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Breast Cancer™ UPDATE

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

EDITOR

Neil Love, MD

FACULTY

Patrick I Borgen, MD

D Craig Allred, MD

Frank A Vicini, MD, FACR

Adam M Brufsky, MD, PhD

CME Certified

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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** 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**.

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic 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 medical oncologist must be well informed of these advances.To bridge the gap between research and patient care, *Breast Cancer Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists 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 treatment.
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 7 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Borgen, Allred, Vicini and Brufsky on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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Patrick I Borgen, MD
No financial interests or affiliations to disclose

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
celecoxib	Celebrex®	Pfizer Inc
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan® Neosar®	Bristol-Myers Squibb Company Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin® Rubex®	Pfizer Inc Bristol-Myers Squibb Company
epirubicin hydrochloride	Ellence®	Pfizer Inc
exemestane	Aromasin®	Pfizer Inc
fluorouracil (5-FU)	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals
paclitaxel	Taxol®	Bristol-Myers Squibb Company
raloxifene hydrochloride	Evista®	Eli Lilly and Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech BioOncology
vinorelbine	Navelbine®	GlaxoSmithKline

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Editor's Note

Team in need of a coach

Every medical oncology fellow quickly learns about interdisciplinary cancer care, but thank God for the American College of Surgeons' mandate for tumor boards, because without them, we might be strangers. Personally, I don't like to think about any surgeon, radiation oncologist or medical oncologist not regularly attending one of these valuable meetings. However, the truth is that we really don't report to anyone, and our collaboration is pretty much voluntary.

This issue of our audio series attempts to demonstrate how critical it is that interdisciplinary team members talk to each other. We begin with the local control guys, and Pat Borgen and Frank Vicini comment on a plethora of surgical and radiation therapy research issues that profoundly affect systemic management decisions.

For example, Dr Vicini is the principal investigator of a critical NSABP-RTOG randomized clinical trial evaluating partial breast irradiation (PBI). This historic collaboration between two premier collaborative clinical trial groups will provide much-needed answers about PBI, albeit many years from now.

In the interim, the pace at which this accelerated and patient-friendly treatment strategy permeates into the nonprotocol management algorithm utilized in the community treatment setting is anyone's guess.

While we wait for definitive research results, patients should seek input from every team member regarding the advisability of PBI and which technique is preferable. Pat Borgen cautions us that local control may have much more of an impact on long-term survival than previously recognized, and one might imagine that PBI could either have a deleterious effect (if it results in suboptimal local tumor control) or could be a more effective modality (because treatment can be implemented prior to chemotherapy).

With an increasing number of patients receiving taxane-based adjuvant regimens that can take up to six months to complete, earlier radiation therapy could have a potential antitumor advantage.

From a quality of life perspective, avoiding six weeks of daily treks for radiation therapy is appealing, particularly after the physical and emotional trauma of adjuvant chemotherapy. However, patients will surely want to know what their medical oncologist has to say on this issue before they opt for an unproven treatment modality.

Input from Craig Allred, the pathologist for the interdisciplinary team collaborating on this issue of *Breast Cancer Update*, is unfortunately very disheartening. I have nothing personal against pathologists or Craig, who is a really nice man, but if Adam Brufsky's interview provides ample documentation that contemporary systemic therapy of breast cancer is essentially target-driven, then Craig's comments leave us wondering if we have the ability to measure the most critical targets every oncologist must consider — ER, PR and HER2 status. (My apologies to Phillip Roth for that very long sentence.)

I keep expecting some rebel breast cancer patient advocacy group to stage a massive protest at the NCI to demand that pathologists provide impeccable ER, PR and HER2 assays. At the present time, however, women are going to continue to relapse unnecessarily or receive suboptimal palliative care because we can't get their pathology right. Even if recent history tells us that our usually capable nation is not totally effective in military intelligence gathering, we should be able to at least gather accurate information for the war on cancer.

Maybe we need more than ACOS-mandated tumor boards. Maybe we need someone to rally and guide the entire team — including nurses, pharmacists, radiologists, psychologists, social workers and others — and take a deep breath, and really figure out how to work together better so patients can receive the very best care we have.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

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

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**

Kurosumi M. **Significance of immunohistochemical assessment of steroid hormone receptor status for breast cancer patients.** *Breast Cancer* 2003;10(2):97-104. **Abstract**

Layfield LJ et al. **Assessment of tissue estrogen and progesterone receptor levels: A survey of current practice, techniques, and quantitation methods.** *Breast J* 2000;6(3):189-96. **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**

Press MF et al. **Comparison of HER-2/Neu status determined by fluorescence in situ hybridization (FISH) in the BCIRG central laboratories with HER-2/neu status determined by immunohistochemistry or FISH in outside laboratories.** *Breast Cancer Res Treat* 2002;76(Suppl 1);**Abstract 238**.

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**

Zarbo RJ, Hammond ME. **Conference summary, Strategic Science symposium. Her-2/neu testing of breast cancer patients in clinical practice.** *Arch Pathol Lab Med* 2003;127(5):549-53. **Abstract**

Patrick I Borgen, MD

EDITED COMMENTS

Clinical value of local control

I believe we're on the precipice of a new appreciation for the value of local control in breast cancer. In the 1990s, the perception may have been that medical therapy could compensate for inadequate surgery or radiation therapy. However, recent studies, including the postmastectomy radiotherapy trials, have demonstrated that improved local control results in increased survival rates.

A meta-analysis published in the *Journal of the National Cancer Institute* evaluated virtually all of the lumpectomy and radiation therapy trials (1.1). Local control was defined by whether or not disease relapsed in the breast, and they specifically examined patients who received radiation therapy versus those who did not.

Whereas the NSABP-B-06 trial failed to show a survival disadvantage in the patients who experienced a local failure, when combined with all these studies and better follow-up, the importance of local control became very clear. The analysis demonstrated that patients with good local control had an eight percent better survival rate than those who experienced a local failure.

Impact of local failure

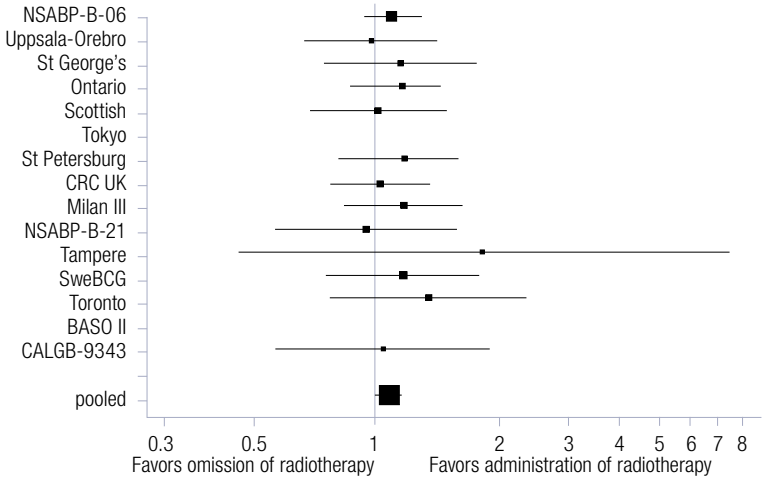
Studies in Milan and the United States, comparing mastectomy to lumpectomy and radiation therapy, demonstrated that the subset of patients who had positive nodes, received chemotherapy and were treated by breast-conserving therapy fared better than patients who underwent mastectomy. It has been postulated that a synergy exists between chemotherapy and radiation that we don't understand. Nothing suggested the mastectomy group would do better in the future, and I don't believe the long-term outcome of mastectomy will ever be superior to lumpectomy and radiation therapy.

I don't agree with those who contend that local recurrence is just a predictor of "bad biology." A fascinating analysis from Canada by Dr Fortin and colleagues evaluated patients who had a breast cancer recurrence and patients who did not relapse (1.2). They found that all the patients had a certain risk of systemic disease, but the patients who had a local failure in the breast had a second risk of

Dr Borgen is Professor of Surgery at Weill Medical College of Cornell University and Chief, Breast Service, Department of Surgery at Memorial Sloan-Kettering Cancer Center in New York, New York.

future systemic disease. They were able to demonstrate that as a time-dependent variable, local relapse was a *cause* rather than a *marker* of systemic relapse.

