BCU SURGEONS | 2006 VOL 5 | ISSUE 1

Breast Cancer® UPDATE

Conversations with Clinical Research Leaders

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

Patrick I Borgen, MD

J Michael Dixon, MD

John Mackey, MD

Clifford Hudis, MD

CME Certified

Download MP3 files of this audio program at BreastCancerUpdate.com/Surgeons

Breast Cancer Update for Surgeons
A Continuing Medical Education Audio Series

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 in order to incorporate these data into management strategies in adjuvant and neoadjuvant disease.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing aromatase inhibitors after tamoxifen.
- Counsel appropriately selected patients about emerging clinical trial data and ongoing trials in the prevention and treatment of noninvasive (DCIS) and invasive breast cancer.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy.
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients.

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

The purpose of Issue 1 of *Breast Cancer Update* for Surgeons is to support these global objectives by offering the perspectives of Drs Borgen, Dixon, Mackey and Hudis on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

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 **blue underlined text**.

TABLE OF CONTENTS

3 INTERVIEWS

Patrick I Borgen, MD
Professor of Surgery
Weill Medical College of Cornell University
Chief, Breast Service, Department of Surgery
Memorial Sloan-Kettering Cancer Center
New York, New York

8 **J Michael Dixon, MD**
Consultant Surgeon and Senior Lecturer
Academic Office
Edinburgh Breast Unit
Western General Hospital
Edinburgh, United Kingdom

12 **John Mackey, MD**
Medical Oncologist, Cross Cancer Institute
Associate Professor of Oncology, University of Alberta
Chair, Northern Alberta Breast Cancer Program
Director, Cancer International Research Group
Edmonton, Canada

16 **Clifford Hudis, MD**
Chief, Breast Cancer Medicine Service
Solid Tumor Division, Memorial Sloan-Kettering Cancer Center
New York, New York

18 POST-TEST

19 EVALUATION FORM

If you would like to discontinue your complimentary subscription to *Breast Cancer Update* for Surgeons, please email us at **Info@ResearchToPractice.net**, or fax us at (305) 377-9998. Please include your full name and address, and we will remove you from the mailing list.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

The scientific staff and consultants for Research To Practice are involved in the development and review of content for educational activities and report the following real or apparent conflicts of interest for themselves (or their spouses/partners) that have been resolved through a peer review process: Richard Kaderman, PhD, Neil Love, MD, Douglas Paley, Michelle Paley, MD, Margaret Peng, Lilliam Sklaver Poltorack, PharmD, Kathryn Ault Ziel, PhD and Chris Thomson, MD — no real or apparent conflicts of interest to report; Sally Bogert, RNC, WHCNP — shareholder of Amgen Inc. Research To Practice receives education grants from Abraxis Oncology, Amgen Inc, AstraZeneca Pharmaceuticals LP, Biogen Idec, Genentech BioOncology, Genomic Health Inc, Roche Laboratories Inc and Sanofi-Aventis, who have no influence on the content development of our educational activities.

In addition, the following faculty (and their spouses/partners) have reported real or apparent conflicts of interest that have been resolved through a peer review process:

Dr Borgen — No financial interests or affiliations to disclose. **Dr Dixon** — No financial interests or affiliations to disclose. **Dr Mackey** — Consulting Fees and Speaking Honoraria: Amgen Inc, AstraZeneca Pharmaceuticals LP, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis. **Dr Hudis** — Consulting Fees: Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech BioOncology, Novartis Pharmaceuticals, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis; Fees for Non-CME Services Received Directly from Commercial Interest or Their Agents: AstraZeneca Pharmaceuticals LP, Roche Laboratories Inc, Sanofi-Aventis; Contracted Research: Amgen Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech BioOncology, Kosan Biosciences, Novartis Pharmaceuticals, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis; Ownership Interest: Genomic Health Inc.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

UPCOMING EDUCATIONAL EVENTS

ASCO 2006 Annual Meeting
June 2-6, 2006
Atlanta, Georgia
Event website: **asco.org**

Toronto Breast Cancer Symposium
June 15-16, 2006
Toronto, Canada
Event website: **cme.utoronto.ca**

48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology
November 5-9, 2006
Philadelphia, Pennsylvania
Event website: **astro.org**

29th San Antonio Breast Cancer Symposium
December 14-17, 2006
San Antonio, Texas
Event website: **sabcs.org**

Miami Breast Cancer Conference
February 21-24, 2007
Miami, Florida
Event website: **cancerconf.com**

Society of Surgical Oncology Annual Meeting
March 15-18, 2007
Washington, DC
Event website: **surgonc.org**

American Association of Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **aacr.org**

