

Breast Cancer™

U P D A T E

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 5 of *Breast Cancer Update for Surgeons* is to support these global objectives by offering the perspectives of Drs Morrow, Dixon and Burstein on the integration of emerging clinical research data into the management of breast cancer.

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HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. BreastCancerUpdate.com/Surgeons includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in red underlined text.

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Dr Morrow – No financial interests or affiliations to disclose

Dr Dixon – Grants/Research Support and Consultant: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals, Pfizer Inc

Dr Burstein – Grants/Research Support: Genentech BioOncology

UPCOMING EDUCATIONAL EVENTS

2005 American Society of Clinical Oncology
Gastrointestinal Cancers Symposium:
January 27-29, 2005

Westin Diplomat
3555 South Ocean Drive
Hollywood, FL
Event website: www.asco.org/ac/1,1003,12-002664-00_18-0034631,00.asp

2005 American Society of Clinical Oncology
Prostate Cancer Symposium:
February 17-19, 2005

Hyatt Grand Cypress
One Grand Cypress Blvd
Orlando, FL
Event website: www.asco.org/ac/1,1003,12-002665-00_18-0034689,00.asp

Miami Breast Cancer Conference:
February 23-26, 2005

Loews South Beach
1601 Collins Avenue
Miami Beach, FL
Event website:
www.cancerconf.com/index.html

10th National Comprehensive Cancer Network
Annual Conference: March 16-20, 2005

Westin Diplomat
3555 South Ocean Drive,
Hollywood, FL
Event website: www.nccn.org/professionals/meetings/10thannual/default.asp

Oncology Nursing Society; 30th Annual Congress:
April 28-May 1, 2005

Orlando, FL
Event website: www.ons.org/nursingEd/Conferences/congress.shtml

41st American Society of Clinical Oncology
Annual Meeting: May 13-17, 2005

Orange County Convention Center
Orlando, FL
Event website: www.asco.org/ac/1,1003,12-002092,00.asp

2005 American Urological Association
Annual Meeting: May 21- 26, 2005

San Antonio, TX
Event website: www.aa2005.org/am05/?CFID=1463668&CFTOKEN=29660692

2005 American Society for Therapeutic
Radiology and Oncology Annual Meeting:
October 16-20, 2005

Denver, CO
Event website:
www.astro.org/annual_meeting/

2005 San Antonio Breast Cancer Symposium:
December 2005

San Antonio, TX
Event website:
www.sabcs.org/Index.asp



Editor's Note

When in doubt, fire the coach

The hapless Miami Dolphins sacrificed their head coach recently, in acknowledgement that this football team is lost at sea. The talent pool had become dry, and every game plan ended in disaster. After years of excuses and pathetic claims that even though they couldn't win games, the margins of loss were decreasing, the team ran up the white flag and decided to start over.

In my pessimistic moments, cancer research seems to have similarly run aground, and while we have made modest improvements over the years, each new "season" seems to end up as another losing one. I have wondered what would happen if, in our search for new ideas and better answers, we approached cancer research like football, looking for promising talent? This issue of our series brings to you three bright minds with novel approaches who would certainly be first round draft choices.

Monica Morrow is the "shut-down cornerback" of breast cancer who, season after season, receives all-pro honors. In this issue, Monica tells us of her latest research endeavor, endocrine assays on the saliva of patients, and the preliminary data are quite interesting. In an ongoing series of premenopausal women on tamoxifen, marked variations were observed in estrogen and progesterone levels, and these correlated with breast density. This suggests the possibility that salivary assays might also correlate with treatment effects or prognosis. The assay is also one of the least invasive approaches available. "All the patient has to do is spit in a cup!" Monica chirps. We need more players like her on our re-engineered cancer squad.

Mike Dixon is another oncologic freethinker, and like Monica, one of a small band of breast cancer surgeons who regularly contributes to the rapidly evolving research database on systemic treatment strategies. I always love listening to Mike — a UK researcher — talk about his fascinating experience with neoadjuvant endocrine therapy, a treatment approach that until recently was largely ignored by clinical researchers in the United States. We are not about to make the same mistake, and despite Mike's European soccer connection, we welcome him as our punter, field goal kicker or both.

As we try to stack our team with hungry talent, a Marvin Harrison-like wide receiver is all but essential. One great candidate is Harold Burstein, a bright young Harvard oncologist who wrote the lead editorial last year to the Goss MA17 paper in the *New England Journal of Medicine*. Harold is part of a rapidly

growing group of investigators who believes in and is committed to molecularly targeted treatment of cancer. In this program, he states, for example, that HER2-negative breast cancer is as different from HER2-positive disease as pneumococcal pneumonia is from staphylococcal pneumonia. We need all the Harolds we can get, and will gladly use a first round draft choice for him.

