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
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
Breast Ultrasound - Small Cancer

Sestamibi Breast Scan

MRI Detection of Breast Cancer

Breast Biopsy Choices

Fine Needle Aspiration Biopsy

Fine Needle Aspiration Biopsy Smear
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
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

- 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

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

NSABP B-06 - 20 Year Results
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

% Surviving

Years from study entry

NSABP B-18: Surgery
Performed

% Surviving

Years from study entry

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

% Surviving

Years from study entry

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

Purposes of Axillary Node Dissection

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

Axillary Node Dissection for Breast Cancer - Disadvantages

- General anesthesia
- Costs; medical and time lost from work
- Complications
  - Seromas
  - Drains
  - Dysesthasias, pain & numbness
  - Shoulder dysfunction
  - LYMPHEDEMA (10-20%)

Axillary Lymph Node Dissection

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

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

NAVIGATOR*

Blue Stained Sentinel Lymph Nodes
IHC Staining for Cytokeratin-Positive Cells in SLN

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 oncprotein, which occurs in 20% to 30% of patients with breast cancer
- High affinity ($K_d = 5nM$) and specificity
- 95% human, 5% murine
- Decreased potential for immunogenicity
- Increased potential for recruiting immune effector mechanisms

Carter et al, 1992; Park et al, 1993; Slamon et al, 1987.; Genentech, data on file

Prognostic Value of Molecular Signatures

Gene Expression Microarray Prediction of Response to Docetaxel

Chang et al., Lancet 2003

NEJM, 2003