National Cancer Institute

Preoperative Therapy in Invasive Breast Cancer

Reviewing the State of the Science and Exploring New Research Directions

Initial Pathology Assessment to Preoperative Therapy

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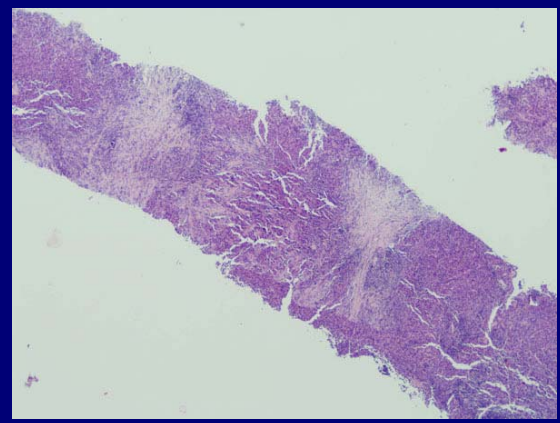
National Institutes of Health

Initial Pathology Assessment Prior to Preoperative Therapy

Needle Core Biopsy

- Diagnosis of invasive carcinoma prior to neoadjuvant therapy is best made by Needle Core Biopsy and not Fine Needle Aspiration
  - Positive predictive value
    98 - 99.8 %
  - Biomarker assessment
  - Tissue procurement for research



Initial Pathology Assessment Prior to Preoperative Therapy

Needle Core Biopsy

- Concordance with Final Pathology
  - Invasive Carcinoma type - 67 - 81 %
  - Size
    - Under/Overestimate 72 – 79%
  - Grade - 59 - 75 %
    - Poorly differentiated carcinoma 84%
  - Lymphovascular Involvement 8%

Initial Pathology Assessment Prior to Preoperative Therapy

Needle Core Biopsy

- Adequacy of Samples
  - Diagnosis
  - Biomarker Analysis
  - Novel Assays
  - Research
- Multiple Cores (4-6)
  - More volume with wider bore needles

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ACCURACY OF DIAGNOSIS

How can the accuracy of breast pathology diagnostics be improved?

- Quality Control Program
- Second Opinion
- Integration of pathologists in patient care teams

Why Current Breast Pathology Practices Must Be Evaluated. The Susan G. Komen Breast Cancer Foundation White Paper: June 2006

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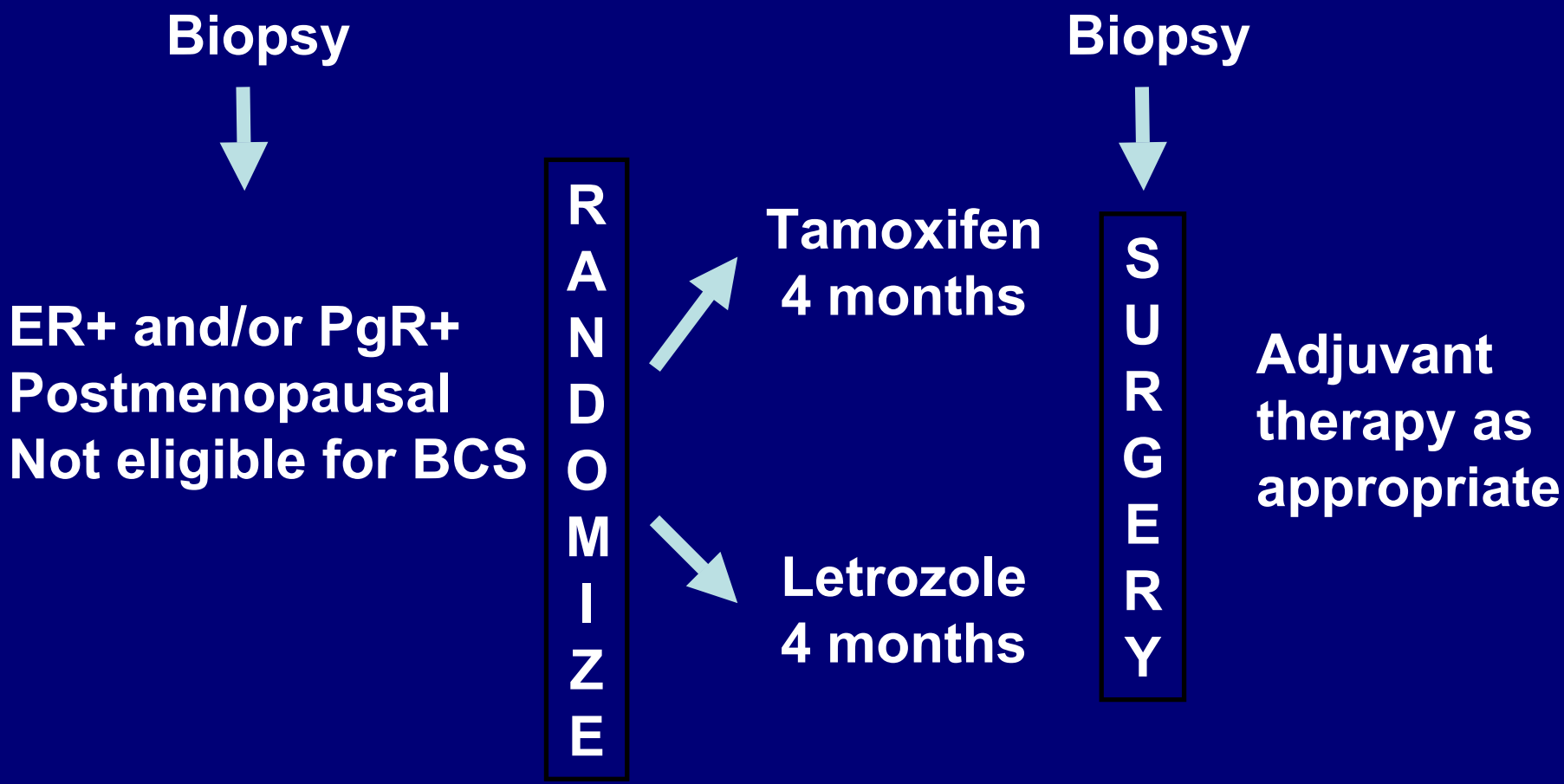
BIOMARKER ANALYSIS

