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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 FOR *BREAST CANCER UPDATE* FOR SURGEONS

- 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 2 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Khan, Henderson, Paik and Boccardo on the integration of emerging clinical research data into the management of breast cancer.

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Soonmyung Paik, MD	Grants/Research Support: Genomic Health Inc
Francesco Boccardo, MD	Grants/Research Support: AstraZeneca Pharmaceuticals LP, Eli Lilly & Company Honorarium: AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals, Eli Lilly & Company, Novartis Pharmaceuticals

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
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aminoglutethimide	Cytadren®	Novartis Pharmaceuticals
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
exemestane	Aromasin®	Pfizer Inc
hydrocortisone	Various	Various
letrozole	Femara®	Novartis Pharmaceuticals
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
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Editor's Note

Visionary

Last fall I had the pleasure of interviewing legendary cancer research leader Dr Aron Goldhirsch for our sister series for medical oncologists. During this conversation about the International Breast Cancer Study Group that Aron heads, I happened to mention a little-noticed Italian study published in 2001 by Dr Francesco Boccardo. Aron perked up immediately at the mention of the paper. "Boccardo is a visionary," he exclaimed. "He has always been two steps ahead of the rest of us." Dr Goldhirsch's comments about his colleague came to mind when I began to gear up for the 2003 San Antonio Breast Cancer Symposium. Our education group invited Dr Boccardo to participate in one of the "Meet the Professor" sessions we hosted during the conference, and he was gracious enough to accept.

As I stood in front of an audience poised to ask questions, I felt compelled to relate Aron's accolades. Dr Boccardo took the podium, smiled and almost blushed. After a modest quip to offset his embarrassment, he answered the many questions from the audience in the cautious and very thoughtful manner for which he is known. Our "Meet the Professor" session took place one day after Boccardo had made a plenary presentation of a study that randomly assigned postmenopausal women on two to three years of adjuvant tamoxifen to either complete five years of therapy or be switched to anastrozole (Arimidex®).

Women who switched to the aromatase inhibitor had fewer relapses and longer survival. In the enclosed program, Dr Boccardo reviews the data demonstrating an advantage for anastrozole and his reflections on the many treatment strategies he has pioneered in the last two decades — five years of tamoxifen, tamoxifen in postmenopausal women, ovarian suppression in premenopausal women, chemotherapy plus tamoxifen, and now anastrozole after two to three years of tamoxifen.

Also during the San Antonio meeting, Dr Paul Goss presented the results of a study demonstrating an advantage to another aromatase inhibitor, letrozole (Femara®), compared to placebo after five years of tamoxifen. A third study has been subsequently published in the *New England Journal of Medicine*, documenting an advantage to switching to another aromatase inhibitor, exemestane (Aromasin®), after two years of tamoxifen.

In this program, Dr Craig Henderson comments that all of this accumulating evidence points in the same direction — aromatase inhibitors clearly seem

superior to tamoxifen in postmenopausal women, and the role of tamoxifen in the adjuvant setting for these women (if any) will likely require redefinition. Dr Henderson and many other research leaders believe that the optimal strategy is to start with the most effective therapy; therefore, he uses up-front aromatase inhibitors.

While the aromatase inhibitor story is rapidly unfolding, this issue of our series also discusses two other research concepts that are worthy of attention. Seema Khan reviews a plethora of clinical research questions in breast surgery, but one of the most interesting to me was a paper she and her colleague, Monica Morrow, published on the role of primary breast surgery in women presenting with metastatic disease. To the surprise of many, this retrospective yet very convincing analysis of SEER data demonstrated a survival benefit in women who had their primary tumors resected.

This paper is just one of a number of recent data sets that focus greater attention on the importance of local tumor control with both surgery and radiation therapy in determining long-term outcome. Perhaps we will eventually see that the blacks and whites of Halsted and Fisher are actually more of a continuum of grays.

