DIAGNOSIS AND STAGING OF BREAST CANCER

Theresa Harrington
MSN, ANP-BC, OCN

Disclosure

Theresa Harrington, MSN, ANP-BC, OCN, Adult Nurse Practitioner, Lombardi Comprehensive Cancer Center, MedStar Georgetown University Hospital, has no financial relationships to disclose.

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DIAGNOSIS AND STAGING OF BREAST CANCER

Theresa Harrington
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Your Presenter

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• Nurse Practitioner Lombardi Comprehensive Cancer Center
  Georgetown University Hospital
• Oncology Certified Nurse (OCN)
• Adjunct Faculty, Georgetown University School of Medicine
Objectives

- The goal of this presentation is to provide information on the current risk factors, screening recommendations, and staging methodology of breast cancer.
- Upon completion of the webinar, learners will be able to:
  - **Identify** breast screening guidelines and current imaging options
  - **Develop** a general understanding of the current multimodality treatments of breast cancer
  - **Describe** the changes and rationale for the recent updates to the AJCC Staging 8th Edition

What Is Cancer?

- Uncontrolled division and growth of abnormal cells
- Multiple changes occur to the cell
- Normal cells divide and stop
- Cancer cells keep dividing, growing, mutating
Cell Division

- Control of cell division resides in the genes
- When genes fail to work it results in:
  - Mutation
  - Altered protein production
  - Abnormal function of the cell
  - Disease (cancer)

Breast Cancer

- Most cancer occurs in cells that divide quickly
- The quicker cells divide, the more chance of damage (multiple mutations to occur)
- Epithelial cells divide the quickest
- Surface of the body
- Lining of internal organs: intestine, bronchi, and mammary ducts

Harris et al. 2014
**Breast Cancer Development**

- Normal Duct
- Intraductal Hyperplasia
- Intraductal Hyperplasia with Atypia
- Intraductal Carcinoma In Situ
- Invasive Ductal Cancer

**TIME**

8-10 years

Harris et al. 2014

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**Breast Cancer**

- Incidence increases with age
- Majority arise from the ducts
- Mammogram does not detect all breast cancers (lobular cancers)
- Can occur in males
  - Genetic mutations
  - Alcoholics
  - Chromosomal abnormalities
Breast Cancer Risk Factors

Breast Density

- Dense breast tissue is common and normal in premenopausal woman
- More likely to have dense breasts if younger, low BMI, or take HRT
- Dense breast tissue is an independent risk factor for breast cancer development
- Density of tissue is largely an inherited trait
- Categorized on mammogram
  - Heterogeneously dense (C) or extremely dense (D)
- Risk of breast cancer increases with increased density
- This is separate from the ability to detect abnormal findings on mammogram

ACS 2017
(first full-term pregnancy: FFTP; hormone replacement therapy: HRT; family medical history: FMH; radiation therapy: XRT)

National Cancer Institute (NCI), 2018
Breast Cancer Statistics

- Breast Cancer remains the most common female cancer: 2007-2013
  - 30% of all female cancer (lung 13%, colorectal 7%)
  - 14% of all female cancer deaths (lung 25%, colorectal 8%)
- Lifetime probability of breast cancer is 12.4% or 1 in 8 woman
- Survival rates continue to improve
  - 91% 5 year survival rate (2008-2014)
  - 84% 5 year survival rate (1987-1989)
  - 75% 5 year survival rate (1975-1977)
- Continues to be a discrepancy in race and survival 2008-2014
  - 92% 5 year survival for Caucasians
  - 83% 5 year survival for African Americans