1.1 Pooled Analysis of the Omission versus Administration of Radiotherapy after Breast-Conserving Surgery: Relative Risk of Death from Any Cause



"In conclusion, this pooled analysis of the data available in the literature finds that omission of radiotherapy after breast-conserving surgery was associated with a threefold increase of ipsilateral breast tumor recurrence and was associated with a marginally statistically significant excess mortality risk of 8.6% (95% CI 0.3% to 17.5%) relative to the delivery of radiotherapy."

SOURCE: Vinh-Hung V, Verschraegen C. **Breast conserving surgery with or without radiotherapy: Pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality.** *J Natl Cancer Inst* 2004;96:115-21, by permission of Oxford University Press. **Abstract**

1.2 Impact of Local Failure (LF) on Distant Metastases and Mortality

"In our study, we demonstrated that LF had an impact on the outcome for our patients. This impact is expressed by a rise in the distant metastasis rate, which translates into a reduced survival, with a hazard ratio of 3.6 for our patients with LF, regardless of initial stage. Whelan et al also found that LF decreases survival by a factor of 2.8. ...

"In conclusion, local failure should be considered not only as a marker of occult circulating distant metastases but also as a source of new distant metastases and subsequent mortality. Every effort should be made to decrease the local failure rate, mainly by obtaining clear surgical margins and possibly by adding antiestrogen therapy."

SOURCE: Fortin A et al. **Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy.** *J Clin Oncol* 1999;17:101-9. **Abstract**

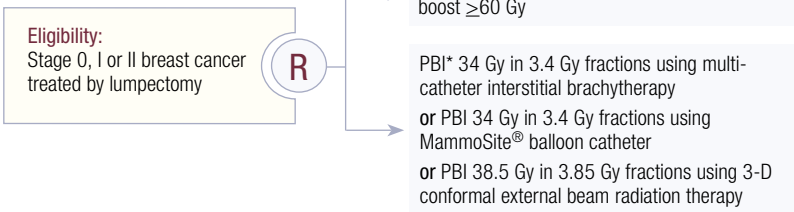
Partial breast irradiation

Conformal external beam radiation therapy is the most patient-friendly of the PBI techniques because it is noninvasive, quick and inexpensive. MammoSite® has generated a huge amount of enthusiasm, but it has limitations. A CT scan is necessary prior to treatment to ensure that the breast tissue abuts the device, and sometimes it doesn't. Also, we teach our fellows that long-term cosmetic results are best when the disrupted tissues are put back together. It concerns me that with this procedure the surgical defect is not repaired. Brachytherapy — the technique with which we probably have the most experience — may prove to be a little too invasive for patients to accept.

All of these PBI technologies lack large-scale prospective studies, so the NSABP is planning a trial in which the clinician can choose one of three different technologies: the brachytherapy technique of Kuske and colleagues, MammoSite® or conformal external beam partial breast radiation therapy (1.3). We are very enthusiastic about this study, and hopefully it will provide the data we need to truly evaluate PBI.

1.3 A Randomized Phase III Study of Conventional Whole Breast Irradiation versus Partial Breast Irradiation

Protocol IDs: NSABP-B-39, RTOG-0413
Target Accrual: 3,000 (Pending)



WBI = whole breast irradiation; PBI = partial breast irradiation

For all PBI techniques: Radiotherapy given to the index quadrant only, twice daily, in five to 10 days, with a fraction separation of six hours.

*The PBI technique utilized will be at the physician's discretion based on technical considerations, radiation oncology facility technique credentialing and patient preference.

SOURCE: NSABP Protocol Summary, June 2004.

Ductal lavage

Leslie Montgomery from our group published a study in *Cancer* (Brogi 2003), in which ductal lavage (DL) was performed on 30 patients, 26 of whom had mammary carcinoma (1.4). The lavage samples were sent to three different pathologists, and none of them was read as cancer — not even one. I don't believe DL should be compared to the Pap smear because it's not an effective screening test, but it's worth discussing as a risk assessment tool to identify atypical cells and select patients for chemoprevention. I believe its best use at this time is to retrieve cells from deep in the breast for intermediate biomarker research studies.

1.4 Lack of Utility of Ductal Lavage (DL) as a Screening Tool for Breast Cancer

"…Our study cases represent an extreme in the spectrum of epithelial neoplasia of the breast and most also contain invasive carcinoma. To avoid sampling of disrupted duct systems, we excluded patients who had undergone a previous ipsilateral surgical procedure or radiotherapy and patients with pathologic processes affecting the nipple. It is, however, possible that invasive carcinoma may also distort the mammary ducts and their branches and thus affect the yield of DL. Our data show that DL has low sensitivity in detecting CIS as none of our DL samples was diagnostic of malignancy. ...

"The current study confirms that sampling of the mammary epithelium by DL is not useful in the diagnostic screening and identification of carcinoma. Only prospective follow-up studies will elucidate the role of DL as a tool for risk assessment."

CIS = carcinoma in situ

SOURCE: Brogi E et al. **Ductal lavage in patients undergoing mastectomy for mammary carcinoma. A correlative study.** *Cancer* 2003;98:2170-6. **Abstract**

Current chemoprevention trials

The STAR trial has suffered from a lower-than-expected accrual due to the unpopularity of tamoxifen and the popularity of raloxifene. In addition, we have 40 years of experience with tamoxifen, and patients often have already decided which drug they want, which makes randomization difficult. These two agents are more alike than different and if raloxifene proves to be as effective as tamoxifen in prevention, it will be more readily accepted.

The IBIS-II chemoprevention trial comparing anastrozole versus placebo is even more exciting. In our experience with large numbers of patients, aromatase inhibitors are better tolerated than tamoxifen (1.5). Despite the results of the randomized trials, patients complain of weight gain on tamoxifen. Other problems include hot flashes, menopausal symptoms and possibly a low level of clinical depression.

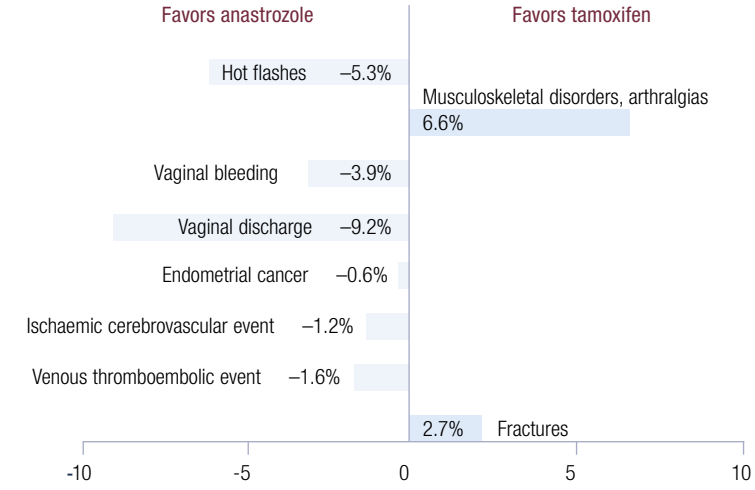
Patients also worry about endometrial cancer and blood clots. With aromatase inhibitors, some arthralgias are reported, but these agents are very well tolerated. Convincing postmenopausal women at high risk to take an aromatase inhibitor rather than tamoxifen for chemoprevention will be an easier task if the trials demonstrate benefit.

Clinical trials of aromatase inhibitors in DCIS

NSABP-B-35 and IBIS-II are important trials, both comparing anastrozole and tamoxifen in postmenopausal patients with DCIS (1.6). Aromatase inhibitors have already been proven to have a significant effect in invasive cancer, and it's highly likely they will impact DCIS as well. We know that the majority of DCIS lesions are likely to be ER-positive. Craig Allred has shown that age-per-age, tumor-for-tumor, DCIS is even more likely to be ER-positive than invasive cancer.

If that's true, then we have even more reason to be optimistic about the studies of aromatase inhibitors in DCIS.