Finally, I interviewed the investigator who presented the most talked-about paper at the San Antonio meeting, Soonmyung Paik. His study of a genomic profiling assay of tumor tissue from participants in the classic NSABP-B-14 trial suggests that this new tissue assay may be able to identify a substantial fraction of women in whom the incremental gain from chemotherapy will be so small that it can be avoided.

Dr Paik also commented on two other current tissue assays that are critical in breast cancer management — HER2 and estrogen/progesterone receptor. Many studies have documented a wide variation in quality control in performance of these evaluations in community laboratories. The importance of accurate measurement of ER/PR in initial primary surgery has been known for two decades but the significance of HER2 has only recently been appreciated. Not only is this assay critical to entry in the current ongoing adjuvant trastuzumab (Herceptin®) trials, but oncologists consider this result in determining prognosis and selecting chemotherapy and endocrine treatment. Dr Paik discusses recent NSABP work clearly documenting that the volume of HER2 testing performed by a laboratory directly correlates with quality control.

The concept of a research "visionary" is interesting to consider. Obviously, endocrine "mavens" like Boccardo saw long before any of us the potential value of these agents. But the truth is that many promising research concepts will fail to live up to expectations. We all must hope that research leaders look past these failures and continue to pursue what their minds' eyes see, so that we all can benefit from a new generation of treatment paradigms.

— Neil Love, MD

Edited comments by Seema A Khan, MD

CALGB-9343: Whole breast irradiation versus no further therapy in elderly women

CALGB-9343 recruited women 70 years of age or older with tumors no greater than two centimeters and negative margins. The patients underwent breast-conserving surgery, received adjuvant tamoxifen and were randomly assigned to receive radiotherapy or not. The major endpoint was local recurrence and now, with at least four years of follow-up, the rate is one percent in the radiated group and four percent in the patients who did not undergo radiation. As this study demonstrates, women age 70 and older have a very low recurrence risk to begin with, so the value of radiation for smaller tumors may be questionable. In these patients, when radiation is utilized, partial breast irradiation might be useful, but we have limited data to suggest cosmesis is equivalent to standard radiation therapy.

Assessment of ER status in patients with DCIS

In the original NSABP-B-24 study, which randomly assigned women with DCIS to adjuvant tamoxifen versus placebo, ER status was not measured. Craig Allred and the NSABP subsequently retrieved 600 to 800 blocks from that trial and found that ER status strongly influenced the benefit from tamoxifen, whereas in patients with ER-negative disease, the recurrence rates were almost identical and the small, nonsignificant benefit seen was probably related to quality control of the ER assay. Quality control in determining estrogen status is an important issue. Grade I DCIS is almost always positive; if it's reported as ER-negative, one should question the accuracy of the assay.

Adjuvant endocrine therapy and the surgeon's role

It is rare for women to discontinue adjuvant tamoxifen due to toxicities and in our experience, adherence to tamoxifen therapy is excellent. We have also found patients very tolerant of the aromatase inhibitor side effects. I've seen slightly more of the musculoskeletal side effects than I expected, particularly arthralgias. A few patients have discontinued anastrozole, but in most patients it's extremely well tolerated.

Dr Khan is an Associate Professor of Surgery at Northwestern University Feinberg School of Medicine and Director of the Bluhm Family Breast Cancer Early Detection and Prevention Program in Chicago, Illinois.

We utilize alendronate more in women receiving anastrozole than in women receiving tamoxifen, but anastrozole's increased efficacy and better tolerability makes it worthwhile to use the aromatase inhibitor. Examining the data from the ATAC trial, the efficacy curves are separating, so there probably is an advantage to anastrozole. Of course, each patient's comorbidities need to be considered. For example, in a frail patient with a history of osteoporosis, the small improvement in efficacy associated with anastrozole may be offset by its effects on bone mineral density.