National Cancer Institute (NCI); American Cancer Society (ACS) 2018

Screening Recommendations for Average Risk Woman

**IMAGING**
- Digital
- 3D imaging (tomosynthesis)

**PALPATION**
- Clinical Breast Exam
- Self examination/observation/awareness

Mammogram

Ultrasound

Baron et al, 2018
# Screening Recommendations for Average Risk Woman

## Mammogram Recommendations

<table>
<thead>
<tr>
<th>Mammogram Recommendations</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S Preventive Services Task Force (1/2016)</td>
<td>Decision should be individual. Discuss potential risk/ benefit and patient can chose biennial mammo</td>
<td>Every 2 years</td>
<td>Every 2 years</td>
<td>Every 2 years</td>
<td>Insufficient evidence to balance benefits and harms of screening</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologist (11/2017)</td>
<td>Every 1-2 years Decision based on shared decision making</td>
<td>Every 1-2 years Decision based on shared decision making</td>
<td>If not started in 40’s, begin age 50, every 1-2 years, shared decision</td>
<td>Every 1-2 years, shared decision making</td>
<td>Shared decision Making</td>
</tr>
<tr>
<td>American Cancer Society (5/2018)</td>
<td>Annual if patient desires</td>
<td>Annually</td>
<td>Annually</td>
<td>Annually</td>
<td>Continue while good health life expectancy &gt;10 years</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>Annually</td>
<td>Annually</td>
<td>Annually</td>
<td>Annually</td>
<td>Use clinical judgment</td>
</tr>
</tbody>
</table>

Baron et al., 2018; USPS Task Force, 2016; ACOG 2017; Keating & Pace, 2018

## Breast Examination Recommendations

<table>
<thead>
<tr>
<th>Breast Examination Recommendation</th>
<th>40-44</th>
<th>45-49</th>
<th>50-54</th>
<th>55-74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S Preventive Services Task Force (1/2016)</td>
<td>Insufficient evidence to support CBE</td>
<td>Insufficient evidence to support CBE</td>
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<td>Insufficient evidence to support CBE</td>
<td>Insufficient evidence to support CBE</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologist (11/2017)</td>
<td>Annual clinical breast exam (CBE) and breast awareness</td>
<td>Annual clinical breast exam and breast awareness</td>
<td>Annual clinical breast exam and breast awareness</td>
<td>Annual clinical breast exam and breast awareness</td>
<td>Annual Self-awareness</td>
</tr>
<tr>
<td>American Cancer Society (5/2018)</td>
<td>No clear benefit of CBE Woman should be familiar with breast and report a change</td>
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</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>Annual CBE Self-awareness</td>
<td>Annual CBE Self-awareness</td>
<td>Annual CBE Self-awareness</td>
<td>Annual CBE Self-awareness</td>
<td>Annual CBE Self-awareness Upper age limit not established</td>
</tr>
</tbody>
</table>

Baron et al., 2018; USPS Task Force, 2016; ACOG 2017
Breast MRI for High Risk Woman

- Lifetime risk of breast cancer of 20% or greater
- Can consider if risk is between 15-20%
- BRCA 1/2 carriers, TP53 mutation
- Consider for following mutations: ATM, CDH1, CHEK2, NBN, NF1, PALB2

Risk Assessment Models

- Gail Model Risk Assessment
  - Factors in age, race, menarche, FFTP, biopsies, FMH of first-degree relatives
- IBIS
  - Factors in age, menarche, FFTP, biopsies, height and weight
  - Menopausal status, HRT use, breast (uni/bilateral) and ovarian cancer, 1st and 2nd generation, room to add males, cousins, nieces, genetic testing, Ashkenazi descent, includes likelihood of BRCA gene
Findings Which May Warrant Further Evaluation

- Mammogram
  - Calcifications
  - Persistent asymmetric tissue
  - Mass
  - Persistent distortion
- Ultrasound
  - Solid mass
  - Distortion
- MRI
  - Mass like enhancement
  - Non-mass like enhancement
- Exam
  - Breast mass
  - Adenopathy
  - Skin changes
  - Retraction
  - Asymmetry