- Concordance of biomarker status between NCB and surgical excision specimen
  - Estrogen Receptor 79 - 95%
  - Progesterone Receptor 69 - 95%
  - Her2/neu (IHC) 80 - 96%
  - Her2/neu (FISH) 100 %

Burge et al. *Breast.* 2006 Apr; 15(2):167-72.

Sarakbi et al. *Int Semin Surg Oncol.* 2005 Aug 22;2:15.

Double-Blind Randomized Study of Neoadjuvant Tamoxifen vs Letrozole



Eiermann W et al. *Ann Oncol*. 12:1-6, 2001.

Clinical Results Summary for "On-Study Biopsy"
Confirmed ER+ and/or PgR+ Cases

12 % CASES ER-/PR- ON CENTRAL ANALYSIS

	Letrozole	Tamoxifen	*P* Value
Confirmed (ER+/PgR+)	**124 (100%)**	**126 (100%)**	
Overall tumor response (CR+PR)			
Clinical	74 (60%)	52 (41%)	0.004
Ultrasound	48 (39%)	37 (29%)	0.119
Mammography	47 (37%)	25 (20%)	0.002
Breast-conserving surgery	60 (48%)	45 (36%)	0.036
Clinical disease progression	10 (8%)	15 (12%)	0.303

[1]Stratified Mantel-Haenszel chi-squared test

Ellis MJ et al. *J Clin Oncol.* 19:3808-3816, 2001.

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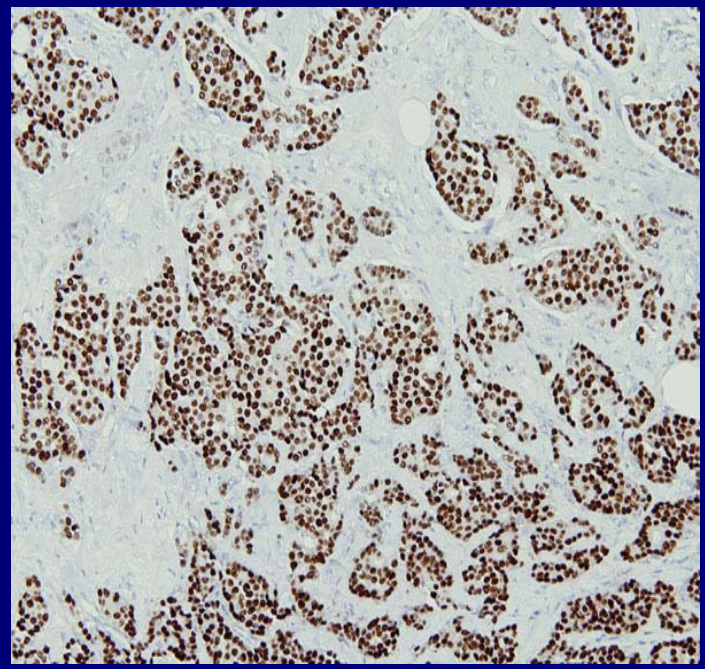
BIOMARKER ANALYSIS

Estrogen And Progesterone Receptor Status Assessment

By IHC Is Not a Standardized Test



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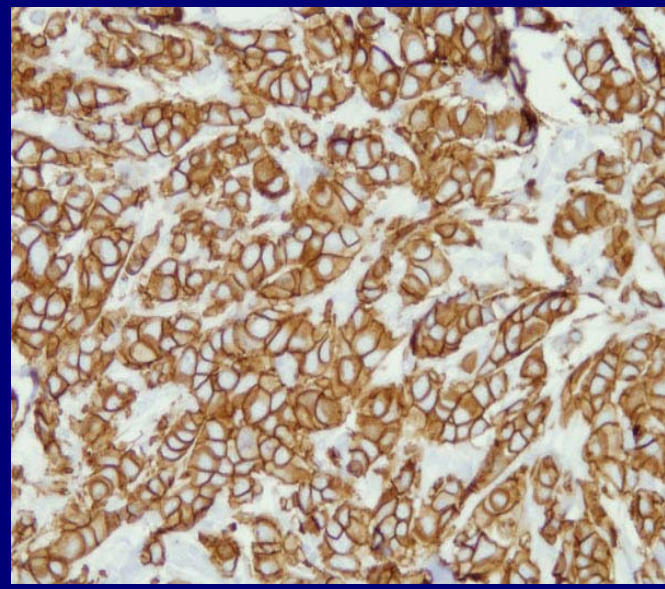
HER2 ASCO/CAO Testing Guidelines