INTERVIEW

Patrick I Borgen, MD

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

Tracks 1-15

Track 1 Introduction
Track 2 Margin status: Impact on re-excision and local control
Track 3 Partial breast irradiation techniques being evaluated in clinical trials
Track 4 Postlumpectomy radiation therapy for women over the age of 70
Track 5 Postlumpectomy radiation therapy and hormonal therapy for women with DCIS
Track 6 Perspective on the role of aromatase inhibitors in the prevention and adjuvant settings
Track 7 Side effects associated with aromatase inhibitors
Track 8 Case 1: A patient with a low recurrence score on the Onco*type* DX™ assay
Track 9 Case 2: A patient with a high recurrence score on the Onco*type* DX assay
Track 10 Cost effectiveness of the Onco*type* DX assay
Track 11 Sentinel lymph node biopsy
Track 12 Axillary dissection after identification of a positive sentinel node
Track 13 Considerations in the selection of patients for nipple-sparing mastectomy
Track 14 False-negative rates in sentinel node biopsies
Track 15 Surgical volume and outcomes for patients with breast cancer

Select Excerpts from the Interview

Track 2

DR LOVE: What do you consider an acceptable surgical margin in breast cancer?

DR BORGEN: Nationally, no consensus exists on what constitutes an acceptable margin with either ductal carcinoma in situ (DCIS) or invasive carcinoma. I believe it does a disservice to insist on one-millimeter margins or four-millimeter margins.

For example, if you have a single duct with DCIS a millimeter or two from a margin, in my opinion that margin is okay. However, if you have a field of ducts, all of which are one millimeter from a margin, the pathology report

will still read, "DCIS, one millimeter from a margin," but the tumor burden at that margin makes it very likely that disease will be left behind.

DR LOVE: How has the Oxford Overview on the effects of radiation therapy and surgery affected your view on the importance of margins and local control (Clarke 2005)?

DR BORGEN: Margins always come into play, whether we're dealing with invasive or in situ breast cancer. One of the outcomes of this overview should be that surgeons pay more attention to margins and local control so that we don't have patients slipping through the cracks and not receiving radiation therapy.

Nationally, the re-excision rates approach 50 percent, and at Memorial, almost half our patients go back for more surgery. We're currently evaluating whether we can design a smarter operative field with preoperative MRIs.

However, this is a problem because MRI is an expensive technology and not everyone has access to it. Also, the MRI can display phantoms and has a relatively high false-positive rate associated with it.

The Oxford Overview raises the bar on the value of local control, which causes some concern in the national trials of partial breast radiation therapy. I'm not a naysayer. In fact, we are participating in the NSABP-B-39 trial.

However, as a cautionary note, whole breast radiation now has an established track record in a meta-analysis, with proven deleterious effects among patients who did not receive whole breast radiation (1.1, 1.2).

DR LOVE: Can you elaborate on how you assess margins and make decisions about whether to re-excise?

DR BORGEN: We have recently changed our approach to margins. In the past, we performed a lumpectomy, either by palpation or by image guidance with a wire, and oriented that specimen in space with silk sutures. The pathologists then applied six different colors of ink to the mass that we removed.

However, we have determined that this technique was not accurate. The definition of what was anterior or superior was left up to a pathologist who was not present during the surgical procedure and could not be certain.

1.1

Overview Analysis: Effects of Radiation Therapy and Surgery on Local Recurrence and 15-Year Survival

"In these trials, avoidance of a local recurrence in the conserved breast after BCS and avoidance of a local recurrence elsewhere (eg, the chest wall or regional nodes) after mastectomy were of comparable relevance to 15-year breast cancer mortality. Differences in local treatment that substantially affect local recurrence rates would, in the hypothetical absence of any other causes of death, avoid about one breast cancer death over the next 15 years for every four local recurrences avoided, and should reduce 15-year overall mortality."

SOURCE: Clarke M et al. *Lancet* 2005;366(9503):2087-106. **Abstract**

Today when we do a lumpectomy, we shave the margins individually, intraoperatively. We place a silk suture on the new margin, on the shave, so we know that the orientation of the specimen being sent to the pathologist is correctly identified.

This approach has been very successful. We've dropped our re-excision and positive-margin rates, and when we have to go back for a positive margin, we have been more successful in finding residual cancer.

1.2

Effect of Radiation Therapy (RT) After Breast-Conserving Surgery (BCS) on Local Recurrence and Breast Cancer Mortality: An Overview of 10 Randomized Trials (N = 7,311)

Isolated local recurrence: Five-year risk

Extent of radiation therapy	Events/woman-years		Ratio of annual event rate	2*p*-value
	BCS + RT	BCS	(BCS + RT):BCS	
Radiation therapy only to conserved breast*	7.2%	25.6%	0.31	<0.00001
Radiation therapy to conserved breast and other sites†	7.7%	26.7%	0.32	<0.00001
All cases	7.3%	25.9%	0.31	<0.00001

Breast cancer mortality

Extent of radiation therapy	Deaths/women		Ratio of annual death rates	2*p*-value
	BCS + RT	BCS	(BCS + RT):BCS	
Radiation therapy only to conserved breast: 15-year risk*	28.0%	33.2%	0.84	0.004
Radiation therapy to conserved breast and other sites: 10-year risk†	28.2%	35.1%	0.81	0.02
All cases: 15-year risk	30.5%	35.9%	0.83	<0.0002

* Radiation therapy limited to the conserved breast, sometimes with an additional boost to the scar; 14% of the cases were node-positive.

