ER/PR RETESTING CHRONOLOGY

MAY 18, 2007

Eastern Health

April 2004: Eastern Health (then the Health Care Corporation of St. John's) installed a new Ventana system for use in our immunohistochemistry laboratory. This more extensively automated system replaced the Dako System, a complicated, manual and multi-phase procedure with more than 40 steps. The Dako system was an advance from biochemical assay, used prior to 1997.

May 2005: One of our oncologists was treating an individual whose ER/PR was originally tested in 2002 (using the Dako system) and shown to be negative. Given the nature of this woman's cancer, her age and other factors, the oncologist requested that the test be repeated. The second test was conducted on the new Ventana system, and converted to a positive result.

Representatives from the Laboratory Program met with oncologists to discuss this new result and a decision was made to retest five more negative patients, who all converted to positive.

June 2005: It was decided to retest all negative results from 2002 to determine if these were isolated cases or symptomatic of a bigger issue. The chief of pathology wrote to all Laboratory directors in the province to return all negative ER/PR specimens for the year 2002 for retesting on the new, more sensitive Ventana system.

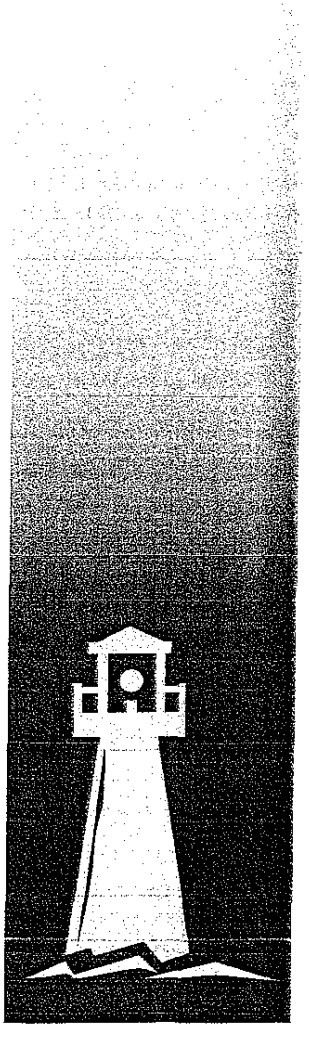
Early July 2005: A meeting was scheduled and the decision was made that all patients who were ER/PR negative from 1997-2004 would be retested internally on the Ventana System with testing to take place over the next number of weeks.

Late July 2005: The decision was made to stop reporting ER/PR in our laboratory and to arrange for an independent and external laboratory to complete our retesting as well as ongoing work.

August 2005: Mt. Sinai Hospital, considered to be a "gold standard" laboratory internationally, agreed to take on the project. Our laboratory began the process of collecting, packaging and shipping all negative* test results from 1997-2005 to Toronto.

** The definition of "negative" has changed within the seven year period in question. Originally, oncologists believed that tumors with less than 30% positivity for ER/PR should be considered negative. With advancing understanding of cancer and treatment, the negative rate has dropped, first to 10% and now to 1%. Today, oncologists believe that any positivity may be worth treating with hormonal therapy.*

Early October 2005: The first set of results arrived from Mt. Sinai.



Mid October 2005: The organization established a Tumor Board comprised of two (2) oncologists, two (2) surgeons, two (2) pathologists, one (1) representative from the Quality Department and one (1) support person. The Tumor Board was tasked with reviewing the results as they arrived, reviewing charts, and making treatment recommendations for each patient. The Tumor Board met once a week from October 2005 to May 2006 reviewing individual cases and making recommendations.

Mid October 2005: The organization conducted the first of numerous media interviews, and provided whatever background information was available at that time. Advertising was also purchased informing the general public of the retesting.

October 2005: Patient Relations representatives from Eastern Health telephoned all individuals whose specimens were being sent away for retesting. The laboratory conducted the first of a number of external review processes. During this period, the laboratory also attempted to gain insight from other laboratories across Canada regarding their experiences with ER/PR testing.

November/ December 2005: The organization expressed concerns to Mt. Sinai about the slow pace of reports. However, they were experiencing unexpected manpower issues and were unable to move the tests through the system any faster.

Late January 2006: The last batch of samples arrived at Eastern Health from the other provincial health authorities. They were forwarded to Mt. Sinai for review.

February 2006: The last test results were received from Mt. Sinai.

February - May 2006: Concentrated effort of the Tumor Board to review test results, write recommendations and conduct disclosures. A six month period *(May to October)* follows to ensure that the organization has completed all the disclosures possible and that every patient has had every opportunity to contact their physicians.

June – November 2006: The new Chief Pathologist and the new Vice-President, Medical Services worked on the results of the quality review process; established a centre of excellence for breast cancer pathology; assigned a head pathologist for immunohistochemistry; and generally prepared for the continuation of ER/PR testing in our laboratory.

September 2006: A statistical review was initiated to examine the numbers and arrive at conclusions. This information will form the basis of the quality review. Analysis is continuing.