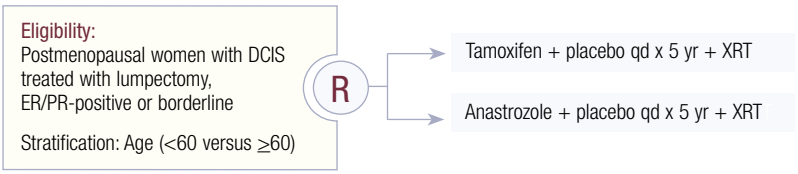
1.5 Significant Differences in Predefined Adverse Events in the ATAC Trial



DERIVED FROM: 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**

1.6 NSABP-B-35: Tamoxifen versus Anastrozole in Postmenopausal Patients with Ductal Carcinoma *In Situ*

Projected Accrual: 3,000 Patients (Open)



Study Contact: Richard Margolese, Chair, National Surgical Adjuvant Breast and Bowel Project
Tel: 514-342-3504

SOURCE: NCI Physician Data Query, August 2004.

Clinical status of sentinel lymph node biopsy

It's irrefutable that a sentinel node exists. Eighty studies around the world with over 10,000 patients — all with backup dissections and performed with a variety

of techniques: methods, dyes and tracers — had the same results. I believe that the breast has a sentinel node, but I don't believe it's geographically specific or that we have to inject the dye close to the tumor. The challenge is to reliably find the sentinel node and recognize when the technique has failed.

Sentinel lymph node biopsy (SLNB) has moved to "prime time" faster than any other surgical approach for breast cancer. It took 80 years to advance from radical to modified radical mastectomy and 20 years to then adopt breast-conservation therapy.

It's only taken approximately six years to move from axillary dissection to SLNB. With a relatively small amount of experience and coordination between nuclear medicine, surgery and pathology, SLNB is absolutely appropriate in the community setting.

SLNB in patients with DCIS

The indications for SLNB are still evolving. The easy answer to the question as to whether we should perform this procedure in patients with DCIS is, "No."

Approximately 30,000 cases of DCIS occur annually in the United States. If we performed SLNB on slightly more than half, say 17,000 patients, with a positivity rate of approximately seven percent, which is what's reported, 1,200 would have node-positive disease. Treating those 1,200 with chemotherapy would save approximately 61 patients, and that's a high price to reduce mortality by 61 lives.

DCIS is the most rapidly growing subset of our breast cancer population. Not every case is pure DCIS, however, and the challenge for the surgeon is to identify the DCIS cases with invasion. We find that approximately 10 to 15 percent of our DCIS cases have a hint of invasion, such as architectural distortion on a mammogram or a palpable mass, so we perform SLNB on those cases and approximately 10 percent are positive.

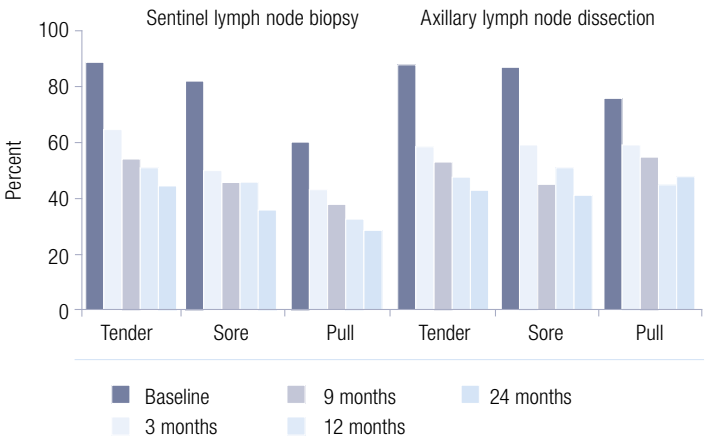
We are conducting an exciting multi-institutional study, along with Mel Silverstein, examining a large number of patients with DCIS who underwent SLNB, and we're following those cases longitudinally.

I do believe that all patients with DCIS who require a mastectomy should undergo SLNB. When we performed mastectomies in the past, we almost always removed two to four lymph nodes from the axillary tail. SLNB probably allows us to remove fewer nodes.

Neurosensory sequelae of SLNB

Roberta Baron from our group has conducted a study comparing the neurosensory morbidity of SLNB versus axillary node dissection (1.7). Surgeons have billed SLNB as relatively free of side effects, but Ms Baron's study demonstrated that, although the intensity of symptoms was less following SLNB, the number of complaints about sensory morbidity in this study include pain, a pulling sensation, achiness and tenderness — which was the same after SLNB and post-axillary node dissection. The symptoms may be present for two or more years.

1.7 Comparison of Select Sensations Experienced after Sentinel Lymph Node Biopsy or Axillary Dissection



SOURCE: With permission from Baron RH et al. **Eighteen sensations after breast cancer surgery: A two-year comparison of sentinel lymph node biopsy and axillary lymph node dissection.** *Oncol Nurs Forum* 2004;31(4):691-8. **Abstract**

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**

Baron RH et al. **Eighteen sensations after breast cancer surgery: A two-year comparison of sentinel lymph node biopsy and axillary lymph node dissection.** *Oncol Nurs Forum* 2004;31(4):691-8. **Abstract**

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**

Benk V et al. **Effect of delay in initiating radiotherapy for patients with early stage breast cancer.** *Clin Oncol* (R Coll Radiol) 2004;16(1):6-11. **Abstract**

Brogi E et al. **Ductal lavage in patients undergoing mastectomy for mammary carcinoma: A correlative study.** *Cancer* 2003;98(10):2170-6. **Abstract**

Edge SB et al. **Emergence of sentinel node biopsy in breast cancer as standard-of-care in academic comprehensive cancer centers.** *J Natl Cancer Inst* 2003;95(20):1514-21. **Abstract**

Fortin A et al. **Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy.** *J Clin Oncol* 1999;17:101-9. **Abstract**

King TA et al. **Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for $T_{is,1,2}$ breast cancer.** *Am J Surg.* 2000 ;180(4):299-304. **Abstract**

Vinh-Hung V, Verschraegen C. **Breast-conserving surgery with or without radiotherapy: Pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality.** *J Natl Cancer Inst* 2004;96:115-21. **Abstract**

Estrogen receptor status and tamoxifen efficacy in patients with 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 lab, we later measured the estrogen and progesterone receptors by immunohistochemistry (IHC) on approximately 600 paraffin blocks distributed between the two arms of the study. The data convincingly demonstrated that the benefit from tamoxifen was entirely restricted to the ER-positive cohort, and there was no evidence of benefit in the ER-negative cohort. We know that approximately 25 percent of DCIS cases are truly ER-negative.

Approximately two thirds of the cases analyzed had hormone receptors previously evaluated in their community hospitals and, using the central lab as the standard, the community data demonstrated a 30 percent error rate — mostly false negatives (2.1). In the patients with ER-negative tumors, as defined by community labs, the relative risk for benefit from tamoxifen was approximately 0.5, which is unbelievable biologically.

2.1 NSABP-B-24 Data: Clinical Comparison of ER-Negative Results from Outside and Central Labs

		Events/patients (%)			
Lab	N	Placebo	Tamoxifen	Relative risk	*p*-value
Outside lab ER-negative results	64	10/39 (26%)	3/25 (12%)	0.43 (↓57%)	0.20
Central lab ER-negative results	89	11/48 (23%)	11/41 (27%)	0.99 (↓1%)	0.98

SOURCE: Allred DC. **ER status and response to tamoxifen in ductal carcinoma in situ (DCIS).** Presentation. San Antonio Breast Cancer Symposium, 2002. **Abstract**

Dr Allred is a Professor of Pathology at the Baylor College of Medicine Breast Center in Houston, Texas.

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 truly ER-negative DCIS.

Contributing factors resulting in false negatives in estrogen receptor analysis

I consult on several hundred difficult cases each year. Many of these are sent for repeat estrogen receptor 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 estrogen receptor status in patients with DCIS.

The single biggest contributor to error 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.

Setting the cut point for positivity too high is another significant error. 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 (2.2), but when applied to the NSABP-B-24 DCIS study, the results were very reasonable.

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

2.2 Allred Score for ER Status (0-8)*

% Staining score	Proportion of positive staining cells	Intensity score	Average intensity of positively stained cells
0	none	0	none
1	<1/100	1	weak
2	1/100 to 1/10	2	intermediate
3	1/10 to 1/3	3	strong
4	1/3 to 2/3	—	—
5	>2/3	—	—

*Allred score = % staining score + intensity score

DERIVED FROM: 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**

Biochemical ligand-binding versus IHC for estrogen receptors

Few clinical trials have used IHC to assess hormonal status. Those that have, such as NSABP-B-24, found significant problems with false-negative results, in terms of response, from outside laboratories. The international overview meta-analysis of adjuvant endocrine therapies is based almost entirely on biochemical ligand-binding testing. Similar to our experience with IHC today, the ligand-binding test initially suffered from a great deal of variability in results from different labs.