What about the existing, longstanding therapies for breast cancer? Richard Margolese has been telling me for 15 years that someday, surgery will not be used to treat breast cancer and will be relegated to a leech-like role in the history of medicine. Notwithstanding the hundreds of thousands of women with local tumors who have been cured, surgery in this situation conceptually seems a bit like doing a pneumonectomy in someone with pneumonia. The problem is that no penicillin has yet arrived on the scene, although the molecularists will point to trastuzumab on good days as the beginning of the end.

Should we fire the coach (whomever that might be) or just keep plugging away? Who knows? I just hope there is a strong-armed quarterback out there, or maybe a couple of humongous defensive ends, who will help us win a few more games... soon.

— Neil Love, MD
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Recent Faculty Publications

Monica Morrow

Hollingsworth AB, Singletary SE, Morrow M et al. **Current comprehensive assessment and management of women at increased risk for breast cancer.** *Am J Surg* 2004;187(3):349-62. [Abstract](#)

Hynes DM, Weaver F, Morrow M et al. **Breast cancer surgery trends and outcomes: Results from a National Department of Veterans Affairs study.** *J Am Coll Surg* 2004;198(5):707-16. [Abstract](#)

White J, Moughan J, Pierce LJ, Morrow M et al. **Status of postmastectomy radiotherapy in the United States: A patterns of care study.** *Int J Radiat Oncol Biol Phys* 2004;60(1):77-85. [Abstract](#)

J Michael Dixon

Barber MD, Jack W, Dixon JM. **Diagnostic delay in breast cancer.** *Br J Surg* 2004;91(1):49-53. [Abstract](#)

Cameron DA, Kerr G, Jack W, Bowman A, Kunkler I, Dixon M, Chetty U. **Does everyone need letrozole after 5 years tamoxifen and breast conservation?** *Breast Cancer Res Treat* 2004;[Abstract 108](#).

Dixon JM. **Role of endocrine therapy in the neoadjuvant surgical setting.** *Ann Surg Oncol* 2004;11(1 Suppl):18-23. [Abstract](#)

Harold J Burstein

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](#)

Burstein HJ et al. **Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm.** *J Clin Oncol* 2003;21(15):2889-95. [Abstract](#)

Current status of sentinel lymph node biopsy for staging breast cancer

We now have clear data that sentinel lymph node biopsy (SLNB) is the staging procedure of choice for clinically node-negative breast cancer. Previously no long-term follow-up data was available, but now over 4,000 cases have been published with a mean follow-up of at least two years, which is when most axillary recurrences occur.

The incidence of isolated axillary failure is one tenth of one percent, which is very low. Additionally, we now have two randomized

trials evaluating the incidence of nodal positivity in women staged by sentinel node biopsy versus axillary dissection (Mansel 2004, Veronesi 2003).

The known false-negative rate of SLNB has always been a concern to some people. Even in the best of hands, a false-negative rate of three to five percent occurs — closer to 10 percent in multi-institutional studies. From these randomized trials in patients who were stratified by tumor size, the likelihood of finding a positive node is the same in the SLNB group as those who underwent axillary dissection, which suggests those are false negatives, probably in axillary dissection as well. I suspect these are the failure of the pathologist to identify the nodal metastases as opposed to failure to remove the proper node as seen in SLNB.

Sentinel node biopsy provides staging accuracy equivalent to axillary dissection, and the morbidity is clearly less — not only the immediate postoperative morbidity but also two years later in measurable differences in pain, paresthesia, arm motion and lymphedema. Additionally, we now know long-term local tumor control is good.

NSABP and American College of Surgeons trials of SLNB

The NSABP study included women with clinically node-negative disease who underwent a sentinel node biopsy. If the sentinel node was positive, they underwent an axillary dissection. If the sentinel node was negative, they were randomly assigned to undergo complete axillary dissection or observation. Many people, including myself, consider that an unusual question to ask. Why would removing negative axillary lymph nodes contribute to survival, given that



the NSABP asked and answered that question a number of years ago in their B-04 trial?

You could say their trial is a complicated quality control check. That study has closed to accrual but the data have not yet been presented. The other important question the study is addressing is the prognostic significance of “micrometastases” — immunohistochemically detected cells in the sentinel node.

