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Breast Cancer® UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

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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.
- Develop an algorithm for ER and HER2 testing and implement a treatment plan for patients with HER2-positive breast cancer.
- 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 Dixon, Dickler, Wood and Mackey on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

31st Annual Symposium of the American Society of Breast Disease
April 12-14, 2007
San Francisco, California
Event website: **www.asbd.org**

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

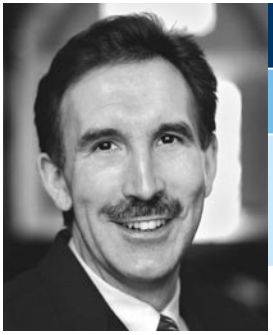
The American Society of Breast Surgeons Eighth Annual Meeting
May 2-6, 2007
Phoenix, Arizona
Event website: **www.breastsurgeons.org**

American Society of Clinical Oncology 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **www.asco.org**

ECOG Semi-Annual Meeting
June 8-10, 2007
Washington, DC
Event website: **www.ecog.org**

CALGB Semi-Annual Meeting
June 21-24, 2007
Baltimore, Maryland
Event website: **www.calgb.org**

American Society of Clinical Oncology 2007 Breast Cancer Symposium
September 7-8, 2007
San Francisco, California
Event website: **www.asco.org**



INTERVIEW

J Michael Dixon, MD

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

Tracks 1-13

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: What are some of the most common questions you receive from surgeons in practice?

DR DIXON: How much extra tissue around the tumor do you need to remove to say the tumor is completely excised? In consults from all over the world, the surgeons remove the cancer with clear margins, but the oncologist is unhappy and says, "Go back and remove more tissue."

We have good data because we treat large numbers of women and we accept a one-millimeter margin. Do you achieve better control rates with two millimeters, three millimeters or four millimeters? Certainly not. A fantastic review by

Eva Singletary concluded that wider margins will not necessarily reduce local recurrence rates. Also, it is important to understand that wider margins will produce more detrimental cosmetic outcomes.

The main purpose of performing breast-conserving surgery is to leave a reasonable amount of breast tissue, and to do that, you have to remove the cancer with a minimal margin of normal tissue. If you don't remove the cancer or you remove it and leave the breast looking terrible, you've failed. It's that simple.

DR LOVE: What is your procedure, and do you see any technical caveats?

DR DIXON: First, it's useful to have the radiologist determine how deep the tumor is in the breast before you begin surgery. If it's one and a half centimeters deep, it is not necessary to scrape all the fat off under the skin when performing the wide excision because that leaves a poor cosmetic result.

Second, if you have a defect in the breast after removing the tumor, in most instances you're better off trying to mobilize tissue from around the margins and closing the defect. That requires skill and a little more surgery, but it tends to produce better cosmetic results.

Additionally, segmental excision is a waste of time. You do not need to remove tissue beyond the periphery of the breast or down toward the nipple. There is no evidence that more frequent local recurrence occurs down toward the nipple than out peripherally or around the edges.

Track 7

DR LOVE: For a woman who has received five years of adjuvant tamoxifen and is now off of therapy, how do you calculate the residual risk of recurrence, and how do you decide whether or not to start her on an aromatase inhibitor?

DR DIXON: You consider the factors associated with recurrence beyond five years of tamoxifen. If she had Grade I, node-negative disease, for example, I wouldn't start her on anything because the rates of local recurrence are low over a long period.

We've found that after five years, the recurrences for patients with Grade II disease were similar to those with Grade III disease. The reason is that patients with Grade III disease tend to experience recurrence early, and then their rates of recurrence come down and are similar to those of patients with Grade II disease. I consider treating Grade II disease.

The other issue is duration of endocrine treatment. Five years is almost certainly not enough. One of the important lessons from MA17 (Goss 2005) is that breast cancer is a chronic disease. It requires chronic care in terms of follow-up and treatment. Even if you switch women after two or three years of adjuvant tamoxifen to an aromatase inhibitor, you will probably need to use five years of an aromatase inhibitor.