THE PROBLEM

- False positive IHC (3- 50%)
  - Non-standardized Methods
  - No automation
  - Small Volume
- FISH laboratory variability 5-23 %



THE SOLUTION

- **ASCO/CAP Guidelines**
  - Specimen handling
  - Exclusion criteria
  - Assay validation
  - Laboratory testing
  - Controls
  - Reporting Criteria

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BIOMARKER ANALYSIS

- Hormone receptor negative
- Her2 negative
- Discordance with histology

- REPEAT ASSAY

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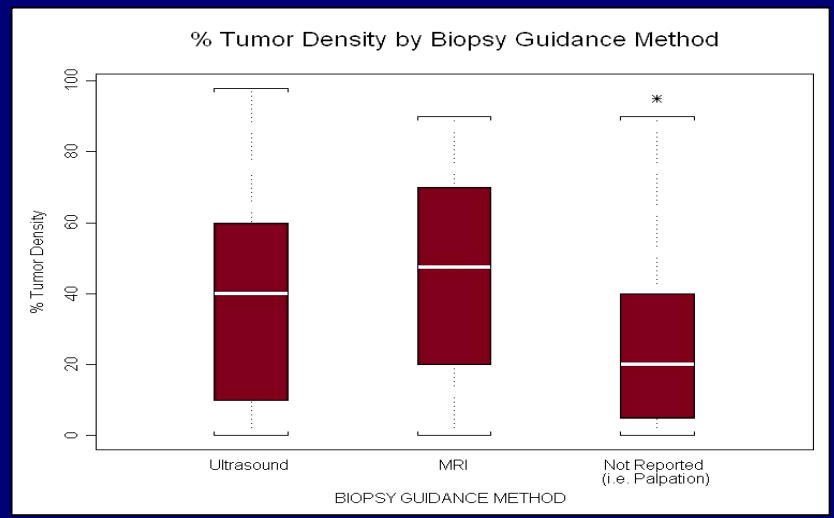
Image Guided Core Biopsy – Tumor Yield

- Tumor Yield is higher
  - Image guidance
  - First pass
  - Prior to any chemotherapy

biopsy method	number of cores	tumor yield (% of core) >=30%	>=50%
US	160	90 (56%)	67 (42%)
MR	58	43 (74%)	29 (50%)
palpation	212	84 (40%)	44 (21%)
all	430	217 (50%)	140 (33%)



Rosen M et al. Factors Affecting Quality of Tumor Core Biopsy Specimens in ISPY TRIAL. SABCS 2006

Image Guided Core Biopsy

Image Guided Core Biopsy should be the standard diagnostic procedure prior to neoadjuvant therapy

TISSUE BANKING

Guidelines from BIG/North American Cooperative Groups breast cancer specimen collection working groups

- **Goals:**

- To promote and ensure proper collection of high-quality research specimen such that each patient diagnosed with breast cancer can have a reliable, interpretable molecular diagnosis.
- To provide a known baseline of standardization of specimen collection and handling procedure, to the extent possible, such that more global biomarker analysis across studies is possible.
- To promote specimen collection that would allow for future technologies, particularly in the molecular arena, to be applied to specimens for research.
- Ultimately, to increase scientist confidence in pre-analysis variable control, to guarantee excellent quality of breast cancer specimens.

- **Concrete aim:**

- To develop SOP templates that Group trial leadership can incorporate into clinical trial protocols.

TISSUE BANKING

Guidelines from BIG/North American Cooperative Groups breast cancer specimen collection working groups

FRESH TISSUE GUIDELINES

- Background and rationale for fresh tissue collection
- Notable "Do's and Don't's"
- Recommended SOP's:
- 1. Brochure used by EORTC p53 study (Protocol 10994)
- 2. SOP for TuBaFrost (European Human Frozen Tumour Tissue Bank)
- 3. MIND ACT SOP's (drafts now developed)
- Settings for specimen acquisition:
- Diagnostic setting
- Post-diagnostic preoperative setting
- Surgical setting

http://ctep.cancer.gov/guidelines/spec_bc_grptrials.html

Initial Pathology Assessment Prior to Preoperative Therapy
SUMMARY

- Image guided core biopsy is the standard diagnostic procedure for preoperative diagnosis
  - Multiple cores (4-6)
- Accuracy of diagnosis
- Biomarker Assays can be accurately performed on core biopsy specimens with appropriate quality control measures
- Tissue should be collected for research using published guidelines