† Sites other than the conserved breast were radiated, such as the axilla and supraclavicular fossa; 24% of the cases were node-positive.

SOURCE: Clarke M et al. *Lancet* 2005;366(9503):2087-106. **Abstract**

Track 5

DR LOVE: How are you treating patients with DCIS in terms of endocrine therapy?

DR BORGEN: We have viewed tamoxifen as a highly appropriate option for treating ER-positive DCIS since the NSABP-B-24 trial (Fisher 1999).

However, when we sit down and look at risks, benefits and quality-of-life issues, it's common for our New York patients to demur, so we probably have one of the lowest percentages of patients with DCIS on tamoxifen in the country.

The same can be seen in the prevention setting, in which we've not been successful in getting patients to take tamoxifen.

DR LOVE: What are the concerns about tamoxifen in these settings?

DR BORGEN: The two most obvious concerns are endometrial cancer and gynecological events.

Even when we provide the raw numbers on how infrequent those events are, I believe that because we are talking about minimal, if any, impact on long-term survivorship and moderate impact on local control, it simply is not an attractive option.

DR LOVE: For a postmenopausal patient with DCIS who is interested in endocrine therapy but finds tamoxifen intolerable because of side effects, do you offer an aromatase inhibitor?

DR BORGEN: We'd like to have more information about DCIS and aromatase inhibitors, but since the initial publication of the ATAC data (Baum 2002), aromatase inhibitors have certainly become our endocrine therapy of choice for postmenopausal patients with ER-positive, invasive cancers.

That literally happened overnight, like gangbusters, and so a "bleedover" to postmenopausal patients with DCIS is completely natural.

Track 7

DR LOVE: What side effects have you observed in patients who are receiving aromatase inhibitors?

DR BORGEN: Aches and pains — particularly of the knees and hips — are the most common complaints. However, these are far less than the complaints we heard from patients on tamoxifen.

DR LOVE: In clinical practice, what is your protocol for monitoring bone density and the use of bisphosphonates in patients on aromatase inhibitors?

DR BORGEN: If we are concerned about a bone density report, we will refer the patient to an endocrinologist for further workup prior to beginning aromatase inhibitor therapy.

In New York, patients are very proactive and they come into the office aware of their bone density and, if there's a problem, they are generally already on a bisphosphonate or similar agent.

DR LOVE: Have you utilized neoadjuvant aromatase inhibitors to downsize tumors in order to convert a mastectomy to a lumpectomy?

DR BORGEN: Absolutely. Certainly in the older patient population we have utilized that approach. However, it's not so much to convert a mastectomy to a lumpectomy as it is to downstage the disease.

Track 8

DR LOVE: What is your opinion of the Onco*type* DX assay, and how do you utilize it clinically?

DR BORGEN: We're very excited about the possibility of a truly genomic approach to breast cancer. We use the Onco*type* DX assay in borderline cases in which a low recurrence score would preclude cytotoxic chemotherapy (Paik 2004; Mamounas 2005).

For the patient who has a larger tumor, a higher-grade tumor or other mitigating factors, we're not using the Onco*type* DX as a sole factor in precluding chemotherapy, but it's been enormously helpful in the borderline cases. ■

1.3

Practical Impact of Onco*type* DX Assay: Two Patients from Dr Borgen's Practice

A 59-year-old postmenopausal woman with a 9-mm, ER-positive, HER2-negative, node-negative breast cancer. No lympho-vascular invasion.

Onco*type* DX assay: Very low

Rx: Aromatase inhibitor; no chemotherapy

A 57-year-old postmenopausal woman with a 0.9-cm, ER-positive, HER2-negative, node-negative breast cancer. Questionable LVI. The patient was very fearful of chemo-therapy, having seen a neighbor go through this treatment.

Onco*type* DX assay: Very high

Rx: Aromatase inhibitor; dose-dense AC → T chemotherapy

SELECT PUBLICATIONS

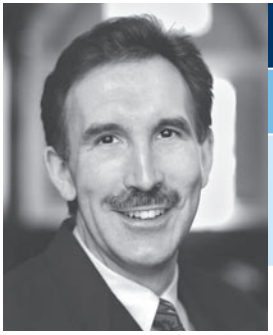
Baum M et al; ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359(9324):2131-9. **Abstract**

Clarke M et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;366(9503):2087-106. **Abstract**

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**

Mamounas E et al. **Association between the 21-gene recurrence score assay (RS) and risk of locoregional failure in node-negative, ER-positive breast cancer: Results from NSABP B-14 and NSABP B-20.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 29**.