The American College of Surgeons (ACOS) is conducting two major studies. The first is simply an observational study in patients who had clinically node-negative disease and were sentinel node-negative by H&E. They had no further axillary treatment, but immunohistochemistry was performed for prognostic purposes with a companion bone marrow study to evaluate “ultrastaging.” Some impressive data sets from Europe suggest that bone marrow micrometastases are independent prognostic factors, and this study attempts to validate that concept.

The more important study from the ACOS is the Z-11 trial in which patients with an H&E-positive sentinel node are randomly assigned to complete axillary dissection or axillary observation. The main aim of the trial is to definitively answer the question: Does axillary dissection offer a survival benefit?

SLNB and IHC-detected micrometastases

In our practice we ask the pathologist not to routinely perform IHC on the sentinel node because we’ve concluded that we don’t know what it means based on the available data, which continues to be confusing. A prospective study from the John Wayne Cancer Institute separated patients with standard H&E-detected macrometastases, patients with micrometastases less than two millimeters detected by H&E, patients with IHC-positive disease and patients with truly node-negative disease.

At a follow-up of approximately four and a half years, the patients with macrometastases had a significantly lower disease-free survival than anticipated. The disease-free survival curves for the other arms were completely overlapping.

The Italians discovered a disease-free survival difference in the patients with IHC-detected micrometastases. These findings illustrate that in this complicated arena — where different adjuvant therapies and the limitations of nonprospectively designed studies will influence the outcome — we have to wait to know for certain the meaning of IHC-detected micrometastases from the NSABP and American College of Surgeons trials.

From a practical standpoint, if a patient has multiple sentinel nodes with IHC-positive cells, it’s a matter of tumor burden, and we would treat her as if she had node-positive disease. The problem occurs when you see a couple of cells in a subcapsule or sinus, and you don’t know if they have the potential to grow or are just intransigent.

We don’t really know what to do with those patients. If the patient has ER-positive disease, administering endocrine therapy is perfectly satisfactory. The clinical

dilemma arises when you identify the patient as having node-positive disease, because then you would administer chemotherapy and endocrine therapy.

SLNB in the neoadjuvant setting

Initially, based on a number of small neoadjuvant studies in which the accuracy of the sentinel node biopsy was highly variable, my preference was to perform the sentinel node biopsy prior to the initiation of neoadjuvant therapy, so that it wasn't confounded in any way. If the sentinel node was positive, I would perform the axillary dissection later at the time of definitive breast surgery.

The SLNB data from the NSABP neoadjuvant trial made me much more comfortable performing the sentinel node biopsy after delivery of chemotherapy, recognizing this was not part of the trial design, but nonetheless, is a 427-patient data set that shows the same kind of accuracy of staging as seen in all multi-institution sentinel node trials.

From a practical point of view, in a patient who has received neoadjuvant therapy the decision is made whether to administer more treatment postoperatively based on the total extent of tumor response. In these cases, the lymph node is not nearly as decisive as it might be in a conventional patient who's having pure postoperative therapy.

The one argument in favor of continuing to perform pretreatment SLNB comes from our radiation oncology colleagues who have a great deal of difficulty figuring out what volume to treat. Those who are in favor of more aggressive irradiation in patients with positive nodes claim that knowing the nodal status prior to chemotherapy helps them, for example, to decide whether or not to treat supraclavicular or nodal fields.

MD Anderson study of neoadjuvant trastuzumab and chemotherapy

The pathologic complete response rate in the MD Anderson neoadjuvant trastuzumab trial (Buzdar 2004) of about 65 percent was unlike anything we've seen in any other trial of combination chemotherapy. Given that tumors overexpressing HER2 are often large and more rapidly growing, those findings have the potential to benefit many women.

My medical oncology colleagues expressed a lot of concerns about the small number of patients reported and potential toxicity in that setting. If I could see similar responses repeated in another data set, I would consider neoadjuvant trastuzumab and chemotherapy a worthwhile option for patients who met their criteria.

I would be uncomfortable with adjuvant trastuzumab in a nonprotocol setting; however, the line between inflammatory and metastatic breast cancer is not significant. Certainly, in a patient who receives conventional up-front chemotherapy and does not achieve a complete response to their inflammatory disease, and you can't operate on them and can't achieve local control, the addition of trastuzumab is perfectly reasonable.

Use of aromatase inhibitors in the adjuvant setting

Whether surgeons prescribe adjuvant aromatase inhibitors will depend on their level of comfort with the literature, counseling patients and dealing with any potential side effects. Adjuvant endocrine therapy has become much more complex in terms of the various options and what's known and unknown.