DR LOVE: Would you consider delayed adjuvant endocrine therapy for a woman who declined tamoxifen five years ago for a moderately high-risk, node-negative tumor?

DR DIXON: Absolutely. All the evidence we have indicates that it doesn't matter when you start tamoxifen or an aromatase inhibitor — you still derive a benefit (Delozier 2000; Robert 2006).

Track 9

DR LOVE: What is your approach to monitoring bone density in patients who are receiving an aromatase inhibitor?

DR DIXON: Rob Coleman and some of the metabolic bone specialists in the United Kingdom have drawn up sensible guidelines. If the initial DEXA scan shows osteoporosis, then those patients definitely need treatment with a bisphosphonate, but we use the aromatase inhibitor anyway if their cancer requires it.

If they have osteopenia, we will still use the aromatase inhibitor, but then we'd monitor the bone. If they have normal bone density, then we would repeat their DEXA scan, and if it was normal within a couple of years, we probably wouldn't repeat it again during their treatment with an aromatase inhibitor.

We don't do as many DEXA scans as you do in the United States. When we first heard about the bone data, there was a bit of worry and panic, but the fracture rate levels off after you stop the aromatase inhibitor (Buzdar 2006; [1.1]). The bone effects have not been nearly as bad as we thought they might be.

Track 11

DR LOVE: What is your approach to neoadjuvant endocrine therapy?

DR DIXON: Neoadjuvant endocrine therapy is valuable for our group, partly because we have an elderly population. Currently, between 40 and 45 percent of all patients with breast cancer are older than 70 years of age. Most of these women aren't candidates for neoadjuvant chemotherapy if they present with larger tumors. However, they are eligible for neoadjuvant endocrine therapy because increasing age is associated with increasing ER expression.

DR LOVE: Is the intent to make them eligible for a lumpectomy, or is it the overall treatment?

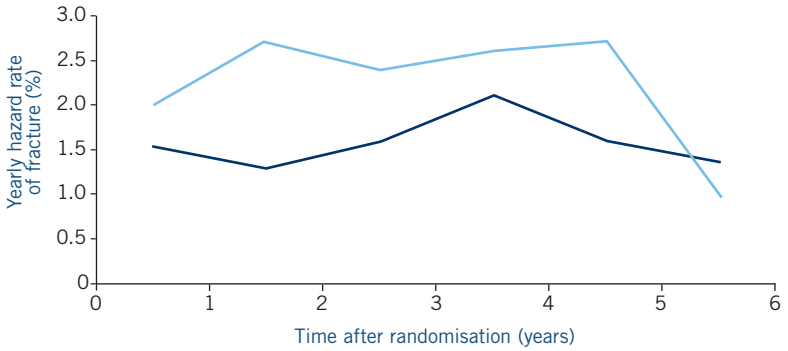
DR DIXON: Both. In patients who aren't fit for any other treatment, neoadjuvant aromatase inhibitors alone will often provide a prolonged response and allow them to survive long enough to die of something other than breast cancer.

DR LOVE: What about the patient who wants to have breast-conserving surgery, but it's not technically feasible?

DR DIXON: Most of these patients have tumors with high levels of ER. In patients with high-ER tumors, you have a greater than 75 percent chance of obtaining a response within three to four months. That's a pretty high response rate, even for some of the more potent chemotherapies. There is also very little chance of progression. ■

1.1

ATAC Trial: Yearly Hazard Rate of Fractures During and After Treatment



Number at risk						
Anastrozole	3092	2923	2724	2553	2393	2070	845
Tamoxifen	3094	2932	2741	2579	2401	2100	846

Frequency of first fracture before recurrence by treatment group
Data calculated by Kaplan-Meier estimates

SOURCE: Reprinted from The Lancet Oncology, Vol 7, Buzdar A et al, **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: Long-term safety analysis of the ATAC trial**, 633-43, Copyright 2006, with permission from Elsevier. **Abstract**

SELECT PUBLICATIONS

Buzdar A et al. **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: Long-term safety analysis of the ATAC trial.** *Lancet Oncol* 2006;7(8):633-43. **Abstract**

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

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**

Robert NJ et al. **Updated analysis of NCIC CTG MA.17 (letrozole vs placebo to letrozole vs placebo) post unblinding.** *Proc ASCO* 2006;**Abstract 550**.

