Diagnosis and Management of Breast Cancer

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Signs and Symptoms of Breast Cancer

- Mass or “Thickening”
- Skin dimpling
- Nipple retraction or scaling
- Skin erythema or peau d’orange
- Focal breast pain – 10%
- Spontaneous nipple discharge
- Occult mass or calcifications

Diagnosis of Breast Diseases
Physical Examination

- Start with palpation of supraclavicular fossa and then axillary nodes
  - Initial patient “contact”
  - Hold arm and elbow while rolling axillary contents against chest wall
- Inspection
  - Skin discoloration or edema
  - Skin dimpling
  - Nipple retraction

Palpation of Axillary Nodes

Examination of Axillary Nodes

Inspection for Skin Changes and Nipple Retraction
Skin Dimpling

Nipple Retraction

Peau D’Orange

Palpation of the Breast

- Patient supine with ipsilateral hand behind head
- Use 2 hands
- Use “pads” of fingers, not fingertips
- Systematically examine all breast tissue

B. Supine position with arm raised over head allows breast to flatten over chest wall, which provides optimum condition for palpation of breast and axillary tail

Pillow under shoulder to tilt body so that breast does not fall to side
Diagnosis of Breast Complaints

- Physical Examination
- Mammography
  - Characteristics of the mass
  - Other masses
  - CANNOT RULE OUT CANCER –
    - 10% false negative rate

Mammograms of a Woman with a Palpable Right Breast Mass

Mammography - Multiple Cancers

Diagnosis of Breast Complaints

- Physical Examination
- Mammography
  - Characteristics of the mass
  - Other masses
  - CANNOT RULE OUT CANCER –
    - 10% false negative rate
- Ultrasound - Selectively
Role of Breast Ultrasound

- Can determine whether a mass (occult or palpable) is solid or cystic
- To clarify indeterminate exam or mammogram findings
- Image-guided biopsy/aspiration
- NOT as a screening test

Occult Mass on Mammogram

Breast Ultrasound – Simple Cyst

Sonogram of Mass - Complex Cyst

Ultrasound Guided Aspiration of Breast Cyst

Ultrasound - Breast Cancer
Triple Negative Test

- Non-suspicious physical exam (weak link; cannot be a definite mass)
- Negative imaging (mammogram +/- US)
- Benign FNA cytology
- Nearly 100% accurate – must follow-up

Missed Breast Cancers Triad of Error

- Young age
- Self-discovered mass
- Negative mammogram

Screening Mammography

- Annually after Age 40
- Earlier for strong family history at young ages
  - Start 5 years earlier than youngest prior cancer
- NOT just for high risk patients
- Emerging role for selective use of MR Mammography

Mammographic Signs of Cancer

- Mass
- Calcifications
- Dilated duct
- Skin changes
- Architectural distortion
- Asymmetry
- Enlarged axillary nodes

Mammograms - Spiculated Density

Mammography - Pleomorphic Calcifications
Mammography - Calcifications

Stereotactic Breast Biopsy

Stereotactic Breast Biopsy

Breast Diagnosis - Mammographic Localization

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Breast Diagnosis - Mammographic Localization
Carcinomas in Situ
Ductal and Lobular

Duct Carcinoma In Situ

Breast Pathology is Treacherous
Atypical Ductal Hyperplasia

Defining Risk for Breast Cancer

Gail Model
- Age
- Age at menses
- Age at first live birth
- Number of first degree relatives with BC
- Number of prior breast biopsies
- Biopsies with ADH

Breast Cancer Risk Assessment
**Options for Mutation-Positive or Other High Risk Women**

- Intensive screening
- Chemoprevention
- Prophylactic mastectomies +/- oophorectomies

**Clues to Effective Chemoprevention**

- Estrogen has a role in breast cancer etiology
- Anti-estrogen therapy can cause regression of breast cancers that express hormone receptors
- Tamoxifen, used to decrease recurrence of ER+ breast cancer also decreased incidence of contralateral breast cancers by almost half