For postmenopausal patients who have been on adjuvant tamoxifen for two to three years, I refer them to the oncologist to determine if they should be switched to an aromatase inhibitor, unless they have very low-risk disease. In patients with tumors less than two centimeters who have node-negative disease and are tolerating tamoxifen, my threshold to switch to an aromatase inhibitor is higher. Any patient who has a higher risk of relapse deserves to have a discussion about switching to an aromatase inhibitor (Boccardo 2003, Coombes 2004) as we do in women who have completed five years of tamoxifen (Goss 2003).

The aromatase inhibitors cause some non-life-threatening side effects — such as musculoskeletal aches and pains — more than I expected based on the clinical trial data (1.1). On the other hand, I have been favorably impressed by the clear difference in vasomotor symptoms encountered with the aromatase inhibitors and the decreased rate of thrombosis and endometrial cancer compared to tamoxifen.

1.1 Side effects of anastrozole versus tamoxifen

Anastrozole significantly better tolerated with respect to:

- Endometrial cancer
- Vaginal bleeding
- Vaginal discharge
- Ischemic cerebrovascular events
- Venous thromboembolic events
- Hot flashes

Tamoxifen better tolerated with respect to:

- Musculoskeletal disorders
- Fractures

SOURCE: The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10. [Abstract](#)

Select publications

Buzdar AU et al. **Significantly higher pathological complete remission rate following neoadjuvant therapy with trastuzumab [Herceptin (H)], paclitaxel (P), and anthracycline-containing chemotherapy: Initial results of a randomized trial in operable breast cancer with HER-2 positive disease.** Presentation. ASCO, 2004; [Abstract 520](#).

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003; [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 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](#)

Mansel RE et al. **Sentinel node biopsy in breast cancer: The first results of the randomized multicenter ALMANAC Trial.** *Proc ASCO* 2004; [Abstract 506](#).

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

IMPACT neoadjuvant trial: A comparison of anastrozole, tamoxifen and the combination

Initially, the main objective of the IMPACT trial was biologic — to determine how cancer changes after treatment with anastrozole, tamoxifen or the two combined. In fact, the initial plan was to solely focus on biologic endpoints, and rigorous clinical evaluation was added in later.

The trial included patients regardless of their tumor size, and many of the patients had small tumors. It is clinically difficult to detect responses

in small tumors; therefore, I was not surprised that the IMPACT trial didn't demonstrate major clinical differences (Smith 2003). A difference was found in the patients with larger tumors; they were more likely to have breast-conserving surgery if they were treated with neoadjuvant anastrozole (2.1) — about twice that rate.

Those findings support the results from the neoadjuvant letrozole study, which demonstrated that a larger percentage of patients treated with letrozole had breast-conserving surgery than those receiving tamoxifen (Ellis 2001).

I believe the IMPACT trial demonstrates the poor utility of clinical response as an endpoint in neoadjuvant trials. In many respects, reduction in tumor volume is more valuable. If reduction in tumor volume had been evaluated for the patients in the IMPACT trial, I suspect the trial would have demonstrated that anastrozole was superior, as evidenced by the fact that more patients with larger tumors had breast-conserving surgery.

For surgeons who want to shrink larger tumors and be able to perform breast-conserving surgery, it's not just response but the degree of response that is important. In our neoadjuvant studies, the reduction in tumor volume was much better with all of the aromatase inhibitors (including anastrozole) compared to tamoxifen.

IMPACT neoadjuvant trial: Biologic endpoints

We collected tissue at baseline, 14 days and three months from the patients on the IMPACT study. We're currently completing the microarray assays on those



samples and have sufficient samples from the different treatment groups to determine which genes are switched on or off and whether the tumors become less aggressive at the end of the treatment period.

In a previous uncontrolled study, we found that anastrozole and letrozole reduced proliferation after 14 days of treatment. In the IMPACT trial, tamoxifen alone and the combination were identical after two weeks in terms of their ability to reduce proliferation. On the other hand, anastrozole was significantly better at reducing proliferation than either of the other two treatments (2.1) (Dowsett 2003a).

I don't suppose the biologic endpoints would have been believable if the ATAC adjuvant trial hadn't demonstrated that anastrozole was superior to tamoxifen and the combination (Baum 2003). For those of us who believe in these biologic models, it's great that the biologic model was validated in a large adjuvant study. I hope this will allow us to use some of these biologic markers as endpoints in future trials.

2.1 IMPACT Trial: Anastrozole (A) versus Tamoxifen (T) versus the Combination (C) as Neoadjuvant Endocrine Therapy for Postmenopausal Patients with Estrogen Receptor-Positive Breast Cancer (N=330)

	A	T	C
Objective clinical tumor response ¹	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery* after 3 months of treatment ¹	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after 2 weeks of treatment ^{2†}	76%	59%	64%

* Of the 220 patients with the surgeons' preferred surgery recorded at baseline, 56% were deemed to need a mastectomy. $p = 0.03$ for anastrozole versus tamoxifen.