INTERVIEW

Maura N Dickler, MD

Dr Dickler is Assistant Attending Physician in Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-18

Select Excerpts from the Interview

Track 5

DR LOVE: Where are we right now in terms of adjuvant endocrine therapy for postmenopausal women?

DR DICKLER: I tend to use an aromatase inhibitor up front with my postmenopausal patients. I believe the aromatase inhibitors are a little better

than tamoxifen. You can prevent some of the earlier events with the aromatase inhibitors, and I like to use my best drug going forward.

I am still interested in defining a sequencing strategy and anxiously await the results of BIG 1-98 (BIG 1-98 2005; Coates 2007) to see if the sequence of an AI to tamoxifen may be better than an AI alone for five years. But, until I know otherwise, I tend to start with an aromatase inhibitor up front.

Track 7

DR LOVE: Another question is the duration of aromatase inhibitors in the adjuvant setting. Past trials have gone up to five years, and now we have trials that go beyond five years. Right now, in a clinical setting, how do you approach the issue of when to stop an aromatase inhibitor?

DR DICKLER: It is easiest to make these decisions for patients with node-positive disease, for whom we've seen a survival benefit with extended adjuvant therapy with letrozole (Goss 2005). They are the patients who are most likely to benefit. With close monitoring of their bone density, I don't see much of a downside to continuing, in that I'm not concerned that an aromatase inhibitor may be detrimental the way we think tamoxifen might be detrimental after more than five years. Ultimately, talking with the patient and weighing the risks and benefits is important.

Where we struggle, however, is with a patient who has node-negative disease, whose risk of a recurrence is lower and who may have comorbid problems. I find that a much more difficult decision. I talk with each patient, but I would, for select patients, offer more than five years of an aromatase inhibitor if I thought they might benefit.

It was fascinating to see from the Overview analysis how many recurrences happen after year five. I don't believe we fully understood that before. We all have patients who have relapsed 10 and even 20 years out, but seeing that just as many patients relapse after five years as they do in the first five years makes us realize it truly is a chronic disease.

The MA17 trial not only showed us that patients experience recurrence during that period but that we can prevent those recurrences. I believe that was a practice-changing study because now we can affect the natural history of this disease five to 10 years out and maybe more (Goss 2003, 2005).

Patients are being randomly reassigned for 10 versus 15 years. We could possibly be considering 15 years of endocrine therapy, and if we could improve survival, that's important.

DR LOVE: Most recently the NSABP reported on exemestane after five years of tamoxifen (Mamounas 2006), which demonstrated a benefit also.

DR DICKLER: It was interesting that 45 percent of the patients crossed over from placebo to exemestane, and yet there was still a reduction in the hazard

ratio. I believe it shows the potency of the aromatase inhibitors and that estrogen suppression is a useful therapy.

Tracks 13-14

DR LOVE: Can you provide an overview of the available clinical trial data on the use of trastuzumab in the adjuvant setting?