As the palate of endocrine therapy increases in complexity, probably more surgeons will defer to medical oncologists rather than prescribe adjuvant endocrine therapy. I've started many women on tamoxifen in my surgical career, fewer on aromatase inhibitors, but in general I encourage women to discuss adjuvant endocrine therapy with a medical oncologist. I discuss adjuvant therapy with them as well, but I believe it's helpful for patients to have two perspectives on this issue. The level of comfort each surgeon has with these discussions varies, as does the amount of information they will provide and how much they'll participate in the decision making.

Resection of the primary in women with *de novo* metastatic disease

SWOG published data from a study of Stage IV renal cell carcinoma in which patients with intact primary tumors were randomly assigned to systemic therapy with or without resection of the primary tumor. A statistically significant median increase in survival of approximately three months was seen in patients who underwent resection. Prompted by this data, we examined the National Cancer Data Base (NCDB) for the utilization of resection of the primary tumor in women with *de novo* metastatic breast cancer and whether resection impacted survival (Figures 1.1, 1.2).

We found that 60 percent of women who present with metastatic breast cancer and intact primary tumors are resected, and those women have a better survival rate. In addition, a clear margin status had a significant impact on survival, extending the three-year mean from approximately 19 months in patients who did not have their primary tumor resected, to 32 months in patients receiving a total mastectomy. Chest wall disease is a major concern for patients and physicians alike, which is one of the reasons these patients undergo resection of the primary tumor. However, we currently don't have good data on how often uncontrolled chest wall disease occurs.

The SWOG trial offers the first suggestive evidence from a large data set that there may be an advantage to resection of the primary tumor with metastases present. In the absence of randomized trial data, individual practitioners are left with the decision of how to manage these cases. I see a handful of these cases each year and, in consultation with the medical oncologist, we begin with systemic therapy. If the woman responds well to systemic therapy and is relatively free of co-morbidities, then I discuss resection of the primary tumor with her.

Figure 1.1

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 mo
Clear margins			
Partial mastectomy	34.7%	16.6%	22.9 mo
Total mastectomy	35.7%	18.4%	25.3 mo
Involved margins			
Partial mastectomy	26.4%	11.3%	17.6 mo
Total mastectomy	26.1%	11.5%	20.0 mo

DERIVED FROM: Khan SA et al. **Does aggressive local therapy improve survival in metastatic breast cancer?** *Surgery* 2002;132(4):620-6; discussion 626-7. **Abstract**

Figure 1.2

Emerging Evidence of Benefit from Local Control of the Primary Tumor in Patients with Metastatic Disease

"Data from other tumor types may also point to a possible survival advantage for patients with distant metastases undergoing resection of the primary tumor. A retrospective analysis of 13,175 cases of gastric carcinoma in the Birmingham Cancer Registry showed the best survival for patients undergoing palliative resection, in the presence of both locally advanced and 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):620-6; discussion 626-7. **Abstract**

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**.

Flanigan RC et al. **Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer.** *N Engl J Med* 2001;345:1655-9. **Abstract**

Hughes KS et al. **Comparison of lumpectomy plus tamoxifen with and without radiotherapy (RT) in women 70 years of age or older who have clinical stage I, estrogen receptor positive (ER+) breast carcinoma.** *Proc ASCO* 2001;**Abstract 93**.

Khan SA et al. **Does aggressive local therapy improve survival in metastatic breast cancer?** *Surgery* 2002;132(4):620-6; discussion 626-7. **Abstract**

Edited comments by I Craig Henderson, MD, FACP, FRCP

Role of the aromatase inhibitors in the adjuvant setting

The aromatase inhibitors are now clearly viewed as the most effective and important adjuvant endocrine therapy for postmenopausal women. In the last three or four years we've seen an unexpected shift from tamoxifen, the "star" for 30 years, to the aromatase inhibitors. After the presentation of the initial ATAC trial results, ASCO did not recommend the aromatase inhibitors as adjuvant therapy because there were no survival data. Interestingly, the FDA approved adjuvant anastrozole as adjuvant therapy. It's also clear to me that community-based doctors are using adjuvant anastrozole to a greater extent than most academic physicians.