The cooperative groups, particularly the NSABP, moved quickly to require that hormonal profiles be assessed by labs with proven proficiency in ligand-binding assays before the patient could be enrolled in clinical trials. By the early 1980s, a relatively small number of qualified laboratories were performing the majority of tests.

Understanding the current variability problems with IHC assessment, reagent companies like Dako are working with my lab and others to develop a reliable kit-based test to measure hormone receptors and to provide labs with little experience or low test volume the capacity to perform high-quality tests. Unlike the HercepTest™, which was clinically available before it was properly validated, this kit will be based on clinical correlative studies.

Effect of phenotype on benefit in the ATAC trial

The ATAC data analyzing ER and PR phenotypes and benefit from therapy was fascinating. Compared to tamoxifen, anastrozole had approximately a 20 percent additional benefit in the ER-positive, PR-positive and ER-negative, PR-positive subsets. In the ER-negative, 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 (2.3).

We don't know why the ER-positive, PR-negative phenotype behaves so differently, but Dowsett and Osborne have formulated a hypothesis that involves contrasting the effect of tamoxifen to that of anastrozole on the classical nuclear versus nonclassical membrane estrogen receptor 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 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 from anastrozole seen in the ER-positive, PR-negative subset, which is the phenotype for 20 percent of breast cancer patients.

The HER2 assays have not yet been performed in the ATAC trial, but some have speculated that the subset of patients with the ER-positive, PR-negative phenotype may also be HER2-positive. However, we've known for years that only 10 or 15 percent of HER2-positive tumors are ER-positive and, while most of those are PR-negative, I don't believe that small subset could be entirely responsible for these intriguing results.

2.3 Recurrence Rates in the ATAC Trial According to Estrogen and Progesterone Receptor Status

Receptor status	N	Hazard ratio for anastrozole versus tamoxifen (95% CI)*	Anastrozole	Tamoxifen
ER-positive, PR-positive	5,704	0.82 (0.65-1.03)	7%	8%
ER-positive, PR-negative	1,370	0.48 (0.33-0.71)	9%	17%
ER-negative, PR-positive	220	0.79 (0.40-1.5)	22%	26%
ER-negative, PR-negative	699	1.04 (0.73-1.47)	27%	27%

*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**.

Quality control for HER2 testing

We still have substantial problems with HER2 testing in clinical practice. Most labs rely on IHC, but the quality varies tremendously (2.4). I don't believe one should resort to FISH in every case for a number of reasons, including cost. If performed properly, IHC can provide an accurate answer 80 to 85 percent of the time. Using the HercepTest™ IHC criteria, I believe only the 15 or 20 percent of cases that are scored 2+ should be evaluated by FISH for resolution.

Another problem is that we don't have a perfect algorithm for HER2 testing from which to make all decisions because the biology of HER2 is so complex. We know that approximately 10 percent of patients without gene amplification overexpress the protein, and it seems reasonable that those tumors would be as responsive to a targeted therapy, like trastuzumab, as tumors whose overexpression is the result of a HER2 gene amplicon.

A tremendous economic incentive exists to order FISH, which doesn't necessarily translate to benefit. At the 2003 San Antonio Breast Cancer Symposium, two posters demonstrated a wide variation in 2+ positivity rates. These labs are either conducting or scoring the test differently. I suspect overinterpretation with IHC is more common than underinterpretation, possibly to justify resorting to FISH for resolution.

2.4 Percent of Patients with HER2 Gene Amplification According to Immunohistochemistry Score (IHC)

Author	IHC Antibody	N	0	1+	2+	3+
Mass	CTA	529	4.2%	6.7%	23.9%	89.3%
Mass	CTA	451	—	—	31.0%	89.0%
Schaller	A0485	142	0	0	25.0%	100.0%
Lebeau	A0485 CB11 TAB250	79	— — —	— — —	25.0% 81.8% 66.7%	100.0% 100.0% 100.0%
Buehler	A0485	142	0	0	30.5%	100.0%
Tubbs	A0485	145 CB11	— —	— —	12.5% 23.5%	75.0% 85.0%
Hoang	A0485 e2-4001	100	0 1.6%	0	16.7% 5.9%	88.9% 75.0%
Ridolfi	A0485	117	1.8%		35.9%	100.0%
Seidman	A0485 CB11	78	9.1% 14.3%		82.2% 94.4%	
Persons	A0485	100	1.3%		68.2%	

IHC = immunohistochemistry score; CTA = clinical trial assay (4D5 and CB11 antibodies)

SOURCE: Genentech Inc. **HER2 assays and trastuzumab (Herceptin™) patient selection: A review of the medical literature.** Research To Practice; Miami, FL:2001. No abstract available

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**.

Bubis JA et al. **HER-2/neu overexpression: Immunohistochemistry (IHC) or fluorescence in-situ hybridization (FISH)?** *SABCS* 2003; Poster 602. No abstract available

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;82(Suppl 1);**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**

Rugo HS et al. **Low to moderate protein expression of HER2/neu in breast cancer by immuno-histochemistry (IHC) correlateswith low level ERBB2 gene amplification by fluorescence in situ hybridization (FISH).** *SABCS* 2003; Poster 668. No abstract available

Development of partial breast irradiation (PBI)

In the early 1990s, patients who did not have easy access to radiation facilities did not have the option of breast conservation, so institutions began offering interstitial implants to shorten the treatment time from six and a half weeks to four days. While hundreds of these cases were performed with very good results, the procedure required four days of hospitalization, which was impractical.

High-dose rate brachytherapy was then developed — a similar interstitial procedure performed on an outpatient basis. With brachytherapy, a series of hollow catheters placed during lumpectomy or shortly thereafter encircle the surgical cavity. At the time of treatment, cables connected to a high-dose rate unit are attached to the catheters, and a computer transmits the source to a predetermined position along the length of the catheters, delivering a targeted dose of radiation around the cavity.

The whole process of transferring the source into the catheters and back into the housed radioactive unit takes five to 10 minutes. Then the cables are detached from the catheters and the patient returns six hours later for a second treatment. That procedure is repeated eight to 10 times over a course of four or five days and then the catheters are removed.

While patients tolerated this new type of interstitial therapy very well, it was unpleasant to have 15 to 20 needles placed in the breast and inconvenient to come twice daily for treatments. Approximately five or six years ago the MammoSite® was designed to deliver the same type of radiation to the lumpectomy cavity either shortly after surgery or a few weeks later. It's an easier procedure for physicians to learn and perform, and it's much easier on the patient, requiring only one catheter.

Alongside the development of the MammoSite®, 3-D conformal external beam radiation came into existence. When this technology is applied to breast cancer, the same areas around the lumpectomy cavity are treated with 10 fractions of radiation therapy over five days on an outpatient basis. The procedure is not

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

invasive and we can use the same equipment that we already have in the radiation facility. At our institution, we are able to offer patients all three types of PBI and select the technique most appropriate for the individual case.

Interstitial brachytherapy

At William Beaumont Hospital, we have the largest single experience with interstitial brachytherapy (3.1). 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.

In the past 10 years of published data, the collective experience for patients treated with interstitial brachytherapy with over five years of follow-up consists of approximately 500 to 600, compared to tens of thousands of women treated with whole-breast radiation. With brachytherapy, we have only small numbers of highly selected patients treated at single institutions (3.2). We don't really know what the efficacy will be in larger patient populations with less restrictive criteria.

3.1 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**

Experience with PBI

One of the advantages of PBI is that it can be completed quickly before systemic therapy is begun. Our surgeons have been very progressive in this field and we're one of the few institutions that offers interstitial brachytherapy, MammoSite® and 3-D conformal external beam radiation. Each technique has its advantages, and none of them is applicable in 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.