Breast Cancer Diagnosis

- Biopsy for microscopic analysis – mandatory for diagnosis
  - Core needle biopsy (tissue biopsy)
    - Palpable and non palpable lesions
    - Image guided (Mammogram, US, or MRI)
    - Clip is placed to mark area biopsied
    - Possible under classification with smaller tumor at time of surgery
  - Fine needle biopsy (cytology)
    - Consider for palpable lesions
    - Quick diagnosis, lower cost
    - If questionable findings, may need to proceed with Core biopsy
  - Surgical
    - Should be performed only if core needle biopsy inconclusive or not feasible, i.e. location of abnormality
Types of Breast Cancer

• **In situ**
  – Cancer cells are contained within the ducts
  – Ductal Carcinoma In Situ (DCIS)
  – May or may not progress to invasive cancer

• **Invasive**
  – Cancer cells have broken outside of the ducts or lobules and into the surrounding breast tissue
  – 80% of breast cancers are invasive
    • Ductal
    • Lobular
    • Inflammatory

Breast Cancer

• Breast cancer is now felt to be a group of diseases
• Breast cancer groups have different molecular characteristics
• Molecular characteristics can effect
  – Prognosis
  – Rate/Pattern of Recurrence
  – Treatment Recommendations
    • Type of treatment
    • Order of therapy
## Tumor Grade

Grade is determined by assessing the morphologic features of the tumor.

<table>
<thead>
<tr>
<th>Grade (GX)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Low combined histologic features Favorable</td>
</tr>
<tr>
<td>G2</td>
<td>Intermediate combined histologic features Moderately favorable</td>
</tr>
<tr>
<td>G3</td>
<td>High combined histologic features Unfavorable</td>
</tr>
<tr>
<td>GX</td>
<td>Can not be assessed</td>
</tr>
</tbody>
</table>

## Molecular Biomarkers

- **ER status (Estrogen Receptor)**
  - When positive, cancer cells are stimulated by estrogen
  - 1% or more of cells stain positive for ER expression
  - Tested on invasive and non invasive disease
  - 80% of breast cancers are ER positive

- **PR Status (Progesterone Receptor)**
  - When positive, cancer cells are stimulated by progesterone
  - 1% or more of cells stain positive for PR expression
  - Tested on invasive and non invasive disease
  - 65% of breast cancers are ER/PR positive

- **HER2 (Human Epidermal Growth Factor Receptor 2)**
  - A protein which promotes growth of cancer cells
  - ~ 1 in 5 breast cancers have a gene mutation that makes an excess of the HER2 protein
  - Tested on invasive cancer only, not non invasive
**HER2 Testing**

- Immunohistochemistry staining (IHC)
  - 0 to 1+ = Negative
  - 2+ = Equivocal
  - 3+ = Positive

- Fluorescent in situ hybridization (FISH)
  - HER2/CEP17 ratio < 2.0 AND HER2 copy number < 4 = Negative
  - HER2/CEP17 ratio ≥ 2.0 = Positive
  - HER2/CEP17 copy number ≥ 6 regardless of ratio = Positive
  - HER2/CEP17 ratio <2.0 AND copy number ≥ 4 but < 6 = Equivocal

**Four Main Molecular Subtypes**

- **Luminal A**
  - Hormone Receptor positive/HER2 negative
  - Low proliferation rate
  - Usually grade I or II tumors
  - Most favorable prognosis
    - Respond well to endocrine therapy but not chemotherapy

- **Luminal B**
  - ER and/or PR+ but lower receptor % status
  - High Ki67
    - High number of actively dividing cells - high proliferation rate
  - Usually grade III
    - Less likely to respond to endocrine therapy but better to chemotherapy compared to Luminal A

- **HER2 Amplified**
  - HER2 positive
  - ER/PR positive or negative
  - Usually grade III tumors
  - Aggressive but when treated with anti Her2 therapy have a good prognosis

- **Basal**
  - ER negative, PR negative, HER2 negative
  - Usually grade III tumors
Treatment Modalities