Late November 2006: The organization completes its quality review.

December 2006: Public release of results and media briefing.

February 1, 2006: Testing begins again in our laboratory.

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STATEMENT OF STATISTICS

Eastern Health

(AS FILED IN COURT AFFIDAVITS DATED FEBRUARY AND MARCH 2006)

Eastern Health reviewed 2709 ER/PR tests conducted between 1997 and August 2005. Of those cases reviewed, 939 of the tests were originally reported as ER-negative. The negative test samples were sent to Mount Sinai Hospital to be retested. Results were obtained and reviewed for 763 patients.

Of the 763 patients whose samples were retested and results obtained, 433 patients saw no change in their ER/PR results and therefore no change in treatment was recommended. Specifically,

- 341 patients were confirmed negative by Mount Sinai;
- 28 patients were confirmed negative by the Tumor Board;
- 12 patients were confirmed positive; and
- 52 patients were determined to have ductal carcinoma in situ, and therefore no form of treatment would have been recommended.

A further 13 patients saw no change in their ER/PR test results but a change in treatment was recommended as the standard for interpretation of what constituted an ER-positive test result had changed between the time of original testing and the Tumor Board's review.

The ER/PR test results were different for 317 patients following retesting.

Of the 317 patients, 104 patients required a change in treatment.

- 96 of these patients were recommended for treatment with Tamoxifen or another aromatase inhibitor;
- 4 of these patients saw a change in their original diagnosis; and
- 4 of these patients originally had a degree of ER positivity but were negative on retesting.

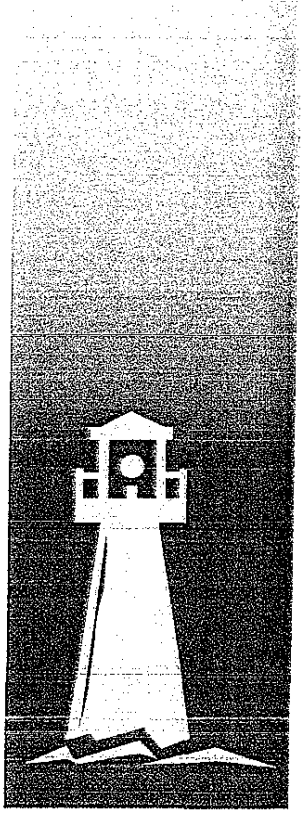
The remaining 213 patients whose ER/PR tests results were different on retesting did not require a change in the treatment that had been originally recommended for them because:

- 60 of these patients had a very low risk of recurrence;
- 148 of these patients had previously been treated with Tamoxifen or another aromatase inhibitor either at their request or their oncologist's recommendation following a review of the test results and their particular medical and family histories; (13 of these patients were not placed on Tamoxifen for their original disease but for subsequent metatstatic disease);
- 5 of these patients received no treatment as they required assessment prior to any recommendation being made.

176 of the patients whose ER/PR tests were originally reported as negative are deceased. Of these 176 patients:

- 105 patient's samples were retested and results have been received;
- Of those 105, 68 saw no change in their results, 1 originally clinically positive result retested as clinically negative, and 36 patient's test results changed from clinically negative to clinically positive.

2214 of the ER/PR breast tissue tests were conducted in the Dako system from 1997 to April 2004. 495 tests were conducted in the Ventana system from April 1, 2004 to August 1, 2005.



IMMUNOHISTOCHEMISTRY

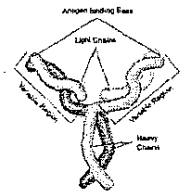
DR FORD ELMS

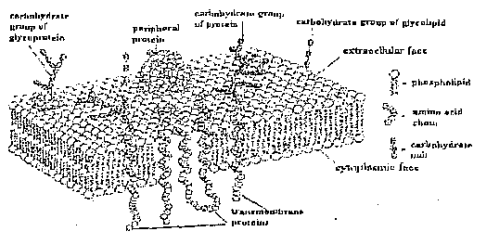
Immunohistochemistry

- Microscopy requires cellular constituents be made visible
- Traditionally done with histochemical dyes
- In IHC, antibodies are used to visualize cellular proteins

- "an antibody is a molecule that has the property of combining specifically to another molecule, termed an antigen."

- The recognition of an antigen by an antibody is based on the three dimensional structure of the protein.





- Antibodies react with specific portions of the Ag, each of these is an "epitope"

Basic concepts

- Antibody is produced specific for the cellular antigen of interest
- The Ab is exposed to the tissue and binds to the Ag
- A detection method is used to identify the presence of the Ab.

Polyclonal Antibodies

- in fact an antiserum, generated in animals.
  - Rabbit, goat, pig, sheep
  - Rabbit is most common: easy maintenance, pooling of antibodies results in less batch-to-batch variations

Monoclonal

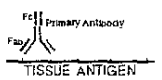
- Immune response raised in mice
- B-lymphocytes harvested from spleen or lymph nodes
- Fused with non-secreting mouse myeloma cells
- Propagated either in tissue culture or by transplantation into peritoneal cavity of syngeneic mice.