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**



INTERVIEW

J Michael Dixon, MD

Dr Dixon is Consultant Surgeon and Senior Lecturer in the Academic Office of the Edinburgh Breast Unit at Western General Hospital in Edinburgh, United Kingdom.

Tracks 1-10

Track 1 Introduction

Track 2 Effect of preoperative aromatase inhibitors on assays of Ki-67

Track 3 Clinical trials of the aromatase inhibitors for DCIS and prevention

Track 4 Hormonal therapy options for premenopausal patients with ER-positive disease

Track 5 Impact of the aromatase inhibitors on bone mineral density and fracture risk

Track 6 Optimal duration of adjuvant endocrine therapy

Track 7 Use of genetic profiling in the neoadjuvant setting to predict response to aromatase inhibitors

Track 8 Neoadjuvant trials for the development of novel therapeutic agents

Track 9 Current status of sentinel lymph node biopsy

Track 10 Partial breast irradiation

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss your trial of neoadjuvant aromatase inhibitors?

DR DIXON: We conducted a study in women with invasive breast cancer: 206 patients with 209 tumors. The patients were randomly assigned to receive 14 days of either letrozole or anastrozole, preoperatively. In terms of switching off cell proliferation, we couldn't find any significant difference between anastrozole and letrozole (Murray 2004; Faratian 2005).

DR LOVE: Can you talk about the data that have been presented on the effect of preoperative endocrine therapy on Ki-67?

DR DIXON: Mitch Dowsett presented data from the IMPACT trial at the 2005 San Antonio Breast Cancer Symposium showing that the 14-day Ki-67 predicts relapse-free survival (Dowsett 2005).

What's interesting about the research is that it validated the idea that if your proliferation goes down or is low after two weeks on a drug, then you will have a better long-term outcome. If you don't have any decrease in prolif-

eration, that indicates your cancer is resistant to endocrine therapy (Dowsett 2005).

DR LOVE: Does the same correlation hold true with chemotherapy?

DR DIXON: That has been investigated, but the problem with chemotherapy, compared to endocrine therapy, is sampling time. Chemotherapy is administered in pulses, and the proliferation rate drops within a few days.

So the question is, when do you sample to find how it is impacting the tumor? In terms of sampling for Ki-67, the favorable aspect of endocrine therapy is that it is administered constantly.

DR LOVE: In your study of women with invasive cancers, what fraction of ER-positive tumors drop in proliferation at two weeks?

DR DIXON: About 90 percent of the patients showed a drop at two weeks (2.1). In that study, we also had our pathologists look through the core biopsies and the final histologies to determine how many of them had DCIS. Then they looked at the effects of the aromatase inhibitors on the DCIS.

Surprisingly, we found that DCIS was proliferating as much as the invasive cancer (Faratian 2005). The second observation was that the DCIS was proliferating at roughly the same rate as the invasive cancer in an individual patient.

In other words, if your cancer was highly proliferative, your DCIS was highly proliferative (Faratian 2005).

DR LOVE: Were the aromatase inhibitors having an effect on the DCIS?

DR DIXON: We could not tell whether the aromatase inhibitors were eliminating the DCIS, but we could see they were remarkably effective at switching off proliferation in the DCIS (2.1).

2.1 Number of Invasive Cancers and DCIS with Reduced Proliferation After 14 Days of an Aromatase Inhibitor

	Anastrozole (n = 15)	Letrozole (n = 13)
Invasive cancer	14	13
DCIS	10	13

SOURCE: Faratian D et al. San Antonio Breast Cancer Symposium 2005;**Abstract 6041**.

We had approximately an 80 percent switch-off of proliferation. If you measure the level at the start, at 100 percent, it was down to 20 percent within a couple of weeks (Faratian 2005).

We saw other biological effects, too. For example, the progesterone receptor was switched off (Faratian 2005). These were potent biological effects on DCIS.

To some extent, this starts to provide us with an insight as to why the aromatase inhibitors are probably more effective at stopping other cancers from developing, because they work on these earlier lesions.

Although some studies are now evaluating the aromatase inhibitors for patients with DCIS, if I were a patient with DCIS, then I'd be thinking that an aromatase inhibitor might be a good idea.

Track 4

DR LOVE: What do you think about the strategy of ovarian suppression and an aromatase inhibitor for a premenopausal patient with node-positive, ER-positive, HER2-positive disease?

DR DIXON: It sounds sensible because we know the aromatase inhibitors are effective in patients with HER2-positive disease. In our preoperative study, we found the aromatase inhibitors were as effective at reducing proliferation in patients with HER2-positive disease as in those with HER2-negative disease. The degree of reduction was identical in patients with HER2-positive and HER2-negative disease (Murray 2004).

It's as though HER2 isn't important in relation to the likelihood of responding to an aromatase inhibitor.

Track 5

DR LOVE: There was an increased rate of fractures associated with anastrozole in the ATAC trial, but they didn't monitor bone density or use bisphosphonates. What is your approach to monitoring bone density in patients on aromatase inhibitors?