**Tamoxifen for Chemoprevention - P1**

- Women at High Risk for Breast Cancer
- Randomize: Tamoxifen for 5 Years or Placebo for 5 Years

**Average Annual Rates of Invasive Breast Cancers in P-1 Trial**


**Tamoxifen for Chemoprevention - STAR**

- Post-Menopausal Women at High Risk for Breast Cancer
- Randomize: Tamoxifen for 5 Years or Raloxifene for 5 Years

**SURGERY FOR BREAST CANCER**

- Diagnosis
- Local Control
- Staging
William Steward Halsted

Halsted’s Radical Mastectomy

PARADIGM SHIFT IN BREAST CANCER BIOLOGY AND THE ROLE OF LYMPH NODES

- Lymph node metastases are a critical step in the sequential development of distant metastases (Halsted)
- Lymph node metastases are simply a prognostic indicator of distant micrometastases present at the time of initial diagnosis (Fisher, B-04)

Mastectomy to Breast Conservation

- 1891-1970’s: Halsted radical mastectomy
- 1970’s-1980’s: “Modified” radical mastectomy
- 1980’s-Present: Breast conserving therapy

NSABP Protocol B-06

Breast Cancers < 4 cm

Randomized

Segmental Mastx + ALND
Segmental Mastx + ALND + Breast Radiation
Total Mastx + ALND

NSABP B-06 - 20 Year Results

NEJM, 2002

NEJM, 2002
Breast Conservation is Under-Utilized

Possible Advantages of BCT

- Psychological
- Cosmetic
- Reduced fear of “mutilation” may encourage earlier diagnosis

True Contraindications to BCT

- Multicentric disease
  - Diffuse calcifications
  - Two or more foci in separate quadrants
- Prior breast irradiation
- Inability to achieve negative margins
- Radiation therapy inaccessible
- Patient choice

Non-Contraindications to Breast Conserving Therapy

- Extensive intraductal component
- High grade histology
- Positive nodes
- Breast size (too large or too small)
- Patient age (too young or too old)
- Multi-focal disease
- Central location/nipple involved

Contraindications to BCT?

- First or second trimester of pregnancy
  - Can be overcome by delaying RT
- Tumor too large
  - Can be overcome with primary chemotherapy

Changes in Breast Cancer Surgery Over Time
Clinical Response to Primary Chemotherapy, Protocol B-18

Before Treatment

After AC X 4
No palpable tumor

NSABP B-18: Overall Survival
Nine Year Update

Postop vs. Preop

NSABP B-18: Surgery Performed

Mastectomy
Lumpectomy

p < .01

NSABP B-18: Overall Survival
According to Primary Tumor Response

p = 0.0008

Cosmetic Results After BCS and Radiation

Cosmetic Results After BCS, Radiation and Contralateral Ptosis Correction
BCT - Long-Term Results

Breast Conservation Surgery
Central Location is NOT a Contraindication

Brachytherapy Delivery of Radiation

Balloon Intracavitary Brachytherapy
• Simplified, reproducible approach
• Placement by
  – Surgeon
  – Radiation Oncologist
• Timing
  – At time of lumpectomy
  – Post-lumpectomy
  – ultrasound guidance
  – CT guidance
• Treatment distance - 1 cm
• FDA approval in May 2002

Mammosite Balloon Catheter
Approaches to Reconstruction After Mastectomy

- Immediate versus delayed
- Prosthetic implant versus autologous tissue transfer
- “Skin-sparing” approach
- Possibility of contralateral prophylactic mastectomy

Prosthetic Breast Implants for Reconstruction

Reconstruction with Implant and Contralateral Reduction Mammaplasty

Transverse Rectus Abdominis Myocutaneous (TRAM) Flap

Bilateral Mastectomies and TRAM Reconstruction: Late Results
Axillary Lymph Node Dissection

Purposes
- Regional control
- Staging:
  - Prognosis
  - Need for systemic therapy