Monoclonal Ab: advantages

- High homogeneity
- Absence of non-specific antibodies
- Ease of characterization
- No batch-to-batch or lot-to-lot variability

Monoclonal Ab: disadvantages

- Test methods for the selection of clones must be identical to method of use (frozen vs paraffin fixed tissue)
- Suboptimal fixation
- Target Ag must be unique. Ab specificity is lost if two different antigens share a similar epitope.



Detection

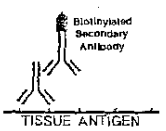
- Once the Ab has bound to the Ag of interest, it must be rendered visible.
- Several methods: Streptavidin-biotin

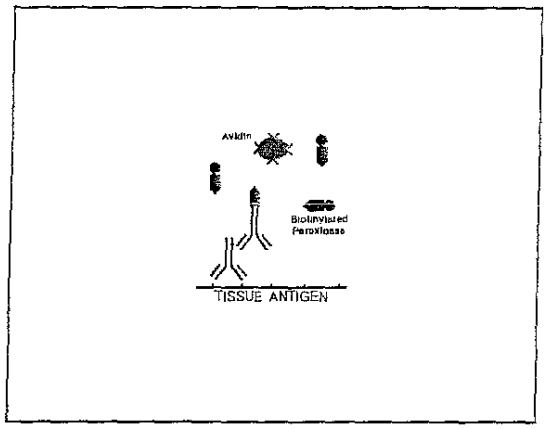
- Biotin is a water soluble B-complex vitamin
- Avidin: protein from egg white
  - Strong affinity for biotin.
  - Streptavidin is an analogue of avidin, found in Streptomyces avidinii

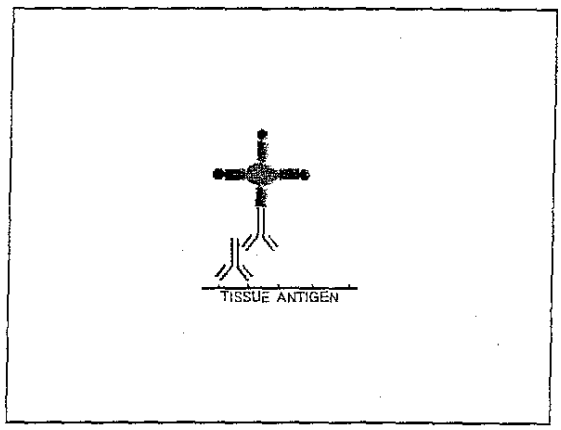
Streptavidin

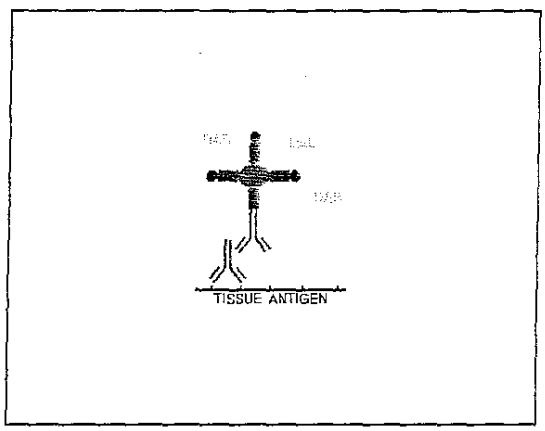
- Advantages:
  - No carbohydrates
  - Isoelectric point closer to neutrality
  - highly stable

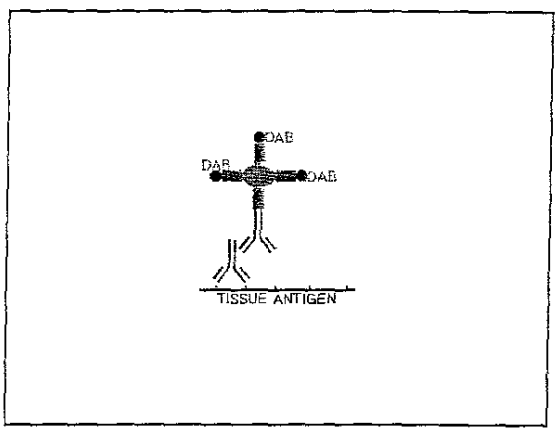
- Chromogen is added to make the Ag-Ab complex visible
- Diaminobenzidine











HIER

- Heat induced epitope retrieval
- Required as a result of fixation

Fixation

- Fixatives work either by coagulating proteins (ethanol based) or cross linking proteins (formalin)
- Either method can cause alterations in the configuration of proteins
- Tissue actually exposed to both.
- Time of exposure
- No single "perfect" fixative.

HIER

- Heat and Ph
- Before application of the primary, tissue is incubated at specific temperature with HIER solution.