† Reductions in Ki67 were virtually maximal at 2 weeks with only marginal changes between 2 and 12 weeks. p -value < 0.01 for anastrozole versus tamoxifen.

SOURCES: ¹ Smith I, Dowsett M, on behalf of the IMPACT Trialists. *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6; [Abstract 1](#).

² Dowsett M, Smith I, on behalf of the IMPACT Trialists. *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6; [Abstract 2](#).

ATAC adjuvant trial: Benefits according to estrogen- and progesterone-receptor status

In the ATAC adjuvant trial, we saw differences between anastrozole and tamoxifen based on their estrogen receptor (ER) and progesterone receptor (PR) expression. In the women with ER-positive and PR-negative tumors, the difference was great and was quite surprising — about a 50% reduction in recurrence rate in anastrozole compared to tamoxifen (2.2) (Dowsett 2003b).

Some data suggest that women with PR-negative disease are more likely to also have HER2-positive disease, whereas other data indicate that this is true for younger women, but not for older women. The great thing about the trans-ATAC trial, being run by Mitch Dowsett, is that they're collecting all of the tumor blocks, and we will soon learn the answer. It is our belief that the aromatase inhibitors have a greater effect than tamoxifen in patients with HER2-positive tumors.

2.2 Retrospective Analysis of the Recurrence Rates in the ATAC Trial According to Estrogen and Progesterone Receptor Status (Median Follow-Up = 47 Months)

Receptor status	N	Hazard ratio for anastrozole versus tamoxifen (95% CI)*	Recurrence reduction
ER-positive, PR-positive	5,704	0.82 (0.65-1.03)	18%
ER-positive, PR-negative	1,370	0.48 (0.33-0.71)	52%
ER-negative, PR-positive	220	0.79 (0.40-1.5)	21%
ER-negative, PR-negative	699	1.04 (0.73-1.47)	—

* Hazard ratios less than one indicate values in favor of anastrozole.

SOURCE: Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6; **Abstract 4.**

Sequential adjuvant hormonal therapy in postmenopausal women

It's not surprising that switching from adjuvant tamoxifen to a more powerful aromatase inhibitor improves outcome. In an era in which most patients will initially receive an adjuvant aromatase inhibitor, the issues include the duration of therapy with the aromatase inhibitor and whether those patients should at some point be switched to tamoxifen.

I believe the optimal strategy will be to start out with an adjuvant aromatase inhibitor. If adjuvant therapy is initiated with tamoxifen, many patients will have a recurrence before the best drug is used. One of the things we've learned in the treatment of cancer is to use the best agent first.

In terms of how long after completing five years of adjuvant tamoxifen an aromatase inhibitor should be initiated, the only relevant data are from a trial in patients who were treated with delayed adjuvant tamoxifen. That trial found that those women, even if they received adjuvant tamoxifen up to five years later, had an improvement in survival compared to women who never received adjuvant tamoxifen (Delozier 2000).

Therefore, I suspect that women who have been off of adjuvant tamoxifen for some time and are treated with an aromatase inhibitor will benefit compared to women who do not receive an aromatase inhibitor. All of our decisions are based on risk-to-benefit ratios. The benefits must be sufficient to consider treating a patient with drugs that have inherent risks.

IBIS-II prevention trial in postmenopausal women

The IBIS-II prevention trial will compare the aromatase inhibitor anastrozole to placebo. We'll all be surprised if anastrozole does not reduce the incidence of breast cancer. Although we're currently fixated on the bone effects associated with the aromatase inhibitors, I believe we will find that with the new powerful bisphosphonates, the bone effects will not be a long-term problem.

One of the strengths of the IBIS-II prevention trial is that it will help identify women in whom we need to do bone scans and those in whom we need to use bisphosphonates. In the separate bone subprotocol of the IBIS-II prevention trial, women with a high baseline bone mineral density (BMD) won't receive a bisphosphonate, women with a low baseline BMD will automatically receive a bisphosphonate, and women with a baseline BMD in the midrange will be randomly assigned to a bisphosphonate or placebo.

Select publications

Baum M. ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer.** *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](#).

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](#)

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](#)

Dowsett M et al. **Molecular effects of anastrozole (A) and tamoxifen (T) alone and combined (C) in the IMPACT trial of neoadjuvant treatment of primary breast cancer.** *Proc ASCO* 2004;[Abstract 537](#).

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003b;82(1 Suppl 1):6;[Abstract 4](#).