3.2 Published Partial Breast Irradiation Results: Brachytherapy

Institution	N	Follow-up (months)	Local recurrence (%)
WBH – LDR patients	120	82	0.9
Ochsner Clinic	51	75	2.0
WBH – All patients	199	65	1.2
NIO – Hungary	45	60	4.4
WBH – HDR patients	59	52	2.1
University of Kansas	24	37	0
Tufts – New England Medical Center	32	33	3
NIO – Hungary Phase III	181	30	1.1
Florence, Italy	90	27	4.4
MGH	48	23	0

WBH = William Beaumont Hospital; LDR = low-dose rate brachytherapy; NIO = National Institute of Oncology; HDR = high-dose rate brachytherapy; MGH = Massachusetts General Hospital

SOURCE: Vicini F. **Partial breast irradiation: Current status.** Presentation. San Antonio Breast Cancer Symposium, 2003. **Abstract**

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 have questioned whether it's worthwhile to study PBI given the high efficacy and low toxicity achieved with breast conservation using whole breast radiation.

However, in the United States, a large proportion of women do not undergo breast-conserving therapy, and a recent study showed that the distance to a radiation facility still factors into a woman's decision-making (3.3). In addition, some people fear radiation and reducing the time and, potentially, the toxicity of radiation 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.

PBI 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 of 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 in single institutions have been treated with this technique, but I suspect that will change in the next few years.

3.3 Advantages of Partial Breast Irradiation in the Management of Early-Stage Breast Cancer

"... A standard course of adjuvant radiation therapy after conservative surgery generally requires up to 6-7 weeks to complete, which can therefore cause a substantial burden to patients. Hence, if a simpler, less burdensome, and quicker technique for the delivery of radiation could be offered to patients with early-stage breast cancer, such an approach could theoretically increase the breast-conserving therapy option to more women and could offer the potential advantages of reduced treatment-related toxicities, improvements in the quality of life, and a logistically simpler and more practical method for breast-conserving therapy."

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**

The NSABP and RTOG plan to jointly conduct a study that will randomly assign 3,000 patients to conventional whole breast radiation or one of three PBI techniques — interstitial brachytherapy, MammoSite® or 3-D conformal external beam radiation. The eligibility will be broad with no age restrictions and it will include patients with DCIS. 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 with limited-field radiation, we're targeting the tissues that most likely require 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 DCIS cases.

MammoSite® procedure

The MammoSite® can be placed either during or after surgery. Approximately 50 percent of the over 1,000 patients on the MammoSite® registry had their device placed intraoperatively; however, it appears the more experienced institutions choose to place it postoperatively. I prefer the postoperative, closed-cavity technique because it allows me to ascertain whether a patient is truly a candidate for PBI — both pathologically and technically — before I discuss it with the patient. It's distressing for someone to learn she is not eligible for PBI after a device or catheters have been placed.

Pathological reasons why a patient may be ineligible include positive nodes, large tumors, lobular histology, DCIS and positive margins, although if the margins are positive, one can re-excise and place the device at re-excision or wait for the subsequent pathology report. Technical suitability can be determined by CT, as it is important in placing the MammoSite® to keep the balloon at least five to seven millimeters away from the skin surface to avoid excessive radiation to the skin. The cavity shrinks postoperatively, so waiting one to two weeks after surgery allows us to work with a smaller cavity, which is better.

If the MammoSite® is deemed appropriate, then the procedure is performed a day or two later on an outpatient basis. The device is placed in the morning and

later that day, conformance is assessed by CT. The breast tissue needs to conform well around the balloon because the dose is prescribed one centimeter away from the surface of the balloon.

Any intervening fluid or air would prevent that one-centimeter rim of tissue from receiving 100 percent of the dose. Typically treatment is then begun within 24 hours, although if the conformance is unacceptable, we can wait a day or two before beginning therapy. The patient is treated twice daily, six hours apart, for five days. After the tenth and final fraction is delivered, the balloon is deflated and removed.

Treatment is generally completed within 10 to 14 days after the patient is assessed for PBI. We always allow a two-week break from the completion of radiation therapy to the start of chemotherapy because of radiation recall concerns with some of the systemic agents, primarily doxorubicin.

Off-protocol use of the MammoSite®

The MammoSite® is easier for surgeons to use and patients to accept, but there's concern that it's being disseminated to the community before it's fully tested in randomized trials. Many physicians argue that we cannot extrapolate the interstitial experience to the MammoSite® and that the interstitial experience 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.

I favor enrolling patients in randomized trials; however, 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 in which 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 just oppose its use off protocol.

Select Publications

Cuncins-Hearn A et al. **A systematic review of intraoperative radiotherapy in early breast cancer.** *Breast Cancer Res Treat* 2004;85(3):271-80. **Abstract**

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

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

Vicini FA et al. **Limited-field radiation therapy in the management of early-stage breast cancer.** *J Natl Cancer Inst* 2003;95(16):1205-10. **Abstract**

Wallner P et al. **Workshop on partial breast irradiation: State of the art and the science, Bethesda, MD, December 8-10, 2002.** *J Natl Cancer Inst* 2004;96(3):175-84. **Abstract**

Adam M Brufsky, MD, PhD

EDITED COMMENTS

Duration of trastuzumab in the metastatic setting

The duration of trastuzumab in metastatic disease has not been studied in a randomized trial, so we are conducting an observational study of 400 patients in approximately 50 centers, and every three months we're recording each patient's treatment. I expect we'll find that about 35 percent of clinicians don't continue trastuzumab after progression. Many believe that progression with a chemotherapy-trastuzumab regimen indicates resistance to trastuzumab, but I don't agree.

I believe it is beneficial to continue trastuzumab beyond an initial progression, but I don't know for how many progressions it continues to be advantageous. In our retrospective analysis of approximately 200 patients who received frontline trastuzumab, those who continued on trastuzumab seemed to have a small benefit, at least in time to progression, compared to those who did not. A retrospective study from the Hellenic Cooperative Oncology Group (Fountzilas 2003) demonstrated time to progression intervals of three to four months with third- and fourth-line trastuzumab plus chemotherapy.

Cardiac effects in adjuvant trastuzumab trials

NSABP-B-31, which randomly assigns patients to AC followed by paclitaxel with or without trastuzumab, evaluated cardiac safety in the first 1,000 patients. The cardiac endpoint was the absolute difference in protocol-defined cardiac events between the two arms, and if it exceeded four percent, accrual would be terminated.

The cardiac event rates were 0.78 and 4.28 percent in the control and trastuzumab arms, respectively, so the study continued and for the vast majority of patients the cardiotoxicity was reversible. Still, the rate in the study arm equates to approximately one in 20 or 25 women, and that concerns me. When I counsel patients, I tell them about trastuzumab's performance in the metastatic setting and that we're excited about its potential in the adjuvant setting, but that it's still unproven.

Dr Brufsky is an Assistant Professor of Medicine at the University of Pittsburgh, Member of the University of Pittsburgh Cancer Institute, Director of the Comprehensive Breast Cancer Center, and Associate Division Chief of the Department of Medicine's Division of Hematology/Oncology at the University of Pittsburgh in Pittsburgh, Pennsylvania.

Trastuzumab-chemotherapy regimens for HER2-positive disease

The BCIRG conducted a Phase II study of docetaxel/cisplatin/trastuzumab in patients with HER2-positive advanced breast cancer and reported dramatic results in terms of time to progression (4.1). At approximately the same time, we began a 40-patient, Phase II trial of docetaxel/carboplatin/trastuzumab and we're seeing similar results. Our response rate is between 70 and 80 percent, and time to progression is approximately 12 to 13 months.

The BCIRG-006 adjuvant trial compared adjuvant AC plus docetaxel with or without trastuzumab versus docetaxel/trastuzumab with either carboplatin or cisplatin in women with node-positive or high-risk, node-negative, HER2-positive, operable breast cancer. I expect the data from the docetaxel/carboplatin/trastuzumab arm will be at least as good as that seen in the Phase II studies with regard to disease-free and overall survival, but with less cardiotoxicity. If that's the case, then that regimen will become the treatment of choice for patients with node-positive, HER2-positive breast cancer.

4.1 Results of Two Multicenter Phase II Studies of Docetaxel, Platinum Salts and Trastuzumab in HER2-Positive Advanced Breast Cancer

The UCLA-Oncology Research Network BCIRG conducted two Phase II studies to evaluate trastuzumab/docetaxel in combination with either cisplatin or carboplatin for the treatment of patients with HER2-positive metastatic disease.