DR DIXON: If you have a drug that is more effective against breast cancer and it causes some minor problems, then I'd rather circumvent the problems and utilize the more effective drug.

One of the clinical applications to arise from the IBIS trial is an easy way to manage bone density in patients on aromatase inhibitors. Rob Coleman, who is a bone expert in the United Kingdom, has developed an algorithm that's very straightforward. If you're starting a woman on five years of an adjuvant aromatase inhibitor, you need to check the bone density beforehand and at regular intervals.

If you're switching women from adjuvant tamoxifen after two to three years to an aromatase inhibitor, you don't really need to bother with the bone density between the ages of 50 and 64. After 64 years of age, you should obtain a DEXA scan at the time of the switch.

Track 6

DR LOVE: Do you think it's justifiable to use more than a couple of years of adjuvant tamoxifen in a postmenopausal patient with an invasive ER-positive tumor?

DR DIXON: For the majority of women who are on tamoxifen now, it's best to switch them to an aromatase inhibitor. For those who are reaching the end of five years on tamoxifen, I would continue them on it and then use extended adjuvant therapy.

The issue is, of course, how long do you switch them for?

One of the things that the MA17 trial has shown us is that five years of treatment is not enough (Goss 2005). So will we use only five years of an aromatase inhibitor? Should we continue the aromatase inhibitor beyond that? Should a woman who was treated with two to three years of tamoxifen receive five, rather than two to three, years of an aromatase inhibitor?

I believe we will find that the overall length of treatment will not be five years but that we will need to use a longer duration.

DR LOVE: An NSABP study will evaluate five years of an aromatase inhibitor beyond the initial five years or in patients who have switched to an aromatase inhibitor at two years who are now five years past their surgery.

DR DIXON: I believe the studies evaluating more prolonged endocrine therapies are likely to show a benefit.

One of the reasons I'm sure they will is because the aromatase inhibitors are very good preventive agents.

Among women who have undergone breast-conserving surgery, almost all the recurrences after five years are second primaries, not recurrences. That's frustrating for me as a surgeon.

The patient is doing well for five, six, seven years, and suddenly she springs up another cancer. She needs to be treated again, and it's devastating for the woman.

So if we can continue her on a drug that suppresses the rate of new cancers, I believe that will be tremendous. ■

SELECT PUBLICATIONS

Delozier T et al. **Optimal duration of adjuvant tamoxifen (TAM) in early breast cancer (EBC): Ten year results of a randomized trial (TAM-01) of the FNCLCC Breast Group.** San Antonio Breast Cancer Symposium 2005;**Abstract 14**.

Dowsett M et al; on behalf of the IMPACT Trialists. **Ki67 after 2 weeks endocrine treatment predicts relapse-free survival (RFS) in the IMPACT trial.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 45**.

Faratian D et al. **Effects of letrozole and anastrozole on ductal carcinoma in situ (DCIS): Results from a randomised trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 6041**.

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

Murray J et al. **Letrozole and anastrozole: A pre-operative study of their effects on ER-positive breast cancers in postmenopausal women.** San Antonio Breast Cancer Symposium 2004;**Abstract 406**.

INTERVIEW

John Mackey, MD

Dr Mackey is Medical Oncologist at the Cross Cancer Institute, Associate Professor of Oncology at the University of Alberta, Chair of the Northern Alberta Breast Cancer Program and Director of the Cancer International Research Group in Edmonton, Canada.

Tracks 1-19

Track 1 Introduction
Track 2 Overview of adjuvant aromatase inhibitors in postmenopausal patients
Track 3 Efficacy of aromatase inhibitors versus tamoxifen
Track 4 Survival benefit of aromatase inhibitors versus tamoxifen
Track 5 Endometrial changes associated with tamoxifen
Track 6 Impact of aromatase inhibitors on bone density
Track 7 Vasomotor symptoms and vascular toxicities associated with tamoxifen
Track 8 Arthralgias associated with aromatase inhibitors
Track 9 Clinical implications of the adjuvant aromatase inhibitor trials
Track 10 Aromatase inhibitors combined with LHRH agonists for premenopausal patients
Track 11 Onco*type* DX assay and benefits of adjuvant chemotherapy
Track 12 Use of the Onco*type* DX assay in clinical practice
Track 13 Clinical trials of adjuvant trastuzumab for HER2-positive breast cancer
Track 14 BCIRG 006: Adjuvant trial of docetaxel/carboplatin/trastuzumab
Track 15 TOPO II assay in patients with HER2-positive disease
Track 16 Delayed adjuvant trastuzumab for patients with HER2-positive disease
Track 17 Combining trastuzumab with dose-dense chemotherapy
Track 18 Adjuvant trastuzumab for patients with node-negative breast cancer
Track 19 Single-agent trastuzumab as adjuvant therapy for elderly patients

Select Excerpts from the Interview

Track 3

DR LOVE: Could you discuss the efficacy findings of the aromatase inhibitors compared to tamoxifen?