Dowsett M, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003a;82(1 Suppl 1):6;[Abstract 2](#).

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

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](#)

Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: The IMPACT trial.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6;[Abstract 1](#).

Incorporation of aromatase inhibitors in the adjuvant setting

Recently, we have received data on adjuvant therapy from the three largest treatment trials in the history of medical oncology — ATAC (Baum, 2003) with 9,000 patients and the CAN-NCIC-MA17 (Goss, 2003) and EU-20149 (Coombes, 2004) trials with approximately 5,000 patients each.

The ATAC trial examined front-line therapy comparing tamoxifen, anastrozole and the combination. The MA17 trial evaluated letrozole versus placebo after five years of adjuvant tamoxifen, and the EU-20149 study evaluated continued tamoxifen versus switching to exemestane after two to three years of adjuvant tamoxifen. A small but important Italian trial evaluated anastrozole after two to three years of tamoxifen.



While these trials provide a tremendous reservoir of data, they each examined a different sequence and utilized a different aromatase inhibitor. Nonetheless, they all showed a benefit with aromatase inhibitors, and it is currently believed that postmenopausal patients diagnosed early with hormone receptor-positive breast cancer probably should receive one of these agents at some point for optimal adjuvant therapy.

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Still, we don't really know the ideal time to begin an aromatase inhibitor or how to sequence these agents around tamoxifen. Nor do we know how long patients should take an aromatase inhibitor or which one is the most beneficial.

Toxicities of adjuvant endocrine therapies

In addition to efficacy, the other important data we can glean from the large adjuvant endocrine trials is the collective toxicity experience. All three studies demonstrated a greater risk of osteoporosis, osteoporotic fractures and musculoskeletal problems with aromatase inhibitors compared to tamoxifen.

A significant difference does not appear to be evident in the rates of bone loss, sexual dysfunction or musculoskeletal events between the steroidal aromatase inhibitor exemestane and the nonsteroidal aromatase inhibitors anastrozole and

letrozole. On the other hand, tamoxifen is associated with an increased risk of endometrial cancer and deep vein thrombosis, which are rare but worrisome side effects.

Bisphosphonates were not utilized in the adjuvant trials and they may reduce the incidence of bone loss; however, we have no substantial data on how best to treat osteopenia or osteoporosis in postmenopausal women taking aromatase inhibitors.

Trials examining this issue are underway and I suspect they will come up with effective strategies to deal with this toxicity. We also need to emphasize other strategies that can reduce bone loss, including weight-bearing exercises, treatment for other medical problems like thyroid conditions, calcium and vitamin D supplementation and smoking cessation.

Sequencing of endocrine therapy in the adjuvant setting

When deciding which endocrine therapy to utilize, I discuss the data with the patient and contrast the side effects of the different agents. If no patient-specific reason exists to avoid a drug — such as a history of deep vein thrombosis or severe osteoporosis — I generally begin with tamoxifen with the intent to switch to exemestane after two to three years, or I use anastrozole up front. Based on the subset analysis from ATAC, in a patient with ER-positive, PR-negative disease, I'm inclined to use anastrozole initially.

For the postmenopausal patient who has been doing well on tamoxifen for two or three years, I generally switch them to exemestane based on the EU-20149 data. Similarly, for patients who are finishing five years of tamoxifen, I frequently offer them letrozole based on MA17. I find the MA17 data particularly compelling for the patients at higher risk, because of the ongoing residual risk for recurrence years after the initial diagnosis.

In women with low-risk disease, the benefit is less and if a patient with a history of a tiny, node-negative breast tumor has been counting the days until she can quit her tamoxifen because she suffers from hot flashes, I'm less certain continued therapy is best for the patient. However, for most women at average risk, I strongly encourage letrozole after five years of tamoxifen.

After a patient completes five years of adjuvant tamoxifen, we don't know whether she benefits from further therapy begun six months, one year or three years later. MA17 included women who had finished tamoxifen within six months, and I believe it's reasonable to extrapolate the data to women who have completed tamoxifen within the past year or so.

However, for a woman who is recurrence-free three years after completing tamoxifen, the risk of recurrence has declined further, and it's difficult to know how the data relate to her. I would only offer that woman further therapy if she was particularly motivated to continue adjuvant therapy.

Adjuvant endocrine therapy and HER2 status

Within the next year or two we will have data from the adjuvant trastuzumab trials, and I expect these will be positive. If this happens, the 20 percent of patients with HER2-positive breast cancer will be treated differently and removed from the pool of patients with ER-positive breast cancer, and the prognosis for the remaining 80 percent will improve because we removed the poor-prognosis group.