(So-called) STANDARD IHC METHOD

- 1. Cut paraffin sections and mount on adhesive slides.
- 2. Deparaffinize slides in xylene and graded alcohols to water.
- 3. Quench endogenous peroxidase activity. Rinse in buffer.
- 4. Incubate with "blocking serum". Rinse in buffer.

(So-called) STANDARD IHC METHOD

- 5. Perform epitope retrieval step if needed. Rinse in buffer.
- 6. Apply primary antibody, incubate, and rinse in buffer.
- 7. Apply secondary (link) antibody, incubate, and rinse in buffer.
- 8. Apply detection complex, incubate, and rinse in buffer.
- 9. Develop reaction product with chromogen, counterstain, dehydrate, coverslip, and view.

In Summary

we use IHC to identify Ags that reveal the line of differentiation of tumours, to classify lymphoma, to identify invasion, and to identify diagnostic and prognostic proteins in tissue

PITFALLS IN ER TESTING

Dr Bev Carter

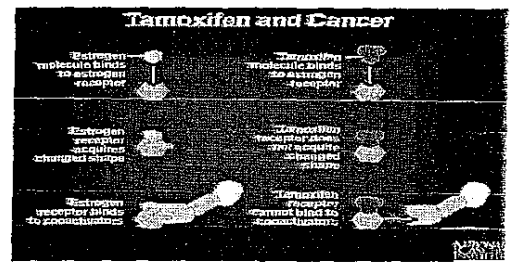
Estrogen Receptor

- Nuclear Receptor
- Transcriptional factor to regulate growth
- Seen in normal epithelium to ***varying*** degrees
- Ducts more than lobules
- Older more than younger

Estrogen Receptor

- Prognostic factor
- Powerful predictive factor
- SABC/St Galen's- the biomarker expression of the tumour cell is the most important determinant of patient outcome/survival- this is the era of the pathologist in oncology patient care
- NIH- one determinant of patient prognosis is a good pathology lab

ESTROGEN RECEPTOR



Estrogen Receptor

- 75- 80%, patient dependant (with new cutoff values)
- 1999 Harvey et al- 1% shows a response
- Increases with age
- Lobular, mucinous, low-grade
- Her2/PR status not helpful in predicting ER
- Most cases are absolutely negative or very obviously positive

Estrogen Receptor Testing

- Began in 1970's
- First 20 years ligand binding assays of whole tissue extracts
- Lots of tissue needed, morphology gone,$
- Early 1990's- IHC

Estrogen Receptor Testing

- Paradigm shift for IHC labs/assessment
- Semi quantitative as compared to usual presence/absence
- Small differences in expression could be vitally important
- Required a whole new approach to testing and analysis (for presence/absence types of staining we were doing a very good job)
- Many labs unprepared

Estrogen Receptor

- Always has been concern over false negatives
- Largely due to poor interlaboratory standardization and lack of validated (technical) testing methods
- Rhodes****- estimated error rate of 20% overall
- Overall HIER most problematic- NEQAS-AM J Clin Pathol-2001

Estrogen Receptor-HIER

- Most important factor for accurate and consistent results
- Lab must determine the optimal time and method (microwave/ pressure cooker etc)
- If precisely determined- choice of antibody, concentration, choice of heater, ph became less important.

Estrogen Receptor- Interlaboratory variability

- Also due to pre-analytic variables, choice of antibody, use of controls, interpretative skills
- These become of little significance when standardized methods and validated testing is used (The Mt Sinai experience)
- Allred-Mod Pathol 2003- NSABP-24-DCIS trial- cases analyzed by participants using non-standardized methods are more frequently falsely ER negative

Estrogen Receptor- Pre-analytic

- Rhodes J Clin Pathol 2000- If participating NEQAS labs stained other participants tumours- 37% could detect a low positive. 66% could not
- If those labs then stained NEQAS prepared tumours- 37% could detect a low positive. 66% could not
- i.e. pre-analytic variables have little to do with it

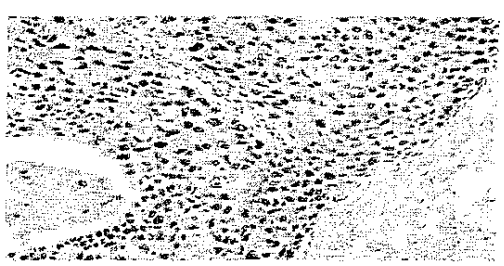
Estrogen Receptor- Ab choice

- ID-5 and 6-F-11 most sensitive
- 6-F-11 has been clinically validated
- ID-5 validated against 6F-11
- SP-1- a new rabbit monoclonal, when compared to ID-5 shows a better correlation with ligand-binding and with response to Tamoxifen- Cheang JCO 2006- may pick up another 5-10%
- i. e. Will I see you here in 2016??