Staging
- Most important predictor of prognosis and need for chemotherapy & regional RT
- Not indicated for DCIS
- May not be needed for DCIS with microinvasion
- May not be needed for elderly

Who benefits from ALND?
- Only patients with positive nodes!
- The 60 - 70% of patients with clinically negative nodes who also have histologically negative nodes derive NO benefit and all the morbidity

Axillary Node Dissection for Breast Cancer - Disadvantages
- General anesthesia
- Costs; medical and time lost from work
- Complications
  - Seromas
  - Drains
  - Dysesthesias, pain & numbness
  - Shoulder dysfunction
  - LYMPHEDEMA (10-20%)

Sentinel Lymph Node Mapping for Breast Cancer
- With radionuclide + visible dye:
  - 90 - 95% success rate
  - 10% found by isotope OR dye only
- SLN biopsy is >95% accurate
- False negative rates are 0 - 11%
- If SLN is negative by H&E and IHC, <3% of patients will have other positive nodes
Sentinel Node Mapping for Breast Cancer

Lymphoscintigraphy of SLN for Breast Cancer

Primary site

2 Axillary SLN

NAVIGATOR®

NAVIGATOR GPS

Blue dye injected around tumor.

Blue Stained Sentinel Lymph Nodes

Blue hot nodes found visually and with Gamma Probe.
IHC Staining for Cytokeratin-Positive Cells in SLN

Clusters of CK+ cells

Staging Work-Up for Breast Cancer

“Routine”
- Mammograms
- CXR (?)
- Metabolic panel (?)
- CBC (?)

Staging Work-Up for Breast Cancer

- For Stage III
  - Bone scans
- NOT normally indicated:
  - Bone scans
  - CT scans
  - Liver scans
  - Liver US

Adjuvant Systemic Therapy

- Cause of deaths from breast cancer is distant metastases, not local tumor
- To impact metastatic disease, systemic adjuvant treatment is needed
  - Hormonal therapy
  - Chemotherapy

Adjuvant Therapy & Risk Reduction

Secondary treatment added to primary treatment to reduce the risk of recurrence and death

Adjuvant Systemic Therapy - Hormonal

- Not useful for ER-/PR- tumors
- Should be offered to most HR+ patients, regardless of age
- Ovarian ablation/suppression is an alternative in pre-menopausal women; adding anti-estrogen may still be beneficial
Benefit of Adjuvant Tamoxifen

Mechanisms of Anti-Estrogen Drugs for Breast Cancer

Anti-Estrogen Therapy
Aromatase Inhibitors

Switching from Adjuvant Tamoxifen to Exemestane

IES Disease-Free Survival graph

Adjuvant Systemic Therapy - Chemotherapy

- Chemotherapy is indicated for most women with tumors > 1 cm or with positive nodes
- Less benefit for older patients, esp. HR+
Benefit of Adjuvant Combination Chemotherapy for Breast Cancer

Adjuvant Therapy & Risk Reduction
- Secondary treatment added to primary treatment to reduce the risk of recurrence and death
- Absolute risk reduction:
  - 40% vs. 30% dead = 10% ARR
- Relative risk reduction
  - 40% vs. 30% dead = 25% RRR

Breast Cancer Therapy New Directions
- Increased dose intensity and density
- Altered sequencing (e.g., neoadjuvant)
- "Targeted" therapies (e.g., Herceptin)
- New prognostic/predictive factors

Immunohistochemical Staining for HER-2/neu

HER-2 Amplification by FISH
Herceptin: Humanized Anti-HER2 Antibody

- Targets HER2 oncoprotein, which occurs in 25% to 30% of patients with breast cancer
- High affinity (Kd = 5 nM) and specificity
- 96% human, 4% murine
- Decreased potential for immunogenicity
- Increased potential for recruiting immune effector mechanisms

Carter et al., 1992; Park et al., 1993; Slamon et al., 1997; Genentech, data on file

Prognostic Value of Molecular Signatures

Chang et al., Lancet 2003

Gene Expression Microarray Prediction of Response to Docetaxel