DR MACKEY: We're excited to see all of the adjuvant aromatase inhibitor trials are showing that disease-free survival is improved (Howell 2005; Jonat 2005). Roughly one in five to one in three recurrences are prevented by the use of an aromatase inhibitor rather than a standard tamoxifen regimen for five years.

DR LOVE: Of course, that's also with tamoxifen lowering the relapse rate significantly compared to no endocrine therapy.

DR MACKEY: Exactly. Tamoxifen is actually a very effective drug. It reduces the risk of recurrence by about 50 percent. The aromatase inhibitors are providing a benefit in addition to that one half improvement in risk.

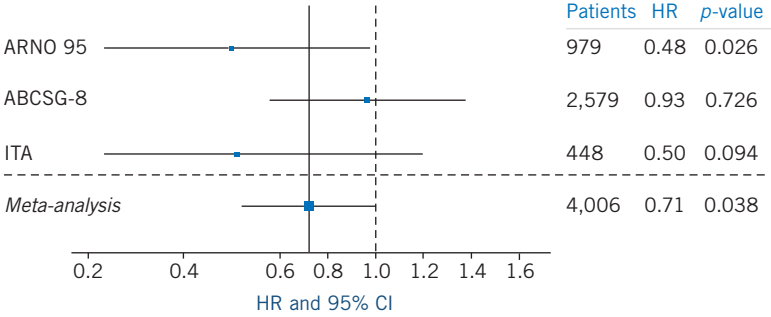
Track 4

DR LOVE: What's been seen in terms of the overall survival of women on aromatase inhibitors versus tamoxifen in the adjuvant setting?

DR MACKEY: With long-term follow-up of the women on these aromatase inhibitor trials, we're starting to obtain a hint that survival might also be improved. It's beginning to look as though the trend is there in a couple of trials and one meta-analysis (Jonat 2005; [3.1]).

3.1

Meta-Analysis of ARNO 95, ABCSG-8 and ITA Trials: Overall Survival Benefit for Patients Switching to Anastrozole After Two to Three Years of Adjuvant Tamoxifen



HR = hazard ratio; CI = confidence interval

SOURCE: With permission. Jonat W et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 18**.

Track 11

DR LOVE: Would you talk about the Onco*type* DX assay and how it can be integrated into the management plan for a patient with an ER-positive tumor?

DR MACKEY: The Onco*type* DX assay is the best example we have of taking our understanding of the biology of breast cancer and trying to make predictions about the behavior of that tumor in the future. It falls into the class of tests we call predictive assays. Whereas a prognostic assay would tell a healthcare provider or a patient the odds of having a negative outcome, a predictive

assay helps in deciding how to manage a person's disease.

A predictive assay tells you, although your prognosis may be such, if we treat with a specific therapy, we can change that prognosis, and this specific therapy is the right therapy for you. Hence, predictive assays are extremely valuable, and prognostic assays are "a dime a dozen."

If you have a woman for whom you're trying to make a treatment decision and you're not clear whether she warrants chemotherapy or whether hormone therapy is enough with an estrogen receptor-positive tumor, you can take the woman's tumor block and send it away for a central laboratory analysis. They analyze the levels of several different genes and send you back an Onco*type* DX score.

The score you receive reflects the spectrum of possible biologic behaviors of the breast cancer, whether it will be highly endocrine sensitive or less sensitive to endocrine manipulation, in which case you might strongly consider chemotherapy. The Onco*type* DX assay is a state-of-the-art technique, and you can determine from the assay results those women who would benefit from chemotherapy in addition to tamoxifen. Although I'm hopeful that we can fully validate this assay and perhaps even improve on it, and I do think it's a major step forward, I would like to see a little bit more validation and a comparison with good quantitative estrogen receptor and HER2 assessment.

Track 13

DR LOVE: Can you review the key findings of recent trials evaluating adjuvant trastuzumab?

DR MACKEY: This is the most exciting story that has happened in my career of treating breast cancer. Trastuzumab is an antibody treatment directed at the HER2 protein, which is found on the surface of breast cancer cells. HER2-overexpressing breast cancers are seen in about one out of five breast cancers.

Trastuzumab for advanced breast cancer was a big breakthrough in 1998. Now we have five studies reporting that if you administer adjuvant trastuzumab to a woman who has a HER2-driven breast cancer, her chances of having a recurrence are markedly reduced (Romond 2005; Piccart-Gebhart 2005; Slamon 2005).

In general, if we put them all together and average the effects, a 50 percent reduction in the risk of recurrence exists in any given year.

From the results of the HERA trial, which was conducted primarily in Europe, we know that utilizing adjuvant trastuzumab for one year after chemotherapy reduces the risk of recurrence by about half (Piccart-Gebhart 2005).

The American trials took advantage of what we knew from the metastatic setting, which was that trastuzumab worked best if you administered it with chemotherapy; therefore, the North American trials combined trastuzumab

with a taxane-based chemotherapy regimen.