The dramatic results from the MA17 trial of letrozole after tamoxifen have thrown everyone into turmoil (Figure 2.1). The levels of significance are so great that neither physicians nor patients can ignore them. Again, we don't have survival data, and it will be difficult to evaluate survival at any point in the future. Additionally, we won't be able to replicate those results because it wouldn't be ethical to repeat that study. In fact, the NSABP trial evaluating exemestane in postmenopausal patients with receptor-positive breast cancer, which was identical in design, was closed to accrual immediately. I also don't think it's possible to ignore the ATAC trial results any longer.

Aromatase inhibitors following five years of adjuvant tamoxifen

It may be reasonable to offer an aromatase inhibitor to patients who completed a five-year course of adjuvant tamoxifen as long as five or 10 years previously. However, with every year that passes, the absolute risk of recurrence decreases; therefore, the risk-to-benefit ratio changes. Every year, the risks become more important relative to the benefit. As the risk of recurrence decreases, the toxicities of therapy become much more important.

Endocrine therapy following five years of adjuvant anastrozole

Kent Osborne proposed the possibility of studying the use of adjuvant tamoxifen in women who have already received five years of adjuvant anastrozole. Most physicians are concerned about this strategy because there are no data to support

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it. Another option would be 10 years of an adjuvant aromatase inhibitor. Most physicians seem to be more comfortable with that strategy.

Figure 2.1

Randomized Phase III Study of Letrozole versus Placebo in Postmenopausal Women with Primary Breast Cancer Who Have Completed at Least Five Years of Adjuvant Tamoxifen

Accrual: 5,187 (Closed)

Protocol IDs: CAN-NCIC-MA17, CLB-49805, E-JMA17, EORTC-10983, IBCSG-BIG97-01, JRF-Vor-Int-10, NCCTG-CAN-MA17, NCCTG-JMA.17, SWOG-CAN-MA17, SWOG-JMA17

Disease-free Survival and Recurrences or a New Contralateral Primary Tumor (median follow-up, 2.4 years)

	Letrozole (N=2,575)	Placebo (N=2,582)	*p*-value
Estimated 4-year DFS	93%	87%	$p < 0.001$
Local or metastatic recurrences or a new contralateral primary tumor	75 (2.9%)	132 (5.1%)	$p < 0.00008$

SOURCES: 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

NCI Physicians Data Query, January 2004.

Italian Tamoxifen Arimidex® (ITA) trial: Adjuvant anastrozole following two years of adjuvant tamoxifen

In the ITA trial, patients received a total of five years of therapy — either tamoxifen alone or tamoxifen for at least two years followed by anastrozole (Figure 2.2). Results from the ITA trial confirm the data from the MA17 trial in which patients received five years of adjuvant tamoxifen and then an aromatase inhibitor. It is unknown whether 10 years of an adjuvant aromatase inhibitor alone would be more effective than five years of adjuvant tamoxifen followed by five years of an adjuvant aromatase inhibitor. Although the ITA trial was a small study, I'm willing to accept it as being fundamentally correct because the results are consistent with those from the MA17 trial. In both trials, a clear advantage was demonstrated for the crossover to an aromatase inhibitor after tamoxifen.

Figure 2.2

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):3;**Abstract 3**.

Switching to adjuvant anastrozole while receiving adjuvant tamoxifen

In a postmenopausal woman who has received two to three years of adjuvant tamoxifen and is doing well, I wouldn't recommend changing to adjuvant anastrozole. I would have the patient finish the five years of adjuvant tamoxifen and then change to an aromatase inhibitor. However, if the patient felt strongly about switching or was having some symptoms on tamoxifen, I'd be very comfortable switching therapy at two or three years.

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):3;**Abstract 3**.