	Responses rates
BCIRG	49/62 (79%, 95% CI = 66% to 89%)
UCLA	34/59 (58%, 95% CI = 44% to 70%)

	Median times to progression
BCIRG	9.9 months (95% CI = 8.3 to 13.1 months)
UCLA	12.7 months (95% CI = 8.6 to 15.5 months)

"In conclusion, TCH appears to be highly active in the treatment of advanced breast cancers that overexpress HER2. More importantly, the median times to progression emerging from the current phase II trials are among the longest times reported to date for a patient population with HER2-positive metastatic breast cancer. The toxicity of the regimen is manageable and is consistent with that observed in other clinical settings for the combination of docetaxel plus platinum salts."

*TCH = docetaxel, platinum salt and trastuzumab
Citations omitted

SOURCE: 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**

HER2 testing

We initially perform IHC for HER2 testing and then FISH if the IHC result is 2+. We view zero and 1+ results as HER2-negative and 3+ results as HER2-positive. However, we know from concordance data that approximately 10 percent of zero and 1+ cases will be FISH-positive and approximately 10 percent of 3+ cases will be FISH-negative, so that has to be taken into consideration.

We have learned that labs must perform a high volume of FISH testing to be proficient, and community labs have low concordance rates. At the 2004 ASCO meeting, an interesting technique for evaluating the HER2 status was presented, called chromogen in situ hybridization (CISH). The concordance rates between this technique and FISH were high, and I believe this new assay will change our current patterns of testing (4.2).

4.2 Concordance Rates between Chromogen *In Situ* Hybridization and FISH in Core Cut Biopsies of Primary T2 Breast Cancers

Samples	N	Concordance rate
IHC score 2+ Differentiation between HER2 positivity or negativity	56	98.2%
IHC score 3+ Differentiation between HER2 positivity	6	100%
All samples (IHC 0/1+, 2+, 3+) Differentiation between HER2 positivity	71	96.6%
All samples (IHC 0/1+, 2+, 3+) Differentiation between HER2 negativity	71	97.9%

"Conclusions: In this selected series of T2 breast cancer core cut biopsies FISH and CISH revealed a very high concordance of HER2 positivity and negativity when IHC showed a score 2+. Therefore CISH should be used as a cheaper and permanent assessable alternative to FISH for HER2 testing."

SOURCE: Raab GH et al. **Chromogen in situ hybridisation (CISH) for HER2 assessment is highly concordant with FISH in core cut biopsies of primary T2 breast cancers.** *Proc ASCO* 2004;**Abstract 569**.

First-line therapy for women with HER2-positive metastatic disease

In selecting first-line therapy for patients with HER2-positive metastatic disease, I consider the pace of the disease and the patient's desires. If a patient can tolerate chemotherapy and has substantial disease in the liver or lungs, I use docetaxel/carboplatin/trastuzumab. In an older woman or a frail patient or a woman who doesn't want to lose her hair, I select vinorelbine/trastuzumab. If the patient has ER- and PR-negative disease with only bone or maybe a few soft-tissue metastases, I use trastuzumab alone. In Vogel's data, approximately 25 to 35 percent of women with metastatic, FISH-positive disease responded to single-agent trastuzumab (4.3).

I've also used a combination of capecitabine and trastuzumab in the first-line metastatic setting in select cases. For example, in patients with very high bilirubin levels, I find it difficult to give a taxane or anthracycline. However, an abstract presented at ASCO several years ago showed it was safe to use lower-dose capecitabine in these patients. In vitro data from Slamon and Pegram showed that perhaps these drugs were additive and many clinicians, I believe, overinterpreted that data and felt capecitabine shouldn't be combined with trastuzumab. I don't necessarily agree and a number of clinicians, including myself, have had some success with this combination.

4.3 Efficacy of First-Line Trastuzumab in HER2-Overexpressing Metastatic Breast Cancer

Subset	Objective response	Clinical benefit*
All assessable patients (n=111)	26%	38%
Trastuzumab		
2 mg/kg weekly (n=58)	24%	34%
4 mg/kg weekly (n=53)	28%	42%
Estrogen receptor		
positive (n=52)	23%	36%
negative (n=54)	30%	39%
HER2		
IHC 3+ (n=84)	35%	48%
IHC 2+ (n=27)	0%	7%
FISH		
positive (n=79)	34%	48%
negative (n=29)	7%	10%
Previous adjuvant doxorubicin (n=57)	32%	41%

*Clinical benefit = complete, partial or minor response or stable disease > 6 months

DERIVED FROM: Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20:719-26. **Abstract**

Adjuvant chemotherapy trials

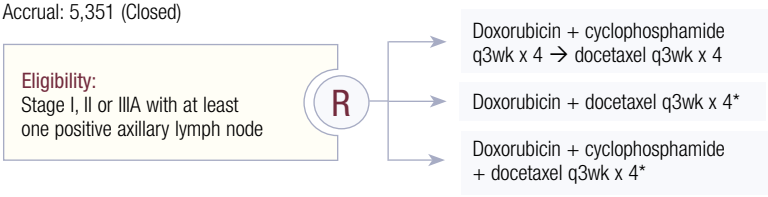
Many of us are concerned that two of the three regimens are suboptimal in the NSABP-B-30 three-arm, Phase III adjuvant chemotherapy trial (4.4). In this study, patients with node-positive disease are randomly assigned to doxorubicin/cyclophosphamide (AC) followed by docetaxel (T) or doxorubicin/docetaxel (AT) or TAC. The TAC regimen is only four cycles rather than six, which I believe is too little chemotherapy. I also believe the AT arm is likely to be inferior to AC followed by docetaxel.

When you look at the neoadjuvant data, the pathologic complete response rate following four cycles of AT was approximately seven percent versus 11 to 12 percent for AC followed by docetaxel. I believe pathologic complete response rates will likely translate to better disease-free and overall survival.

I'm very interested in the NSABP-B-36 study in patients with node-negative disease, which compares AC versus fluorouracil/epirubicin/cyclophosphamide, and then all patients are randomly assigned to celecoxib or a placebo (4.5). They are using the non-dose-dense AC in this trial, which I support. I believe the data from CALGB-9741 favoring dose density was related to the dose-dense administration of paclitaxel rather than AC.

4.4 Phase III Randomized Study of Adjuvant Doxorubicin and Cyclophosphamide Followed by Docetaxel versus Doxorubicin and Docetaxel versus Doxorubicin, Docetaxel and Cyclophosphamide in Women with Breast Cancer and Positive Axillary Lymph Nodes

Protocol IDs: NSABP-B-30, CTSU
Accrual: 5,351 (Closed)



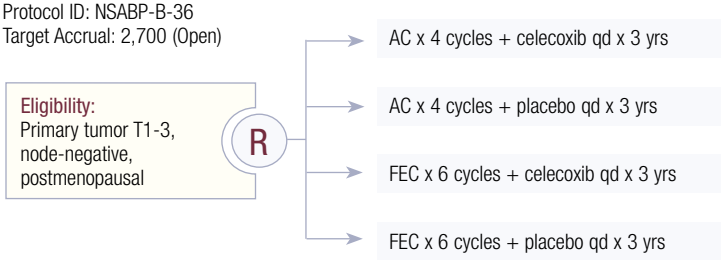
*Note: Primary prophylaxis with growth factors were given.
Some patients may have received postmastectomy radiotherapy on SWOG-S9927 or NCIC-MA20.

Study Contact:
National Surgical Adjuvant Breast and Bowel Project
Sandra Swain, Chair
Tel: 301-496-0901

SOURCE: NSABP website, accessed August 2004.

4.5 Phase III Study of Adjuvant Fluorouracil, Epirubicin and Cyclophosphamide with or without Celecoxib versus Doxorubicin and Cyclophosphamide with or without Celecoxib

Protocol ID: NSABP-B-36
Target Accrual: 2,700 (Open)



Study Contact:
National Surgical Adjuvant Breast and Bowel Project
Richard Elledge, MD
Tel: 713-798-1655

SOURCE: NCI Physician Data Query, July 2004.

Fulvestrant in the adjuvant and metastatic settings

Most clinicians consider fulvestrant a third-line therapy for patients who have failed tamoxifen and an aromatase inhibitor; however, clinical trials have shown fulvestrant is equivalent to anastrozole after tamoxifen failure and, in a recently published European study comparing front-line fulvestrant versus tamoxifen, I did not view tamoxifen as inferior (4.6).