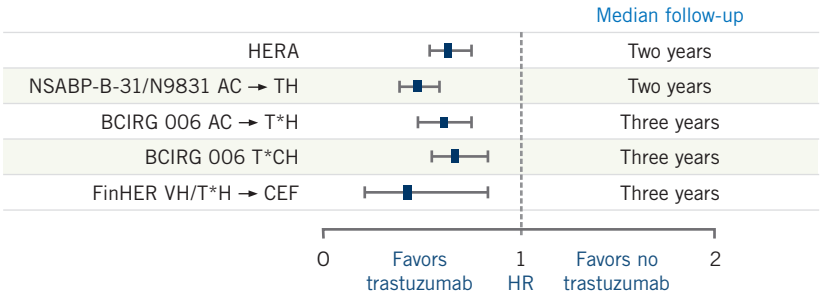
DR DICKLER: Trastuzumab in the adjuvant setting has been the greatest advance we've had in the treatment of breast cancer (2.1). The combined NSABP trial B-31 and Intergroup N9831 study evaluated an anthracycline- and taxane-based regimen (Romond 2005). The Intergroup study evaluated AC followed by weekly paclitaxel.

The NSABP study was conducted a bit differently. They administered every three-week paclitaxel. They merged these studies and combined the results. The arm that contained trastuzumab clearly showed a tremendous reduction in the risk of recurrence and an improvement in overall survival.

The Europeans designed a different type of study that is a great addition to our treatment regimen (Piccart-Gebhart 2005; Smith 2007). Patients were randomly assigned to trastuzumab versus no trastuzumab after completion of their surgery, radiation therapy and chemotherapy. So it was a sequencing of the targeted agent after chemotherapy. They also showed a powerful reduction in the risk of recurrence and an improvement in survival.

DR LOVE: One regimen in particular in the BCIRG 006 trial — TCH (docetaxel, carboplatin and trastuzumab) — seems to have a lot less cardiac

2.1 **Trastuzumab Hazard Ratios for Disease-Free Survival**



H = trastuzumab; T = paclitaxel
T* = docetaxel; V = vinorelbine

SOURCES: Smith I et al. *Lancet* 2007;369(9555):29-36. **Abstract**; Slamon D et al. *Proc SABCS* 2006;**Abstract 52**; Joensuu H et al. *N Engl J Med* 2006;354(8):809-20. **Abstract**; Romond EH et al. *N Engl J Med* 2005;353(16):1673-84. **Abstract**

toxicity and may be as effective as the anthracycline-containing regimens. What are your thoughts on that?

DR DICKLER: Although no statistically significant difference appeared between the two trastuzumab-containing arms, it was suggested that the AC → TH arm may have performed a little better than the TCH arm in the first interim analysis (Slamon 2005). The TCH arm now seems to have caught up and seems to be as good as the AC → TH arm on the second analysis (Slamon 2006). ■

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Dowsett M et al. **Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: An hypothesis-generating study.** *J Clin Oncol* 2005;23(30):7512-17. **Abstract**

Goss PE et al. **Aromatase inhibitor trials — NCIC CTG MA.17: Disease free survival according to estrogen receptor and progesterone receptor status of the primary tumor.** San Antonio Breast Cancer Symposium 2005;**Poster 2042**.

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**

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**

Jakesz R et al. **Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a).** *Proc ASCO* 2005;**Abstract 527**.

Mamounas E et al. **Benefit from exemestane (EXE) as extended adjuvant therapy after 5 years of tamoxifen (TAM): Intent-to-treat analysis of NSABP B-33.** San Antonio Breast Cancer Symposium 2006;**Abstract 49**.

Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. **Trastuzumab after adjuvant chemotherapy in HER2-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. **BCIRG 006: 2nd interim analysis 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 Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

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.** San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

Smith I et al; HERA study team. **2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial.** *Lancet* 2007;369(9555):29-36. **Abstract**

INTERVIEW

William C Wood, MD

Dr Wood is Joseph Brown Whitehead Professor and Chairman in the Department of Surgery at the Emory University School of Medicine in Atlanta, Georgia.

Tracks 1-15

Select Excerpts from the Interview

Track 3

DR LOVE: Are there any new developments in skin-sparing mastectomy?

DR WOOD: We just reported a large series at the Southern Surgical meeting, and skin-sparing mastectomy appears to produce superb results cosmetically, and it does not have a higher failure rate.