Delozier T et al. **Delayed adjuvant tamoxifen: Ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial).** *Ann Oncol* 2000;11(5):515-9. **Abstract**

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**

Edited comments by Soonmyung Paik, MD

Multigene prognostic test for women with node-negative, estrogen receptor-positive breast cancer treated with adjuvant tamoxifen in NSABP trials

Practicing medical oncologists have wanted a prognostic marker to help them select patients with node-negative, estrogen receptor-positive breast cancer who would be candidates for adjuvant chemotherapy. The NSABP developed a strategy to identify a strong, robust prognostic factor that would stratify such patients into low- and high-risk groups. With such a prognostic factor, the NSABP could tailor their clinical trials. For example, in patients with low-risk disease, we could focus our trials on optimizing local therapy with partial breast irradiation. On the other hand, in patients with high-risk disease, we could optimize approaches with chemotherapy or targeted therapy.

Since we could not procure fresh tumor specimens, we had to develop a test that would work, reproducibly, using routinely processed paraffin blocks. About three years ago, the NSABP realized it was best not to develop this strategy in-house because eventually it needed to be available to the public. We decided to work with an industry partner, Genomic Health, who had a readily available technology that we identified as an extremely robust and reproducible methodology.

Cohort selection for multigene prognostic test development and validation

We wanted to make sure that we had two independent cohorts of similar patients — one in which to develop the prognostic test and the other in which to validate it. In the NSABP's tissue bank of paraffin blocks, the most relevant cohort included patients with node-negative, estrogen receptor-positive breast cancer who were treated with adjuvant tamoxifen from two different trials (NSABP-B-20 and NSABP-B-14).

Gene selection for use in the prognostic test

Two hundred and fifty candidate genes were selected from the existing literature on the microarray analysis of breast cancer. Then, a real-time RT-PCR assay for paraffin blocks was developed for each gene. Two different study populations were then evaluated for the expression of the candidate genes, the results of which were presented at the 2003 ASCO meeting.

Dr Paik is the Director of the NSABP Division of Pathology in Pittsburgh, Pennsylvania.

Obviously, not all 250 genes worked, and we ended up with 185 candidate genes to evaluate in the NSABP-B-20 cohort. Out of those, when correlated with more than 10 years of median follow-up, 41 genes were found to relate with clinical outcome on univariate analysis. On multivariate analysis, 12 genes remained highly significant. Then, we went back to two previous studies by Esteban and Cobleigh and determined whether any of those 41 genes were also prognostic in those cases, and we found about 12 common genes that were highly prognostic for all three completely different cohorts. Based on the findings from those three studies, we developed a prognostic algorithm with 16 cancer genes and five reference genes to be tested in the validation study.

Validation study for the multigene prognostic test

The validation study used the material from a prospective randomized clinical trial (NSABP-B-14). A single prognostic algorithm was validated in the NSABP-B-14 cohort. About 50 percent of the patients were identified as low risk (less than a 10 percent recurrence rate at 10 years), about 25 percent as intermediate risk, and the other 25 percent as high risk (Figure 3.1). We found a very significant difference between the risk groups. In a multivariate model, the patient's age and tumor size were significant prognostic factors. However, based on the 21-gene algorithm, the recurrence score prevailed as the strongest prognostic factor.

Figure 3.1

Ten-Year Distant Recurrence Rate According to Risk Group

Risk group	Percent of patients	10-y distant recurrence rate	95% confidence interval
Low	51%	6.8%*	4.0-9.6%
Intermediate	22%	14.3%	8.3-20.3%
High	27%	30.5%*	23.6-37.4%

$p < 0.00001$ for comparison between high- and low-risk groups

SOURCE: Paik S. **Development and validation of a multi-gene RT-PCR assay for predicting recurrence in node negative, ER+, tamoxifen-treated breast cancer patients NSABP studies B-20 and B-14.** Presentation at the San Antonio Breast Cancer Symposium 2003;**Abstract 16**. Available at: **http://www.sabcs.org**. Accessed March 17, 2004.