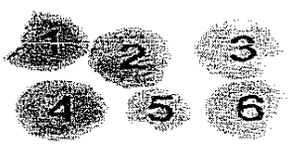
Antigen Retrieval- Controls

- Must be cut within 1 week maximum of test performance
- Must include a variety of expression
- A polyclonal (very rare- most tumours are relatively homogenous) high grade tumour from a young women in the follicular phase of her cycle OR
- A sausage

ER Mild Variability in Tumour



Multiple expression



Estrogen Receptor- Reporting

- Final Diagnosis: Breast, biopsy- Estrogen receptor negative
- Pathologists may use positive or negative based on either 1%, 10% or 30%
- Since 1999 patients with 1% have demonstrated some response to hormone manipulation
- CAP (2000)/ASCO (2000)/StGalens (2001) endorse-0 negative,1-9% low, 10-100 positive

Were we unaware?

Estrogen Receptor - Reporting

- Interobserver variability is large around "low-expressers (1-10%)"
- Low expressers very uncommon
- For negatives and high expressers interpretation does not seem to be a problem

ER Reporting- background

Due to: Antigen diffusion into tissues- delayed fixation

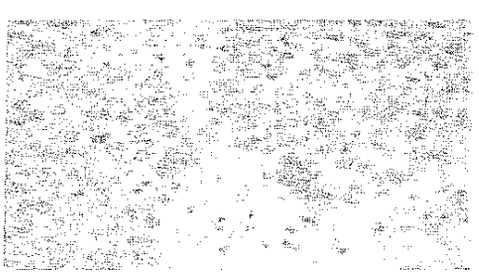
Antibody diffusion into tissue- poor fixation, high concentration, tissue drying

Hydrophobicity of tissue proteins as a result of formaldehyde over- fixation- squamous epithelium, collagen, fat

Exogenous peroxidase- poor quench step

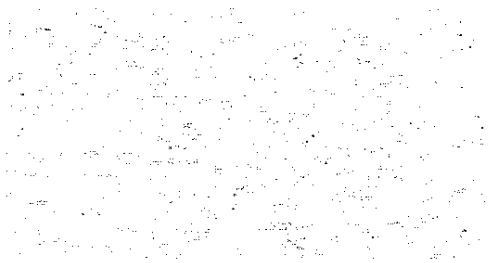
Results in false positives

Excess endogenous biotin/ excess AB/ Antigen diffusion

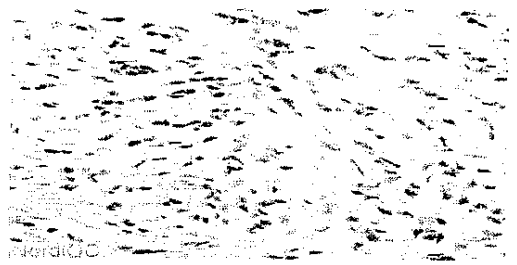


Estrogen Receptor

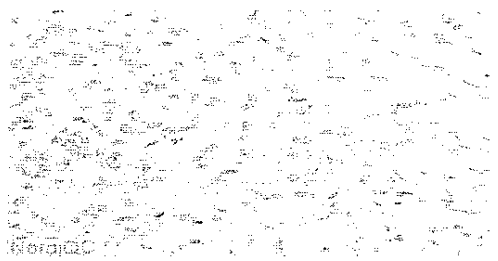
HIER in Alkaline Buffer



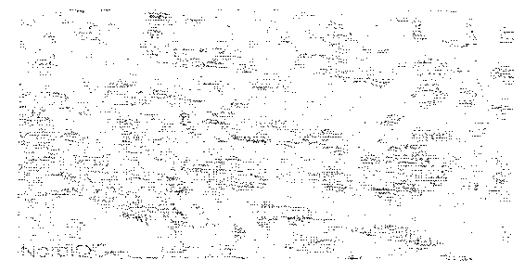
ILC



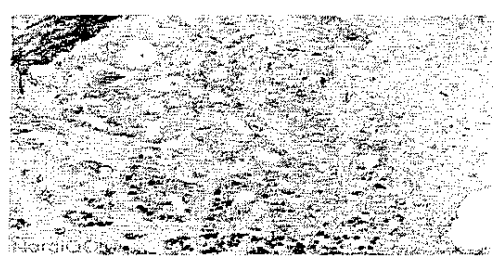
ILC-HIER Citrate ph6



ILC- HIER/ Alk Buffer/ low conc/ excess biotin



PR- Insuff Conc of Antibody/ Endogenous Biotin



How to get a perfect result

- Bread loaf specimens at 5mm
- Place in 10% buffered formalin within 30 mins, out in 24-48 hrs (Goldstein-2003 Am J Clin Pathol). Needle cores out in 8 hours
- 2-4mm slices for blocks
- While alcoholic fixatives may be used (please don't) mercury and decal are no-no's
- ? Keep blocks cool as antigenicity lost over time

How to get a perfect result

- Standardized protocol
- Validated (for your center- ' never believe the manufacturer') protocol
- Validated antibody (?6F11)
- Stringent internal QC program
- External Proficiency Testing (less valuable unless in a court of law)
- Perform 250 cases/year