We learned two things from that study. We only had about 13 patients with a close superficial margin, but we had five failures in that group. These are usually young women who have generous breasts and almost no subcutaneous tissue. Today, I radiate tumors if there is a margin that is positive superficially.

DR LOVE: Can you discuss your technique and any caveats about the procedure?

DR WOOD: My technique is a circumareolar incision and then a full mastectomy with or without an axillary dissection through that incision. If the breast is stiff, you sometimes need to tee that out with approximately a two-centimeter "racket handle" to deliver the specimen. However, you can usually deliver the specimen through a circumareolar incision that's dilatable enough after you make the incision. A little white superficial fascia is present as a guide. If you follow that fascia, you'll have subcutaneous tissue above and the breast is nicely contained within.

Tracks 4-5

DR LOVE: How do you incorporate the Onco*type* DX assay into your practice?

DR WOOD: If a woman has an ER-positive, node-negative tumor that is higher than Grade I and larger than a centimeter, she should seriously consider chemotherapy. That is a patient population who should receive an Onco*type* DX assay because three quarters of them will not be in the group with the high recurrence score that benefited from chemotherapy in the NSABP-B-20 series.

I'm happy not treating those patients with a clearly low recurrence score with chemotherapy, which is approximately half of these patients. For the patients with intermediate recurrence scores, we are excited to be participating in the TAILORx study (3.1) so that we might find out exactly where that borderline lies between the high-risk group, all of whom should be treated, and the low-risk group, who don't need treatment.

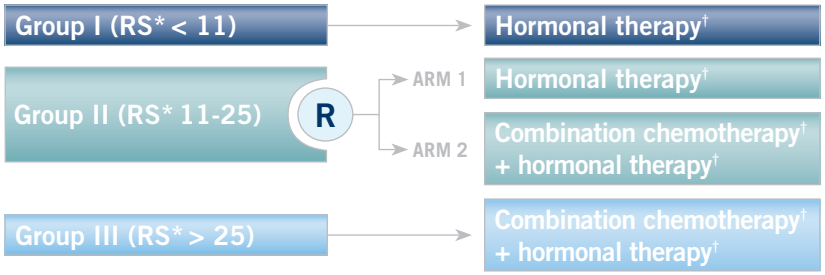
Track 8

DR LOVE: As we move toward more targeted therapy, it will be increasingly important to accurately measure the targets, and a lot of concern has arisen about measuring HER2 and ER. Where are we right now in terms of testing, and how can a surgeon in practice feel comfortable that the patient will have an accurate assay?

DR WOOD: If you are fortunate enough to practice in a quaternary center that runs controls all week, you can be confident. Otherwise, you'll find a 20 percent central lab correction rate on assays. Due to central controls, the Onco*type* DX assay appears promising in being able to give us these data precisely. They may soon begin reporting ER and PR values, and probably HER2. That would be helpful if that reinforced the local value or called it into question. ■

3.1

TAILORx: A Phase III Randomized Trial of Adjuvant Combination Chemotherapy and Hormonal Therapy versus Adjuvant Hormonal Therapy Alone in Women with Previously Resected Axillary Node-Negative Breast Cancer with an Intermediate Score of the Oncotype DX Assay



* Oncotype DX recurrence score
† Physician's choice for hormonal therapy and chemotherapy

Select Eligibility Criteria

- ER-positive and/or PR-positive breast cancer
- Negative axillary nodes
- Tissue from primary tumor available for Oncotype DX assay
- Age 18-75
- HER2-negative
- Tumor size 1.1-5.0 cm (tumors 5 mm to 1.0 cm allowed if intermediate or poor nuclear and/or histologic grade or lympho-vascular invasion)

Target Accrual: 10,046

Date Activated: April 7, 2006

SOURCE: www.clinicaltrials.gov/ct/show/NCT00310180.