Reporting the recurrence score

The recurrence score is a mathematical algorithm developed from the level of expression of the 16 cancer genes and five reference genes. We mathematically transformed the level of gene expression into a score that ranges from zero to 100. In the patients with a very good prognosis, about 82 percent have a score below 50. Actually, the recurrence score is a continuous variable without a cutoff. A linear relationship exists between a recurrence score of up to 50 and the 10-year cumulative recurrence rate. The best use of this recurrence score algorithm

is as a continuous variable, rather than grouping the patients together. When a patient receives a report, it consists of a numerical score with an estimated 10-year recurrence rate, plus or minus a very narrow confidence interval.

Quality control for HER2 testing

When the NSABP designed the B-31 adjuvant trastuzumab trial, we were very reluctant to require central testing for HER2. I always believed that it was not possible for a pathologist to misclassify patients with IHC 3+ overexpression, and the entry criteria for the study required patients' tumors to be IHC 3+. However, we built a safeguard into the protocol such that we would perform central testing in the initial 100 patients entered into the study.

HER2 status was measured by both IHC and FISH, so HER2-negative tumors were truly negative. We were shocked, because the false-positive rate was 18 percent (Figure 3.2). The Intergroup trial demonstrated essentially the same finding, and these results were a big "wake-up call" for the community.

Based on the false-positive rate, we revised the protocol so that patients had to be tested by an approved laboratory, which included those performing over 100 tests per month or those performing fewer tests but demonstrating a concordance rate between IHC and FISH of over 95 percent. The end result was a dramatic improvement in the quality of test results; the false-positive rate dropped from 18 percent to three percent (Figure 3.3).

Clinically, oncologists should demand to know the concordance rate between IHC and FISH in the laboratories they utilize. Over 95 percent of patients with IHC 3+ tumors should have been validated as FISH-amplified (Figure 3.4). Oncologists should also examine the concordance rates between IHC 0 and 1+ and FISH, because false-negative results have extremely important clinical implications. The College of American Pathologists published a recommended format for the HER2 IHC report that clearly indicates this information should be provided by laboratories.

Figure 3.2

Reproducibility of Community Laboratories' Results for HER2-Positive Tumor Specimens from NSABP-B-31

Central laboratory's results	Percent of cases (n=104)
Strongly positive (3+) by the HercepTest™ assay	79%
Positive for gene amplification by the PathVysion™ FISH assay	79%
Neither strongly positive (3+) by the HercepTest™ assay nor positive for gene amplification	18%

SOURCE: Paik S et al. **Real World Performance of HER2 Testing — National Surgical Adjuvant Breast and Bowel Project Experience.** *J Natl Cancer Inst* 2002;94:852-4. **Abstract**

Figure 3.3

False-Positive Rates for HER2 Tests Performed by NSABP-Approved Laboratories

Original assay used by NSABP-approved laboratory	Central PathVysion™ FISH assay not amplified
FISH (n=133)	4.5%
IHC (n=107)	2%
Total (n=240)	3%

SOURCE: Paik S. Presentation, San Antonio Breast Cancer Symposium, 2002. **Successful Quality Assurance Program for HER2 Testing in the NSABP Trial for Herceptin®.** *Breast Cancer Res Treat* 2002;76(Suppl 1);**Abstract 9**.

Figure 3.4

Defining HER2-Positivity

How do you interpret the following lab results?

	IHC 3+	IHC 2+	IHC 1+
HER2-positive	75%	5%	–
HER2-positive only with FISH confirmation	25%	95%	55%
HER2-negative	–	–	45%

How often do you obtain FISH to determine a tumor's HER2 status?

Always	Commonly	Occasionally
35%	38%	27%

SOURCE: 2003 *Breast Cancer Update* Patterns of Care Study.

Select Publications

Cell Markers and Cytogenetics Committees College of American Pathologists. **Clinical laboratory assays for HER-2/neu amplification and overexpression: Quality assurance, standardization, and proficiency testing.** *Arch Pathol Lab Med* 2002;126(7):803-8. **Abstract**

Cobleigh MA et al. **Tumor gene expression predicts distant disease-free survival (DDFS) in breast cancer patients with 10 or more positive nodes: High throughput RT-PCR assay of paraffin-embedded tumor tissues.** *Proc ASCO* 2003;**Abstract 3415**.