The NSABP and the NCCTG trials administered AC for four cycles followed by paclitaxel, and patients were randomly assigned to receive paclitaxel with or without trastuzumab. AC followed by a taxane with trastuzumab outperformed AC followed by a taxane.

The effect was remarkably robust, a 50 percent reduction in recurrence and, in addition, a hint of improved overall survival, even though the median follow-up of those trials is only about two years (Romond 2005).

The Breast Cancer International Research Group (BCIRG) ran another adjuvant trastuzumab trial (BCIRG 006) with 3,200 patients. We knew from the metastatic setting there was a potential for heart damage when you administered doxorubicin or epirubicin with trastuzumab. There was concern that if we administered AC and then followed it with trastuzumab, we would run into cardiac problems. In the NSABP-B-31 and NCCTG-N9831 trials, the heart failure rate was about 2.5 to 4.1 percent.

The design of BCIRG 006 included AC followed by docetaxel for four cycles as the standard arm. The second arm was AC followed by docetaxel with trastuzumab, and the third arm was actually the most interesting and novel — it discarded the anthracycline entirely and relied purely on docetaxel/carboplatin and trastuzumab (TCH), all given from day one of chemotherapy.

At the 2005 San Antonio Breast Cancer Symposium, Dennis Slamon, who designed this study, presented its first results. We saw, in the second arm, a 50 percent reduction in recurrence. So ACTH with docetaxel instead of paclitaxel was a very effective regimen. In the third arm, we found about a 40 percent reduction in the risk of recurrence with TCH. The interesting thing was we had virtually no congestive heart failure in the third arm (Slamon 2005). ■

SELECT PUBLICATIONS

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

Jonat W et al. **Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer: A meta-analysis of the ARNO 95 Trial, ABCSG Trial 8, and the ITA Trial.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 18**.

Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. **Trastuzumab after adjuvant chemotherapy in HER 2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study**. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

INTERVIEW

Clifford Hudis, MD

Dr Hudis is Chief of the Breast Cancer Medicine Service in the Solid Tumor Division at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-10

Track 1 Introduction
Track 2 Clinical use of the Onco*type* DX assay
Track 3 Impact of the Onco*type* DX assay on clinical decision-making
Track 4 Clinical trials of bevacizumab for breast cancer
Track 5 Side effects of bevacizumab
Track 6 Incorporation of bevacizumab into adjuvant clinical trials
Track 7 Fulvestrant: A "pure" estrogen receptor antagonist
Track 8 Using a loading dose of fulvestrant
Track 9 Combining fulvestrant with biologic and/or hormonal therapies
Track 10 Clinical trial of delayed adjuvant fulvestrant

Select Excerpts from the Interview

Track 2

DR LOVE: What are your thoughts about the Onco*type* DX assay?

DR HUDIS: A high recurrence score clearly identifies a subset of patients who are very likely to benefit when chemotherapy is added to hormone therapy. At the same time, it's important to emphasize that for those patients who have intermediate and low recurrence scores, the confidence intervals are somewhat wide. Therefore, one cannot exclude the possibility of a chemotherapy benefit, even in patients with low or intermediate recurrence scores, based on the available data (Paik 2004; [4.1]).

From my perspective, you use the test in the clinical context where it will help you make a decision. For example, in a 32-year-old patient who is worried about fertility and is committed to five years of tamoxifen and says, "You really need to convince me to receive chemotherapy," I see a role for the test. As the patient is already on the "no" side of that equation, if she has a low or intermediate recurrence score, I may not change her mind.

If she has a high recurrence score, I have evidence to say, "You don't want chemotherapy, but you're in the subset of patients in whom we have pretty

good evidence with a tight confidence interval that you'll benefit from it." I do not perform this test on every patient; you need to know what you will do with the results.

DR LOVE: A presentation of the data showed that the patients with a high recurrence score derived a dramatic benefit from chemotherapy, avoiding about 75 percent of recurrence, and it was an older type of chemotherapy that we no longer use.

DR HUDIS: That's exactly right, it was CMF or MF, and it was a really impressive result. At the same time, I have to point out that it was consistent with other data we've recently seen using lower-technology approaches. At the 2004 San Antonio Breast Cancer Symposium, Kathy Albain presented the retrospective analysis of SWOG-8814, evaluating tamoxifen alone or with CAF in patients with exclusively node-positive, ER-positive disease (Albain 2004).

In that study, in general, adding chemotherapy to tamoxifen showed a benefit. When they went back and looked at a centrally performed estrogen receptor analysis, they showed the benefit of chemotherapy was in the patients with low or intermediate ER-positive disease, not so much in the patients with strongly ER-positive disease (Albain 2004). That may all be consistent.