SELECT PUBLICATIONS

Carlson RW et al. **A pilot phase II trial of valspodar modulation of multidrug resistance to paclitaxel in the treatment of metastatic carcinoma of the breast (E1195): A trial of the Eastern Cooperative Oncology Group.** *Cancer Invest* 2006;24(7):677-81. **Abstract**

Muss et al. **Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer.** *JAMA* 2005;293(9);1073-81. **Abstract**

Robert N et al. **Phase III comparison of tamoxifen versus tamoxifen with ovarian ablation in premenopausal women with axillary node-negative receptor-positive breast cancer ≤ 3 cm.** *Proc ASCO* 2003;**Abstract 16**.

Shak S et al. **Subtypes of breast cancer defined by standardized quantitative RT-PCR analysis of 10,618 tumors.** San Antonio Breast Cancer Symposium 2006;**Abstract 6118**.

Sparano JA. **TAILORx: Trial assigning individualized options for treatment (Rx).** *Clin Breast Cancer* 2006;7(4):347-50. No abstract available

Strasser-Weippl K, Goss PE. **Advances in adjuvant hormonal therapy for postmenopausal women.** *J Clin Oncol* 2005;23(8):1751-9. No abstract available

Wood WC. **The role of clinical trials in changing therapy for ductal carcinoma in situ.** *Ann Surg Oncol* 2004;11(1 Suppl):24-7. **Abstract**

Wood WC et al. **Can we select which patients with small breast cancers should receive adjuvant chemotherapy?** *Ann Surg* 2002;235(6):859-62. **Abstract**

INTERVIEW

John Mackey, MD

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

Tracks 1-14

Select Excerpts from the Interview

Track 2

DR LOVE: Can you review where we are currently with adjuvant endocrine therapy?

DR MACKEY: Tamoxifen used to be our only option for hormonal therapy for postmenopausal women. Although tamoxifen is a good drug — in that it shows a significant survival advantage, prevents recurrences and prevents contralateral breast cancer — it still has some Achilles' heels. One of the major problems is that prolonged tamoxifen use can trigger endometrial cancer and blood clots.

The nice aspect of the aromatase inhibitor story is that anastrozole, letrozole and exemestane have been shown in several trials in postmenopausal women to improve the chances of remaining free of breast cancer when used instead of tamoxifen, when used to replace part of the five-year course of tamoxifen and even when used after five years of tamoxifen. For almost any patient you see in your practice who has had breast cancer within the past five years, if she's postmenopausal and has ER-positive or PR-positive disease, there may be a role for an aromatase inhibitor.

The data are maturing over time, and 10 adjuvant aromatase inhibitor trials have reported in one fashion or another. Probably the most exciting element is that several groups have taken the results from these trials, put them all into a hat, shaken them up in a meta-analysis and demonstrated that not only is disease-free survival improved by the aromatase inhibitors, but convincing evidence is also emerging that overall survival is improved (Mauri 2006).

Tracks 4-5

DR LOVE: Where are we in terms of determining the optimal duration to administer aromatase inhibitor therapy?

DR MACKEY: The jury is still out on that issue. The ATAC (Howell 2004) and BIG 1-98 (BIG 1-98 2005; Coates 2007) trials show that if you start postmenopausal women on either anastrozole or letrozole immediately after recovery from surgery, they do quite well and better than with tamoxifen.

However, we also have trials that suggest if patients are halfway through their five-year course of tamoxifen, switching them to any one of the three aromatase inhibitors will provide a disease-free advantage. Even after five years of tamoxifen, switching to an aromatase inhibitor will improve the disease-free survival. The remaining question is whether 15 years is better than 10 years of hormonal therapy.

DR LOVE: What about the issue of delayed endocrine therapy?

DR MACKEY: That is still somewhat of an open question. It appears that the aromatase inhibitors can reduce the chance of breast cancer recurrence, whether used immediately after diagnosis, after two or three years or after five years. There are also data suggesting that even beyond five years after diagnosis you can start a patient on an aromatase inhibitor and see a benefit.

Track 7

DR LOVE: Can you discuss gynecologic issues with aromatase inhibitors compared to tamoxifen (4.1)?