HOW TO GET A PERFECT RESULT

- Positive and negative controls used/ examined
- Select block with internal control
- Pick a representative block- not the highest grade leading edge

How to get a perfect result

- Know about surrogate markers
- Document positivity rates
- Limit the number of readers
- Best to say % of cells with nuclear positivity
- Double reading/ systematic analysis of slide (H-score) of low-expressers
- Correlate to clinical response to therapy

FINAL DIAGNOSIS

- Estrogen receptor is seen in 0% of nuclei in the infiltrating carcinoma
- ***Will I swear on my mothers grave- no .... FN are a fact of life in 'semi-quantitative IHC'***

ER/PR
HOW THE STORY BEGAN

Dr. Don Cook

- May 11, 2005 notified that a patient had converted
  - Patient with lobular carcinoma of breast (2002)
  - ER/PR performed on Dako semi-automated Platform
  - Retested Ventana automated Platform

how lobular vs ductal

- Request: To re-test 4 other patients with ILC diagnosed in 2002
  - All converted on Ventana System

- Meeting (May 17, 2005): Lab and Oncology
  - Agreement to re-test a number of breast cancer cases with emphases on 2002 in order to evaluate the scope of the problem
  - Memo (June 13, 2005) to all Lab Directors
    - Submit all NEGATIVE ER/PR case for re-testing,2002

- HSC Re-Testing (June 29, 2005) on 25 cases
  - 12 converted
- HSC Additional 32 cases re-tested (July 18, 2005)
  - 25 converted
- Mt. Sinai: 11 cases re-tested
  - 2 significant conversions
  - 3 minor variations

- Numerous meetings with senior Leadership Team of Eastern Health, Lab Medicine, Surgery, Oncology, Q.I., Corporate Communications and MAC
  - Decision (July 29, 2005): Stop reporting ER/PR in our Lab
    - Ventana Automated System (? High Positivity Rate, 89%) from April 2004-March 2005
    - High conversion rate Dako to Ventana

- Aug 5, 2005 Arrangement made to Mt. Sinai Lab for Re-testing
  - All ER Negative cases (independent to PR status) of primary breast carcinomas from May 1997 to August 8, 2005
  - All new cases

- ER NEGATIVE (May 1997- Dec 2000): less than 30%
- ER NEGATIVE (Jan 1, 2001 – current): less that 10%

GOAL

To Identify The Patients That Require Treatment Recommendations

At this point: Should we go public?

- August 18, 2005: first batch of cases sent to Mt. Sinai
- August 24, 2005: Memo to all Lab Directors
  - Request for submission all ER Negative cases
- October 5, 2005: first set of results arrived

- Mid October 2005: Tumor Board set up
  - 2 oncologists
  - 2 surgeons
  - 2 pathologists
  - 1 Q.I
  - 1 Secretary
- Mandate: to review the results and assess the impact on patients and make recommendations

Story Broke in Local Newspaper!

- Concerns about slow pace of results being reported from Mt. Sinai (Nov/Dec 2005)
  - Capacity problems
  - Slow pace of cases referred to us from peripheral hospitals

- Mt. Sinai promised (Dec 2005): All cases will be completed by end of January 2006
- Last batch of samples arrived to Eastern Health from peripheral hospital (January 25, 2006)
- Last results from Mt. Sinai received Feb 14, 2006
- Tumor Board activities winding down May 2006

Results

- Out Of 939 Patients Tested, The Tumor Board Panel Recommended Treatment Change For 109 Patients

Hormonal Therapy for Breast Cancer

Dr. Kara Laing
Clinical Chief, Cancer Care Program
Assistant Professor, Faculty of Medicine
Memorial University

Outline

- Epidemiology
- Adjuvant therapy
- Metastatic cancer
- Targeting hormone receptors
- Evolution of endocrine therapies
- Impact on clinical management

Breast Cancer

- 2006 breast cancer facts[1]
  - 22 300 estimated new cases
  - 5 300 estimated deaths
  - Lifetime risk 1:9

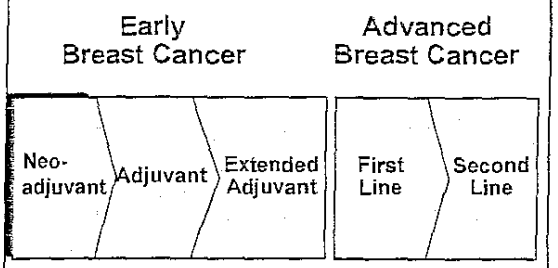
[1]2006 Canadian Cancer Statistics

Incidence and Mortality[1]

2006	New Cases	Mortality	Incidence (per 10^5)	Mortality (per 10^5)
BC	2700	630	94	20
AB	2000	430	107	23
SK	620	150	98	22
MB	810	200	108	24
ON	8400	2000	105	23
QC	6000	1400	115	25
NB	540	130	104	23
NS	700	190	106	26
PE	100	25	111	27
NL	350	100	99	27