In addition, a Phase III study is underway comparing fulvestrant to exemestane for second-line therapy. I do use third-line fulvestrant, but I will use it first-line, particularly in women who can't afford an aromatase inhibitor. In addition, I would estimate that approximately 40 percent of my patients prefer a monthly injection to taking a pill every day (4.7).

4.6 Objective Tumor Response in a Randomized Study Comparing Fulvestrant to Tamoxifen as First-Line Therapy in Postmenopausal Women with Advanced Breast Cancer

	All patients		Patients with ER- and/or PR-positive tumors	
Response	Fulvestrant (n=313)	Tamoxifen (n=274)	Fulvestrant (n=247)	Tamoxifen (n=212)
Complete response	9.6%	6.9%	8.9%	5.7%
Partial response	22.0%	27.0%	24.3%	25.5%
Stable disease ≥24 weeks	22.7%	28.1%	23.9%	31.6%
Objective response rate[1]	31.6%	33.9%	33.2%	31.1%
Clinical benefit rate[2]	54.3%	62.0%	57.1%	62.7%

[1]Objective response indicates a complete or partial response
[2]Clinical benefit indicates a complete or partial response of stable disease >24 weeks

SOURCE: Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13. **Abstract**

4.7 Patient Preference for Method of Administration of Systemic Therapy (N=137)

Question: Assume you were able to start a new cancer treatment and there were two options with the same side effects and anticancer benefits. One option would be an intramuscular injection once a month and the other would be a pill that you would take once a day. Which would you prefer?

Patient's response	N	%
Prefer an injection	48	35%
Neutral, no preference	13	10%
Prefer a pill	76	55%

SOURCE: *Breast Cancer Update* National survey of 155 patients with metastatic breast cancer, 2004.

I believe aromatase inhibitors will be difficult to beat, but many of us are interested in adjuvant studies with fulvestrant. It has a lot of advantages and I would like to see it compared to aromatase inhibitors in postmenopausal women in the adjuvant setting.

Adjuvant therapy in postmenopausal women with ER-positive tumors

Off protocol in a postmenopausal woman, I generally use adjuvant anastrozole up front or, if the patient has been on tamoxifen for two or three years, I switch her to exemestane. After five years of tamoxifen therapy, I offer patients letrozole. The issue here is that because patients generally do well after five years of tamoxifen, we have to carefully weigh the potential benefit and side effects of further adjuvant therapy. A patient with a small tumor may not need it; however, in a patient with multiple positive nodes, it probably is indicated.

In women who have been off adjuvant tamoxifen for a while, my cut-off to start an aromatase inhibitor is approximately one year, although it's probably acceptable to start at any time. At least in preventing new breast cancer, although further therapy is likely advantageous, but again one has to balance side effects with benefit. Even though we know there's still a linear rate of recurrence after five years of tamoxifen, if the disease hasn't recurred two or three years later, I believe that tells me something about the biology of that patient's disease.

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(Suppl 1);**Abstract 3**.

Brufsky AM et al. **First-line chemotherapy for metastatic breast cancer (MBC) with docetaxel (T), carboplatin (C), and trastuzumab (H) (TCH): A phase II trial.** *Proc ASCO* 2003;**Abstract 71**.

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**

Fountzilas G et al. **Continuation of trastuzumab beyond disease progression is feasible and safe in patients with metastatic breast cancer: A retrospective analysis of 80 cases by the Hellenic Cooperative Oncology Group.** *Clin Breast Cancer* 2003;4(2):120-5. **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 Trastuzumab 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**

O'Shaughnessy J, Blum J. **A retrospective evaluation of the impact of dose reduction in patients treated with Xeloda (capecitabine).** *Proc ASCO* 2000;**Abstract 400**.

Pegram et al. **Trastuzumab and chemotherapeutics: drug interactions and synergies.** *Semin Oncol.* 2000;27(6 Suppl 11):21-5. **Abstract**

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. **Abstract**

PowerPoint Atlas: Hormone Receptor Status

Editor's Note: The PowerPoint files of the following slides are located on CD 1 and can also be downloaded at **BreastCancerUpdate.com**.

Slide 1: 1995 Oxford Overview: Chemotherapy versus tamoxifen

Slide 2: Allred score for ER status

Slide 3: Allred score and response to endocrine therapy

Slide 4: ATAC: Time to recurrence according to ER and PR status

Slide 5: Defining ER positivity

Slide 6: ER status and DCIS

Slide 7: ER status and response of DCIS to tamoxifen

Slide 8: Breast cancer events according to ER status and treatment

Slide 9: Effect of tamoxifen relative to placebo by ER status

Slide 10: Comparison of ER between central and outside laboratories

Slide 11: Comparison of ER-negative results from central and outside laboratories

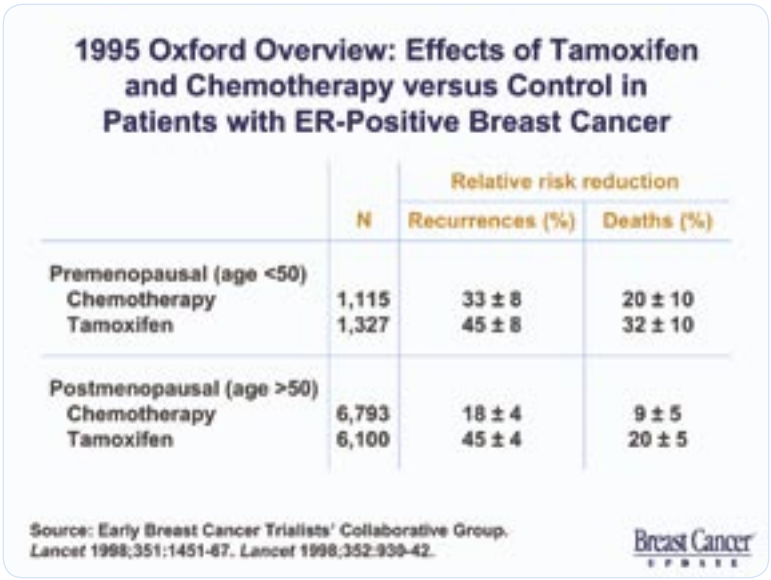
Slide 12: Clinical comparison of ER-negative results from central and outside laboratories

Slide 13: Conclusions: ER status and response of DCIS to tamoxifen

Slide 14: Meta-analysis: Discordance in ER/PR status between primary and metastatic breast cancer

Slide 15: Study of differences in ER/PR status between primary and metastatic breast cancer

Slide 1



Slide 2

Allred Score for ER Status (0-8)*

(%) Staining score	Proportion of positive staining cells	Intensity score	Average intensity of positively stained cells
0	none	0	none
1	<1/100	1	weak
2	1/100 to 1/10	2	intermediate
3	1/10 to 1/3	3	strong
4	1/3 to 2/3		
5	>2/3		

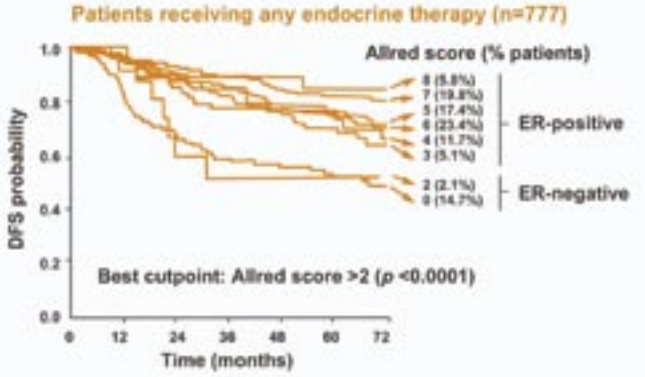
*Allred Score = % staining score + intensity score

Derived with permission from: Harvey JM et al.
J Clin Oncol 1999;17(5):1474-81.

Breast Cancer UPDATE

Slide 3

Allred Scoring of ER Status by IHC Predicts Response to Adjuvant Endocrine Therapy



Derived with permission from: Harvey JM et al.
J Clin Oncol 1999;17(5):1474-81.