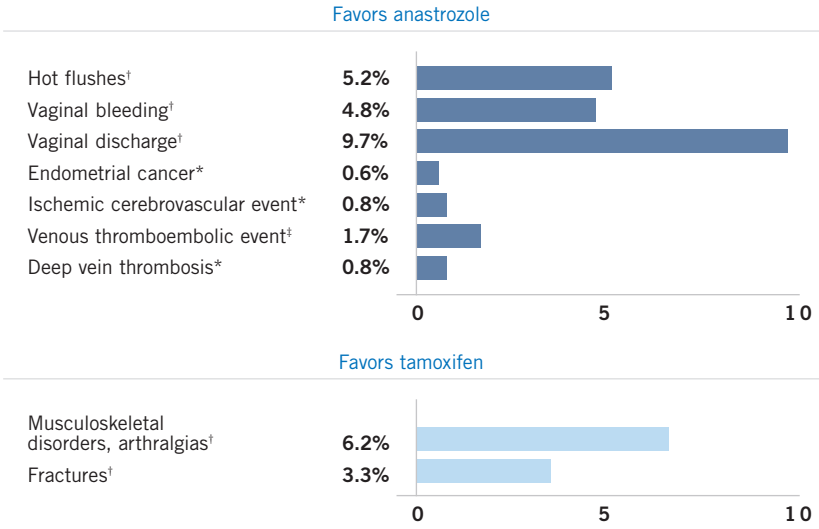
DR MACKEY: Tamoxifen can trigger endometrial cancer. Particularly in the postmenopausal population, the longer a patient is receiving it, the more likely she is to experience endometrial abnormalities. Tamoxifen can also

trigger vaginal discharges and thickening of the endometrium — changes that lead the gynecologist to become concerned and perform D&Cs to rule out endometrial carcinoma.

In fact, the ATAC trial showed that, with long enough follow-up, about five percent of women on tamoxifen ended up having a hysterectomy (Howell 2004). Women who received anastrozole for five years had a rate of endometrial cancer of 0.2 percent. They had fewer problems with vaginal discharge, and the hysterectomy rate was about a quarter of what was seen on the tamoxifen arm.

4.1

Significant Differences Between Anastrozole and Tamoxifen in Predefined Adverse Events (Percent)



* $p < 0.05$; † $p < 0.0001$; ‡ $p = 0.0004$

DERIVED FROM: Howell A et al. *Lancet* 2005;365(9453):60-2. **Abstract**

Tracks 10, 14

DR LOVE: Where are we right now in terms of quality control for estrogen receptor and HER2 testing?

DR MACKEY: Modern management of early-stage breast cancer hinges on two predictive assays, the estrogen receptor status and the HER2 oncoprotein or HER2 oncogene status. There have been a number of rude awakenings in the last decade, such as the realization that the testing we conducted in the past was largely inadequate and relatively difficult to standardize.

DR LOVE: Do you believe that the Onco*type* DX assay will replace the technology we're using right now to measure ER and HER2?

DR MACKEY: It's possible, although technically it is more difficult to do the Onco*type* DX because you're actually taking several sections of the tumor from the block, grinding them up and extracting the RNA, then doing a quantitative RT-PCR assay.

The nice aspect of conducting the assay in that complex fashion is that you have internal controls. You also know whether you have a bad sample or a good sample, and it removes some of the variability associated with tissue fixation differences and some of the biological problems that immunohistochemistry faces. Although these are more expensive and more complex, I believe nucleic acid-based technologies like Onco*type* DX or FISH testing in a multiplex assessment of a patient's tumor will outperform our "old war horses" — immunohistochemical assays.

Track 13

DR LOVE: In what subset of patients with node-negative, ER-positive tumors is Onco*type* DX most useful?