Esteban J et al. **Tumor gene expression and prognosis in breast cancer: Multi-gene RT-PCR assay of paraffin-embedded tissue.** *Proc ASCO* 2003;**Abstract 3416**.

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**.

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**

Edited comments by Francesco Boccardo, MD

Rationale for the use of adjuvant aromatase inhibitors following adjuvant tamoxifen

The newer aromatase inhibitors are as effective as, if not better than, tamoxifen as first-line therapy for advanced disease; they do not affect the uterus or increase the risk of thromboembolic disease. On the other hand, aromatase inhibitors can lead to osteoporosis, and as reported in the ATAC trial, the aromatase inhibitors are associated with an increased incidence of fractures.

Approximately 10 to 12 years ago, we began exploring the role of adjuvant aromatase inhibitors following a course of adjuvant tamoxifen. Although adjuvant tamoxifen is very effective, it is not devoid of serious side effects. Attention to the possible mechanisms of tamoxifen resistance was also growing. One particular mechanism of resistance, an increase in aromatase activity in the breast tumors of women exposed to tamoxifen, provided strong biological support for this sequencing approach.

We believed a sequential approach could have potential advantages over a five-year course of adjuvant tamoxifen or even an adjuvant aromatase inhibitor. A sequential approach would allow women to receive a class of compounds that might help circumvent tamoxifen resistance, while limiting the exposure to aromatase inhibitors and costs of treatment.

Italian Tamoxifen Arimidex® (ITA) trial

In the ITA trial, 448 postmenopausal women with ER-positive, node-positive breast cancer were randomly assigned to continue tamoxifen or switch to anastrozole following treatment with two to three years of adjuvant tamoxifen. The treatment groups were balanced with respect to median age, tumor size and grade, number of involved nodes, type of primary treatment, and prior radiation therapy or chemotherapy. The median age for both groups was 63 years. The median duration of tamoxifen therapy prior to randomization was 28 months in each group.

After a median follow-up of three years, 17 recurrences occurred in the women who switched to anastrozole and 45 recurrences occurred in the women who continued on tamoxifen. The women who continued on tamoxifen had more

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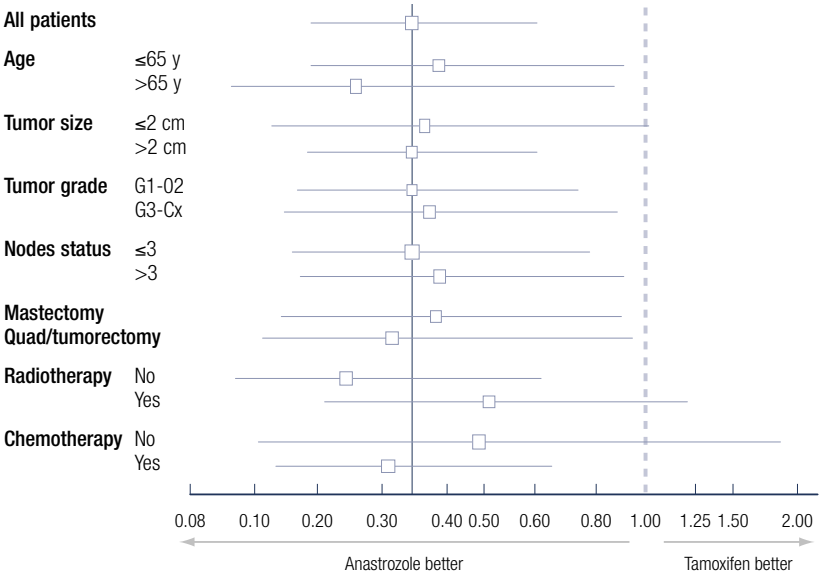
second primary tumors (including five endometrial cancers), distant metastases and locoregional recurrences (including ipsilateral breast recurrences, locoregional node recurrences, or both). According to the Kaplan-Meier curves, the women who switched to anastrozole had a significantly longer event-free, progression-free and local relapse-free survival. They also had a longer, although not significant (p = 0.06), distant metastases-free survival. Overall survival (p = 0.1) was also longer for the women who switched to anastrozole, but there were few deaths since the data are immature.