For those remaining women, hormone therapy will be even more important, because it's the patients with HER2-positive disease that historically have been more resistant to endocrine treatment.

HER2-positive breast cancer is probably less sensitive to the effects of tamoxifen than HER2-negative disease for a couple of reasons. One is the cross talk between the HER2 protein and estrogen- and progesterone-receptor protein pathways. The other is that in tumors that express both ER and HER2, the quantitative level of expression of ER is much less than women with ER-positive, HER2-negative tumors.

Algorithm for HER2 testing

HER2 testing should be ordered up front routinely for all patients. At our institution, we perform IHC initially and if the results are 3+, we consider it positive; zero or 1+ is considered negative, and 2+ results are sent for FISH testing. All clinicians should know the ability of their pathology department to perform these tests accurately. The literature suggests that smaller laboratories and pathology centers that perform relatively few tests tend to have fairly substantial rates of false-positive and false-negative findings (3.1).

Interestingly, that data has spread quickly throughout the pathology community, and I believe tremendous quality improvements have been made. The results today are more reliable than even just a few years ago. Physicians should ask their pathologist what the concordance is between their local testing and a referral lab and if they can't tell you, then you need to have it sent out to a referral lab that can.

3.1 Comparison of Local and Central HER2 Testing in Two Large Trials of Adjuvant Trastuzumab: NCCTG-N9831 and NSABP-B-31

Study	Local testing IHC 3+ confirmed by central HercepTest®	Local testing IHC 3+ HER2 gene amplification exhibited in central testing
NCCTG-N9831 (n=119) ¹	74%	66%
NSABP-B-31 (n=104) ²	79%	79%

SOURCES: ¹ Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7. [Abstract](#)

² Paik S et al. *J Natl Cancer Inst* 2002;94(11):852-4. [Abstract](#)

3.2 Quality of HER2 Testing

Intergroup Adjuvant Trial N9831: Experience with HER2 Testing¹

“The overall performance of HER2 testing by local laboratories in this initial sample of 119 patients was disappointing, with unacceptably high levels of discordance with central testing. Although most of our experience involved IHC, finding three discordant cases of nine tested by FISH indicates the need for further evaluation of this assay as used by local oncology and pathology practices.”

NSABP Experience with HER2 Testing in the Adjuvant Trial B-31²

“We found that an appreciable percentage of community-based assay results, which were used to establish the eligibility of patients to participate in B-31, could not be confirmed when tested in a central facility.”

[Citations omitted]

SOURCES: ¹ Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7. [Abstract](#)

² Paik S et al. *J Natl Cancer Inst* 2002;94(11):852-4. [Abstract](#)

MD Anderson preoperative trial of trastuzumab and chemotherapy

These patients had HER2-positive Stage II or III breast cancer and were randomly assigned to preoperative chemotherapy with or without trastuzumab (3.3). The study was designed to accrue between 150 and 200 patients, but it was closed after treating approximately 40 patients because of a robust difference in the pathologic complete response rates.

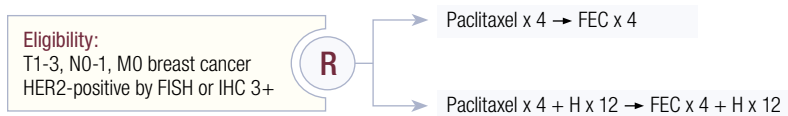
While women receiving anthracycline-containing chemotherapy alone had a pathologic complete response rate of approximately 20 percent, those who received chemotherapy plus trastuzumab had a pathologic complete response rate over 60 percent. They have stopped the randomization; however, they have continued treatment on the trastuzumab arm to acquire greater safety experience and to validate the findings.

Despite the early closure of this randomized trial, its findings are provocative. It demonstrates that trastuzumab is active in the preoperative setting and results in a complete remission in a much larger percentage of patients. If we think about the number of papers reporting on various regimens of preoperative chemotherapy, never stratified by HER2, they’ve always shown pathologic complete response rates of 15 to 20 percent, especially in hormone receptor-negative tumors.

This literature just became irrelevant because we now know that we can triple the pathologic complete response rate in HER2-positive tumors by adding trastuzumab. It’s very exciting to be in clinical research right now, because we’re learning that when we target these subsets of breast cancer with biologically focused therapies, we can radically change everything we know about treating this disease.