DR MACKEY: When you're considering women with node-negative, ER-positive tumors, the first thing to evaluate is tumor size. If they have big tumors — two or three centimeters — and they have Stage II disease, they warrant a discussion of chemotherapy. In that case, I wouldn't send these tumors for Onco*type* DX testing.

The question in my mind involves women who have T1 lesions (which are two centimeters or smaller), particularly the ones that aren't high grade. This is the subset of ER-positive breast cancer cases in which the Onco*type* DX would return information that could inform your chemotherapy decision. ■

SELECT PUBLICATIONS

Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295(14):1658-67. **Abstract**

Breast International Group (BIG) 1-98 Collaborative Group. **A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.** *N Engl J Med* 2005;353(26):2747-57. **Abstract**

Coates AS et al. **Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1-98.** *J Clin Oncol* 2007;25(5):486-92. **Abstract**

Howell T, on behalf of the ATAC Trialists Group. **'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial: Completed treatment analysis.** Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

Kennecke H et al. **Late risk of relapse and mortality among postmenopausal women with estrogen responsive early breast cancer after 5 years of tamoxifen.** *Ann Oncol* 2007;18(1):45-51. **Abstract**

Mauri D et al. **Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: Meta-analysis.** *J Natl Cancer Inst* 2006;98(18):1285-91. **Abstract**

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**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Onco*type* DX assay was validated in patients with ER-negative, node-positive disease.**
   a. True
   b. False

2. **The TAILORx study randomly assigns patients with _____ recurrence scores to hormonal therapy with or without chemotherapy.**
   a. Low
   b. Intermediate
   c. High

3. **The four major adjuvant trials for patients with HER2-positive disease (NSABP-B-31, NCCTG-N9831, HERA and BCIRG 006) demonstrated approximately a _____ reduction in recurrence with trastuzumab.**
   a. 10 percent
   b. 25 percent
   c. 35 percent
   d. 50 percent

4. **In the second interim analysis of the BCIRG 006 adjuvant trastuzumab trial, no significant difference in disease-free survival was observed between docetaxel/carboplatin/trastuzumab (TCH) and AC followed by paclitaxel/trastuzumab (AC → TH), but TCH resulted in significantly more cardiotoxicity.**
   a. True
   b. False

5. **In the ATAC trial, patients receiving anastrozole underwent _____ of the hysterectomies as patients receiving tamoxifen.**
   a. An equivalent number
   b. 10 percent
   c. 25 percent
   d. 50 percent

6. **In the ATAC trial, the fracture rate was roughly equivalent after patients completed five years of tamoxifen or anastrozole.**
   a. True
   b. False

7. **Phase III randomized studies have demonstrated improvement in disease-free survival with _____ in patients with receptor-positive disease who had previously completed five years of adjuvant tamoxifen therapy.**
   a. Anastrozole
   b. Exemestane
   c. Letrozole
   d. All of the above

8. **NSABP-B-33 compared _____ to placebo in postmenopausal women with hormone receptor-positive disease who had received five years of adjuvant tamoxifen.**
   a. Anastrozole
   b. Letrozole
   c. Exemestane
   d. Aminoglutethimide

9. **The use of assay controls is a factor in determining the accuracy of the HER2 measurement.**
   a. True
   b. False

10. **There is a _____ probability of obtaining a response in patients with ER-positive tumors undergoing neoadjuvant hormonal therapy with an aromatase inhibitor.**
    a. 10 to 15 percent
    b. 25 to 35 percent
    c. 40 to 50 percent
    d. ≥75 percent

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

EVALUATION FORM

Breast Cancer Update for Surgeons — Issue 1, 2007

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *BCU* for Surgeons address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer 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
- Develop an algorithm for ER and HER2 testing and implement a treatment plan for patients with HER2-positive breast cancer . . . . . 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
J Michael Dixon, MD	5 4 3 2 1	5 4 3 2 1
Maura N Dickler, MD	5 4 3 2 1	5 4 3 2 1
William C Wood, MD	5 4 3 2 1	5 4 3 2 1
John Mackey, 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

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