The treatment discontinuation rates for both groups were similar (8.4 percent for tamoxifen and eight percent for anastrozole). Women who continued on tamoxifen exhibited significantly more gynecologic changes, many of which were serious and required hospitalization. More severe treatment-related adverse events were reported in the women who continued on tamoxifen (Figure 4.1).

Figure 4.1

ITA Trial: Hazard of Progression by Subgroups



SOURCE: Boccardo F et al. Presentation, San Antonio Breast Cancer Symposium, 2003.

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):3;Abstract 3.

Post-test: *Breast Cancer Update* for Surgeons, Issue 2, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The ATAC trial demonstrated disease-free and overall survival advantages to anastrozole compared to tamoxifen.**
   a. True
   b. False

2. **The MA17 trial randomly assigned patients who had received a five-year course of adjuvant tamoxifen to:**
   a. Letrozole or placebo for five years
   b. Anastrozole or placebo for five years
   c. Exemestane or placebo for five years
   d. None of the above

3. **The Italian Tamoxifen Arimidex® (ITA) trial randomly assigned patients who had received at least two years of adjuvant tamoxifen to:**
   a. Anastrozole or placebo
   b. Anastrozole or tamoxifen
   c. Letrozole or placebo
   d. Letrozole or tamoxifen

4. **In the CALGB study comparing whole breast irradiation versus no further therapy in elderly women, the local recurrence rates were:**
   a. Lower in patients who received radiation
   b. Lower in patients who did not receive radiation
   c. There was no difference in the local recurrence rates between the two groups

5. **When Craig Allred retrospectively evaluated data from NSABP-B-24, randomly assigning women with DCIS to adjuvant tamoxifen versus placebo, it was found that:**
   a. Patients with ER-positive DCIS experienced greater benefit from tamoxifen
   b. Patients with ER-negative DCIS experienced greater benefit from tamoxifen
   c. There was no difference in patient benefit in ER-positive versus ER-negative DCIS

6. **In a nonrandomized study of the National Cancer Data Base, resection of the primary tumor in women with *de novo* metastatic breast cancer resulted in improved survival.**
   a. True
   b. False

7. **The technology used in the multigene prognostic test is RT-PCR.**
   a. True
   b. False

8. **The multigene prognostic test was developed and validated in which types of patients?**
   a. Patients with ER-negative, node-positive breast cancer
   b. Patients with ER-positive, node-positive breast cancer
   c. Patients with ER-positive, node-negative breast cancer
   d. None of the above

9. **Sixteen cancer genes and five reference genes are measured by the multigene prognostic test.**
   a. True
   b. False

10. **Compared to women who completed five years of tamoxifen in the Italian Tamoxifen Arimidex® (ITA) trial reported by Dr Boccardo, those who switched to anastrozole demonstrated:**
    a. Significantly longer event-free, progression-free and local relapse-free survival
    b. A trend for distant metastases-free survival
    c. A trend for improved overall survival, but with relatively few events at this point
    d. All of the above

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

Evaluation Form:
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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 NA
- 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 NA
- Describe and implement an algorithm for HER2 and estrogen receptor testing in the primary breast cancer setting . . . . . 5 4 3 2 1 NA
- 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 NA
- 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 NA
- 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 NA

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I Craig Henderson, MD, FACP, FRCP	5 4 3 2 1	5 4 3 2 1
Soonmyung Paik, MD	5 4 3 2 1	5 4 3 2 1
Francesco Boccardo, MD	5 4 3 2 1	5 4 3 2 1

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Breast Cancer™
UPDATE

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