The blanket statement that chemotherapy is ineffective in patients with ER-positive disease is clearly untrue. The Onco*type* DX assay, among other technologies, may be one of the better ways to separate the wheat from the chaff. ■

4.1

Ten-Year Distant Recurrence-Free Survival According to Recurrence Score in NSABP-B-20 (N = 651)

Risk group	Tamoxifen (n = 227)	Tamoxifen with chemotherapy (n = 424)	Relative risk (95% CI)	*p*-value
Low (RS < 18)	96%	95%	1.31 (0.46-3.78)	0.76
Intermediate (RS = 18-30)	90%	89%	0.61 (0.24-1.59)	0.71
High (RS ≥ 31)	60%	88%	0.26 (0.13-0.53)	0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCE: Paik S et al. San Antonio Breast Cancer Symposium 2004;**Abstract 24**.

SELECT PUBLICATIONS

Albain K et al. **Concurrent (CAFT) versus sequential (CAF-T) chemohormonal therapy (cyclophosphamide, doxorubicin, 5-fluorouracil, tamoxifen) versus T alone for postmenopausal, node-positive, estrogen (ER) and/or progesterone (PgR) receptor positive breast cancer: Mature outcomes and new biologic correlates on Phase III Intergroup trial 0100 (SWOG-8814).** San Antonio Breast Cancer Symposium 2004;**Abstract 37**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **For patients with ER-positive, node-negative invasive breast cancer, the Onco*type* DX assay can be beneficial in identifying patients who are at low, intermediate or high risk of recurrence.**
   a. True
   b. False

2. **According to data from the IMPACT trial, the amount of Ki-67 after 14 days of treatment with hormonal therapy predicts _____.**
   a. Overall survival
   b. Cancer-specific survival
   c. Relapse-free survival
   d. All of the above
   e. None of the above

3. **The Onco*type* DX assay should be used for patients with _____ disease.**
   a. ER-positive
   b. ER-negative
   c. Node-negative
   d. Both a and c
   e. Both b and c

4. **The aromatase inhibitors have been shown to reduce proliferation in DCIS.**
   a. True
   b. False

5. **Adjuvant trastuzumab has been found to significantly reduce the risk of recurrence in women with HER2-positive breast cancer.**
   a. True
   b. False

6. **Patients with a _____ recurrence score on the Onco*type* DX assay are likely to benefit from the addition of chemotherapy to adjuvant hormonal therapy.**
   a. Low
   b. Intermediate
   c. High
   d. Both a and b
   e. None of the above

7. **Patients with ER-negative disease tend to experience recurrence early in the course of the disease, whereas those with ER-positive disease seem to have a constant and chronic risk of recurrence.**
   a. True
   b. False

8. **The overview by Clarke et al evaluating the effect of radiation therapy after breast-conserving surgery showed which of the following?**
   a. Radiation therapy significantly reduced the five-year local recurrence rate
   b. Radiation therapy significantly reduced breast cancer mortality
   c. Both a and b
   d. None of the above

9. **The NSABP-B-39 trial is comparing whole breast irradiation to _____ in patients with DCIS or Stage I/II breast cancer.**
   a. No radiation therapy
   b. Partial breast irradiation
   c. Endocrine therapy

Post-test answer key: 1a, 2c, 3d, 4a, 5a, 6c, 7a, 8c, 9b

EVALUATION FORM

Breast Cancer Update for Surgeons — Issue 1, 2006

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 in order to incorporate these data into management strategies in adjuvant and neoadjuvant disease. . . . . 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
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant and neoadjuvant settings and of switching to or sequencing aromatase inhibitors after tamoxifen. . . . . 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
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about availability and applicability of emerging research data on sentinel lymph node biopsy. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of partial breast irradiation and the clinical trials evaluating this technique with appropriately selected patients. . . . . 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
J Michael Dixon, MD	5 4 3 2 1	5 4 3 2 1
John Mackey, MD	5 4 3 2 1	5 4 3 2 1
Clifford Hudis, MD	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

Which of the following audio formats of this program did you use?

☐ Audio CDs ☐ Audio tapes ☐ Download MP3s from website

EVALUATION FORM

Breast Cancer Update for Surgeons — Issue 1, 2006

REQUEST FOR CREDIT — please print clearly

Name: ..... Specialty: .....

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other .....

Medical License/ME Number: ..... Last 4 Digits of SSN (required): .....

Street Address: ..... Box/Suite: .....

City, State, Zip: .....

Telephone: ..... Fax: .....

Email: .....

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

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?

.....

Additional comments about this activity:

.....

FOLLOW-UP

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity 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 am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at BreastCancerUpdate.com/Surgeons.

Breast Cancer® UPDATE

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	Email: CME@ResearchToPractice.net

This program is supported by education grants from AstraZeneca Pharmaceuticals LP and Genomic Health Inc.

Breast Cancer®

UPDATE

This program is supported by education grants from
AstraZeneca Pharmaceuticals LP and Genomic Health Inc.

Research To Practice™

Sponsored by Research To Practice.

Last review date: April 2006
Release date: April 2006
Expiration date: April 2007
Estimated time to complete: 3 hours