3.3 Phase III Study of Neoadjuvant Therapy with Anthracycline-Containing Chemotherapy and Paclitaxel with or without Trastuzumab in Patients with HER2-Positive Breast Cancer

Accrual: 42 (Early closure by DSMB)



Paclitaxel (P) = 225 mg/m² every three weeks

FEC = 500/75/500 mg/m²

H = trastuzumab 4 mg/kg on day 1, then 2 mg/kg weekly

Overall pathologic complete response

P + FEC (n=19)	26.3%		
P + FEC + H (n=23)	65.2%	95% CI (43%-84%)	p = 0.016

Pathologic complete response by hormonal receptor status

Positive			
P + FEC (n=11)	27.2%		
P + FEC + H (n=13)	61.5%		
Negative			
P + FEC (n=8)	25.0%		
P + FEC + H (n=10)	70.0%		

SOURCE: Buzdar A. Presentation. ASCO, 2004; [Abstract 520](#).

Select publications

Baum M et al. The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **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](#)

Burstein HJ. **Beyond tamoxifen—Extending endocrine treatment for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1857-9. No abstract available

Buzdar AU et al. **Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P), and anthracycline-containing chemotherapy (CT): Initial results of a randomized trial in operable breast cancer (BC) with HER/2 positive disease.** ASCO, 2004; [Abstract 520](#).

Coombes C 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](#)

Dowsett M, on behalf of the ATAC Trialists Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6. [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](#)

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](#)

Post-test:

Breast Cancer Update for Surgeons — Issue 5, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

- The NSABP sentinel lymph node study will evaluate the effect on survival of SLNB compared to SLNB plus axillary dissection in patients who are clinically node-negative.
 - True
 - False
- In the MD Anderson neoadjuvant clinical trial, the addition of trastuzumab to chemotherapy resulted in a pathologic complete response rate of approximately:
 - 15 percent
 - 25 percent
 - 35 percent
 - 65 percent
- Which of the following side effects were more favorable for the third generation aromatase inhibitor anastrozole compared to tamoxifen in the adjuvant setting?
 - Hot flashes
 - Vaginal bleeding/discharge
 - Endometrial malignancies
 - Ischemic cerebrovascular and venous thromboembolic events
 - All of the above
- In the IMPACT trial, patients with larger tumors who were treated with neoadjuvant _____ were more likely to undergo breast-conserving surgery.
 - Tamoxifen
 - Anastrozole
 - Exemestane
 - Letrozole
 - Tamoxifen and anastrozole
- In the IMPACT trial, which neoadjuvant therapy was better at reducing proliferation?
 - Tamoxifen
 - Anastrozole
 - Exemestane
 - Letrozole
 - Tamoxifen and anastrozole
- In the MA17 trial, an adjuvant aromatase inhibitor was used _____.
 - As initial therapy
 - After two to three years of adjuvant tamoxifen
 - After five years of adjuvant tamoxifen
 - All of the above
 - None of the above
- The IBIS-II prevention trial will evaluate _____ in postmenopausal women.
 - Tamoxifen
 - Anastrozole
 - Exemestane
 - Letrozole
 - Tamoxifen and anastrozole
- Three large adjuvant endocrine therapy trials, ATAC, CAN-NCIC-MA17 and EU-20149, have all shown aromatase inhibitors to be beneficial in the adjuvant treatment of early ER-positive breast cancer.
 - True
 - False
- Bisphosphonates were not routinely utilized in the adjuvant endocrine therapy trials that showed increased bone loss with aromatase inhibitors.
 - True
 - False
- The CAN-NCIC-MA17 trial, which evaluated letrozole versus placebo after five years of adjuvant tamoxifen, included patients who had completed tamoxifen within what time frame?
 - Within the past six months
 - Within the past 1 year
 - Within the past 3 years

Evaluation Form:

Breast Cancer Update for Surgeons — Issue 5, 2004

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor 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
Monica Morrow, MD	5 4 3 2 1	5 4 3 2 1
J Michael Dixon, BSc, MBChB, MD, FRCS, FRCSEd	5 4 3 2 1	5 4 3 2 1
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

- Objectives were related to overall purpose/goal(s) of activity. 5 4 3 2 1 N/A
- Related to my practice needs. 5 4 3 2 1 N/A
- Will influence how I practice. 5 4 3 2 1 N/A
- Will help me improve patient care. 5 4 3 2 1 N/A
- Stimulated my intellectual curiosity. 5 4 3 2 1 N/A
- Overall quality of material. 5 4 3 2 1 N/A
- Overall, the activity met my expectations. 5 4 3 2 1 N/A
- Avoided commercial bias or influence. 5 4 3 2 1 N/A

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.....

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

.....

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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:

Yes, I would be willing to participate in a follow-up survey. No, I'm not willing to participate in a follow-up survey.

Additional comments about this activity:

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Breast Cancer™

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