgeons — Issue 4, 2004

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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

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Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
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Debu Tripathy, MD	5 4 3 2 1	5 4 3 2 1
Stephen B Edge, MD	5 4 3 2 1	5 4 3 2 1
D Craig Allred, MD	5 4 3 2 1	5 4 3 2 1

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FOLLOW-UP

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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