Breast Cancer UPDATE

Slide 4

Results of Analysis of Time to Recurrence in the ATAC Trial According to Estrogen- and Progesterone-Receptor Status

Receptor status	N	Anastrozole vs tamoxifen*
ER+PgR+	5,704	0.82 (0.65-1.03)
ER+PgR-	1,370	0.48 (0.33-0.71)
ER-PgR+	220	0.79 (0.40-1.50)
ER-PgR-	699	1.04 (0.73-1.47)

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

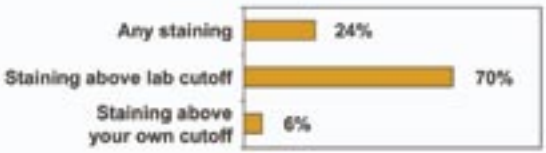
Source: Dowsett M, on behalf of the ATAC Trialists' Group. *Breast Cancer Res Treat* 2003;82(Suppl 1):Abstract 4.

Breast Cancer Update

Slide 5

Determining Estrogen Receptor Status

- How do you define ER positivity?



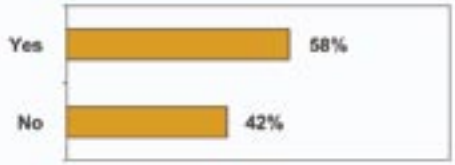
Source: *Breast Cancer Update Patterns of Care Study*, 2004.

Breast Cancer Update

Slide 6

Determining Estrogen Receptor Status

- Do you request ER status for ductal carcinoma *in situ*?



Source: *Breast Cancer Update Patterns of Care* Study, 2004.

Breast Cancer Update

Slide 7

Analysis of ER Status and Response of DCIS to Tamoxifen

Study population

- 1,804 total patients with DCIS (NSABP-B-24)
  - ER results available from 676 patients
    - 344 placebo
    - 332 tamoxifen
      - 450 Central ER IHC assays (standardized)
      - 226 Outside ER IHC assays (variable)

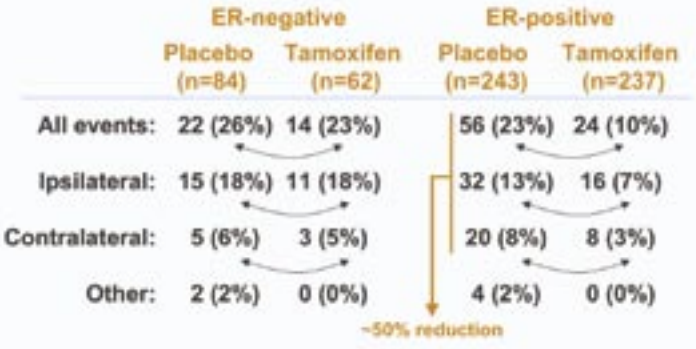
Source: Allred DC. Presentation. San Antonio Breast Cancer Symposium, 2002.

Breast Cancer Update

Slide 8

Sites and Frequency of First Breast Cancer Events by ER and Treatment

(Median follow-up = 8.7 years)



Source: Allred DC. Presentation. San Antonio Breast Cancer Symposium, 2002.

Breast Cancer UPDATE

Slide 9

Effect of Tamoxifen Relative to Placebo by ER Status

All breast cancer events	Relative risk	*p*-value	*p*-value interaction
ER-positive	0.41 (↓59%)	0.0002	0.11
ER-negative	0.80 (↓20%)	0.51	

Source: Allred DC. Presentation. San Antonio Breast Cancer Symposium, 2002.

Breast Cancer UPDATE

Slide 10

Distribution of ER Levels and Comparison Between Central and Outside Labs

	Central assay (n=450)			Outside assays (n=226)
	Score	% Cases	Overall	Overall
Neg	0	19.5	20% negative	30% negative
	2	0.3		
low	3	3.6		
	4	8.0		
	5	13.3		
	6	21.5	80% positive	70% positive
	7	18.7		
high	8	15.1		

Source: Allred DC. Presentation. San Antonio Breast Cancer Symposium, 2002.

Breast Cancer Update

Slide 11

Clinical Comparison of ER-Negative Results from Outside and Central Labs

Outside ER-negative results (n=64)

Events/patients (%)			
Placebo	Tamoxifen	Relative risk	*p*-value
10/39 (26%)	3/25 (12%)	0.43 (↓57%)	0.20

Source: Allred DC. Presentation. San Antonio Breast Cancer Symposium, 2002.

Breast Cancer Update

Slide 12

Clinical Comparison of ER-Negative Results from Outside and Central Labs

Outside ER-negative results (n=89)

Events/patients (%)			
Placebo	Tamoxifen	Relative risk	*p*-value
11/48 (23%)	11/41 (27%)	0.99 (↓1%)	0.98

*no benefit

Source: Allred DC. Presentation. San Antonio Breast Cancer Symposium, 2002.

Breast Cancer Update

Slide 13

Conclusions

- 75% to 80% of DCIS are ER-positive
- Tamoxifen reduces risk approximately 50% in ER-positive DCIS
- Tamoxifen probably ineffective in ER-negative DCIS
- Accurate assessment of ER status is essential

Source: Allred DC. Presentation. San Antonio Breast Cancer Symposium, 2002.

Breast Cancer Update

Slide 14

Discordance in ER and PR Status Between Primary and Metastatic Breast Cancer: A Meta-Analysis

Receptor change	For ER, n=658 Risk ratio (95% CI)	For PR, n=418 Risk ratio (95% CI)
Positive to negative	0.22 (0.17-0.30)	0.20 (0.12-0.33)
Negative to positive	0.11 (0.06-0.22)	0.15 (0.08-0.28)
Total discordance	0.29 (0.18-0.47)	0.27 (0.20-0.36)

Source: Franco N et al. *Proc ASCO* 2004;Abstract 539.

Breast Cancer Update

Slide 15

Differences in ER and PR Between Primary and Metastatic Breast Cancer

Primary→metastatic	ER changes (of 200)	PR changes (of 173)
Positive→negative	41 (20.5%)	10 (5.8%)
Negative→positive	22 (11%)	59 (34.1%)
Totals	63 (31.5%)	69 (39.9%)

Source: Glass EL et al. San Antonio Breast Cancer Symposium, 2003;Abstract 257.

Breast Cancer Update

Post-test:
Breast Cancer Update — Issue 7, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. A meta-analysis published in the *Journal of the National Cancer Institute* evaluating lumpectomy and radiotherapy trials demonstrated patients with good local control had a greater survival rate than those who had a local relapse.
   a. True
   b. False

2. In the Milan and United States studies comparing mastectomy to lumpectomy and radiation, in the subset of patients who had positive nodes and received chemotherapy, which group fared better:
   a. Patients treated by lumpectomy and radiation
   b. Patients treated by mastectomy

3. According to a neurosensory study by Roberta Baron comparing SLNB to axillary node dissection, which of the following statements is true?
   a. The intensity and frequency of neurosensory morbidity is greater with SLNB
   b. The intensity and frequency of neurosensory morbidity is greater with axillary lymph node dissection
   c. The intensity of neurosensory morbidity is less with SLNB, but the frequency of symptoms is the same

4. Across the country, when determining the estrogen receptor status, the average cut point for positivity is 10 to 20 percent, which can lead to misclassification of ER-positive cases as ER-negative.
   a. True
   b. False

5. 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

6. If performed correctly, in what percentage of cases is IHC accurate in determining a patient's HER2 status?
   a. 10 to 15 percent
   b. 50 percent
   c. 80 to 85 percent
   d. 100 percent

7. In the William Beaumont Hospital study matching 199 patients treated with interstitial brachytherapy with 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

8. The proposed NSABP-RTOG trial will randomly assign patients to conventional whole breast radiation 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

9. The ABS's indications for the off-protocol use of brachytherapy include DCIS.
   a. True
   b. False

10. CISH has been shown to have high concordance rates with FISH.
    a. True
    b. False

11. In Vogel's data, approximately 25 to 35 percent of women with metastatic, FISH-positive disease responded to single-agent trastuzumab.
    a. True
    b. False

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

Evaluation Form:
Breast Cancer Update — Issue 7, 2004

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Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic 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, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Patrick I Borgen, 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
Frank A Vicini, MD, FACR	5 4 3 2 1	5 4 3 2 1
Adam M Brufsky, 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
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
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Breast Cancer Update — Issue 7, 2004

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If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

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

.....

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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@researchtopractice.net
For CME Information	Margaret Peng, CME Administrator Email: MPeng@researchtopractice.net

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