[1]2006 Canadian Cancer Statistics

The Continuum of Breast Cancer



Breast Cancer: Risk of Recurrence

- Prognostic factors
  - Lymph node status
  - Tumor size, grade and histology
  - Lymphovascular invasion
  - Age and ethnicity
- Predictive factors
  - ER and PR status
  - HER 2 expression

Adjuvant Therapy

- Additional treatment given after potentially curative surgery
- Eradicate micrometastatic disease
- Goal is to
  - Decrease recurrence rates
  - Improve overall survival

Adjuvant Therapy

- Radiation therapy
- Chemotherapy
- Targeted therapy
- Hormonal therapy

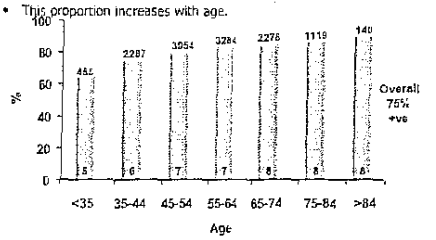
Adjuvant Hormonal Therapy

- Hormone receptor positive disease
- Pre and post menopausal patients
- Given after adjuvant chemotherapy
- Significant improvement in
  - Disease free survival
  - Overall survival

What were we?

Rationale for Hormonal Therapy

- Estrogen and/or progesterone receptor expression is found in 75% of breast cancers (73% are ER+/PR+ and 27% ER+/PR-).
- This proportion increases with age.

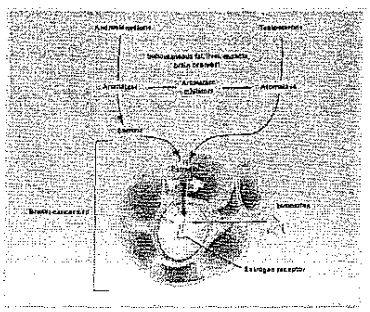


Daidone MG et al. Crit Rev Oncol Hematol 2003;45:313-325

Methods of Targeting ER

- Block estrogen production
- Block estrogen action
- Receptor down-regulation

Mechanism of Action

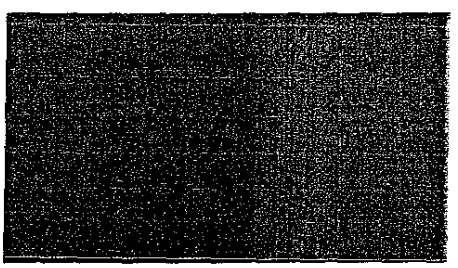


Simpin and Dowsett, N Eng J Med 2001; 345: 2431

Tamoxifen

- "Gold standard" for years
- Optimal duration 5 years
- Side effects
  - Vasomotor
  - Endometrial cancer, thromboembolic

Efficacy of 5 Years of Adjuvant Tamoxifen



EBCTCG, Lancet 1998, 351:1451

Aromatase Inhibitors

- Block conversion of androgens to estrogen
- Effective only if postmenopausal
  - Natural menopause
  - Induced: LHRH agonists, surgery or radiation
- Non-steroidal- inhibitors
  - Letrozole (Femara)
  - Anastrozole (Arimidex)
- Steroidal-inactivator
  - Exemestane (Aromasin)

3 Strategies

- Upfront
  - Instead of tamoxifen for 5 years
- Switch
  - After 2 to 3 years of tamoxifen
- Extended
  - After 5 years of tamoxifen

Metastatic Disease: Goals of Therapy

- Palliative symptoms
- Minimize toxicity
- Maintain/improve quality of life
- Improve length of life
- Long term disease control

Indications for Hormonal Therapy for Metastatic Breast Cancer

- Hormone receptor positive disease
  - ER and/or PR
- Non-life threatening disease
- Bone, soft tissue, lymph node disease
- Long disease free interval
- Previous response to hormonal therapy

Hormonal Therapy

- Aromatase inhibitors
- Tamoxifen
- Faslodex
- Megace

Confounding Factors

- Change in accepted threshold for ER positivity
  - > 30%
  - > 10%
- Change in patients treated
  - Premenopausal in 1998-1999
- Change in agents
  - Tamoxifen
  - Aromatase inhibitors

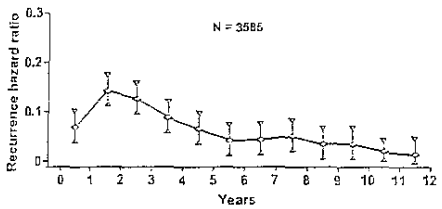
St. Gallen Expert Consensus

- Endocrine responsive
  - ER and PR strongly positive
  - Primary treatment is endocrine
- Endocrine non-responsive
  - ER and PR negative (<1% staining)
  - NO endocrine treatment
- Endocrine response uncertain
  - Between >1% and <10% for ER, PR negative
  - Endocrine and chemotherapy

Impact on Patients

- Did not receive appropriate therapy
- May have received unnecessary chemo
- Increased risk of relapse
- Increased risk of death
- Stress related to re-testing
- Uncertainty regarding care

Annual Recurrence Hazard Ratios for Breast Cancer After Primary Therapy



- Early peak of recurrence risk in first 3 years, followed by long-term continued risk, for all patients (adjuvant chemotherapy ± tamoxifen, or no adjuvant therapy)

Saphner T et al. *J Clin Oncol.* 1996;14:2738-2746.

Clinical Intervention

- All converted ER cases reviewed
- May have received hormonal therapy based on borderline ER or PR status
- Estimated current recurrence risk
- Made recommendation regarding late hormonal therapy
- Communicated to responsible physician

How We Have Responded? What We Have Done To Improve The Service ?

Dr. Nash Denic

- Stopped testing for ER and PR in our Lab
- Reviewed over 3000 cases tested in our lab
- Referred all ER-negative and borderline breast carcinoma cases from May 1997 to March 31, 2004 to Mount Sinai Hospital, Toronto for re-testing
  - Cases tested on Dako semi-automated Platform
- Also all ER-negative cases from April 1, 2004 to June 2005
  - Automated Ventana Platform
- Since then, up to date all cases were sent to Mt. Sinai Hospital for primary testing.

Dako
Ventana

- External review (Oct. 2005 and May 2006):
  - Technical review (Mt. Sinai)
    - All Recommendations implemented/ in progress
  - Professional review (BC Cancer Center)
    - Most of Recommendation Implemented/in progress
      - Subspecialty task groups formed
- All recommendations documented and regularly updated.

Tech
Program

- Designated IHC Lab as separate department
  - Including 3 designated IHC technologists, IHC Lab director and dedicated cutter
- Training:
  - Technologists (Toronto, Montreal, U.S.A)
  - Pathologist
    - IHC Lab Director (U.S.A)
- Consolidated all breast cases for examination and reporting to a designating group of pathologists at the St. Clare's Site

IHC Proficiency Testing

- Involved in external quality assurance program (UK: National External Quality Assurance Scheme for ICC or NEQAS-ICC); quarterly
  - To date highest marks in all 3 submissions (Dec. 2005, March 2006 and May 2006) for ER
- Involved in proficiency program for IHC by College of American Pathologists; bi-annual
  - Passed (May 2006)

- Consolidating and developing Policies and Procedures in IHC
- Quality Control Program in IHC performed on a daily bases and recorded to ensure consistency and reproducibility of results.
- External and Internal Controls verified on each case.

New Resources

- Establishment of Quality Management Program (QA and QC)
  - Pathologists
  - Senior pathology technologist
  - Secretary
- Pathology Assistants (4)
  - Standardization of grossing and tissue fixation
  - Currently in training
- IHC Ventana XT Benchmark autostainer purchased
- Dedicated double-head microscope for IHC

What WasThe Problem In ER/PR Testing ?

- The scientific understanding about ER and PR has evolved.
  - Reporting (scoring cutoffs range 1 to 30%)
- Different technology
  - Immunohistochemical Assay (before 1997) vs. Semi-automated Dako (1999-2004) vs. Automated Ventana platforms (current); All FDA approved
  - Antibodies (1D5 Dako, 6F11 Ventana and SP1)
  - Antigen retrieval techniques (Boiling vs. microwave), etc.
- No standardized IHC testing methodologies worldwide

- No National Laboratory Accreditation Process for Immunohistochemical Labs
  - 2006 Initiative of the CAP
- IHC complex process
  - Over 40 steps (from tissue procurement, fixation, processing to reporting and clinical validation); Something can go wrong on each step
  - Testing Laboratory has no control over pre-analytical phase (e.g. fixation) across the other provincial Labs that utilize the service of the Testing Laboratory

- "THE IMMUNOHISTOCHEMISTRY TESTS ARE PROBABILISTIC, NOT ACURATE" (Dr. Anthony Magliocco, Associate Professor of Oncology, Pathology and Laboratory Medicine, University of Calgary, at the U of T Pathology Update Course November 2005)

- No resources (financial constraints)
  - Affects: educational activities for technologists; absent QMP, Pathology assistants, etc.
- Proper documentation of procedures and technical and clinical quality monitoring of immunohistochemical stains
- Lack of continued external quality assessment programs

- Large turn-over of pathologist
  - Impossible to develop sub-specialized service.
- Large turn-over of oncologists
  - Difficult to monitor, correlate and clinically validate ER results

Conclusions

- In regard to reporting of ER and PR, we conducted self critical internal review of all ER negative breast carcinomas in period from 1997-2004.
- We invited external reviewers and after implementation of their recommendations both recommended to re-instate ER/PR testing.

- We discovered the critical issues and points and the vast majority of them got corrected.
- We are ready to proceed according to standards of practice and resume testing for ER and PR.

DO NOT FORGET!

- "THE IMMUNOHISTOCHEMISTRY TESTS ARE PROBABILISTIC, NOT ACURATE"

Questions?