• Local
  – Surgery
  – Radiation

• Systemic
  – Chemotherapy
  – Endocrine Therapy
  – HER2 targeted Therapy
  – Immunotherapy

Surgery for Breast Cancer

• Mastectomy
• Lumpectomy

The type of breast surgery is based on the extent of the disease in the breast along with personal preference
  – Extensive DCIS (Stage 0) in multiple quadrants requires mastectomy
  – A large breast tumor contained to one quadrant, independent of features, may be able to be treated with a lumpectomy

• Nodal Evaluation
  – Sentinel Node Biopsy
  – Axillary Node Dissection
Radiation Therapy

- Postoperative
  - Whole breast radiation
  - Partial breast radiation
- Intraoperative (IORT)
- Proton Therapy
- Lumpectomy + **Radiation Therapy** = Mastectomy in terms of overall survival
- Postmastectomy radiation


Systematic Therapy

- Chemotherapy
  - Neoadjuvant
  - Adjuvant
  - IV
  - Oral agents
- Endocrine Therapy
  - Tamoxifen
  - Aromatase Inhibitors (AI)
  - Ovarian Suppression + AI
- HER2 targeted Therapy
  - Trastuzumab
  - Pertuzumab
  - Neratinib
  - TDM1
- Immunotherapy
  - Approved in PDL1 positive triple negative metastatic breast cancer
  - Clinical Trials
AJCC (American Joint Committee on Cancer) Cancer Staging

- Tumor Staging began in 1959 with T, N, M staging
  - Anatomic extent of disease
  - Developed to help predict prognosis, risk of distant recurrence/death
  - Primary treatment was local therapy (surgery/radiation)

- T = Size of the tumor
  - Maximum dimension of the largest invasive tumor
  - Satellite foci or multiple tumors are not added to the maximum size

- N = Lymph node involvement
  - Largest contiguous deposit is used
  - Adjacent deposits are not added together

- M = Distant Metastasis

- Now on the 8th edition/revision

American Joint Committee on Cancer (AJCC)

- Updated AJCC effective January 2018 now includes TNM PLUS:
  - ER Status
  - PR Status
  - HER2 Status
  - Grade
    - How much the cells look (or don’t look) like normal breast cells under the microscope
    - I, II, III
    - Important prognostic factor independent of tumor size or nodal status
    - Should be reported on all invasive cancers
  - Oncotype DX recurrence score when applicable/available
    - Recurrence Score (RS) < 11 low risk

Tumor biology can better define prognosis than anatomic extent of disease
**Oncotype Dx**

- Genomic Test based on 21 genes
- Provides an estimated 10 year risk of distant recurrence for ER+, HER2 negative tumor with use of endocrine therapy
- Prospective trial showed a very low recurrence rates in individuals with a recurrence score (RS) of < 11
- Considered Level I Evidence AJCC

*Giuliano et al. 2017*

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**AJCC Staging System 8th Edition**

**Three Stage Groups**

**Anatomic Stage**
- Based on T, N, M
- Used where biomarkers can not be routinely performed

**Clinical Prognostic Stage**
- Based on:
  - History and physical exam/imaging studies
  - Tumor grade
  - ER/PR/HER2

**Pathological Prognostic Stage**
- Used for patients who have had surgery as the initial treatment
- Based on:
  - Pathology from surgery
  - Biomarkers (ER/PR/HER2)
  - Clinical information

*AJCC Breast 2018*
**AJCC 8th Edition Staging**

- Assigns stage based on overall prognosis with treatment
- Lower stage equals
  - Favorable biology
  - Effective therapies available
  - Favorable biopsy plus effective therapy
- Lower stage does not mean less treatment is needed
- Clinical and Pathological Prognostic Stage resulted in reassignment of >35% of patients (either higher or lower stage) than with use of anatomic stage alone

**AJCC 8th Edition**

- Pathologic Stage
  - Abbreviated as (p)
  - Based on the findings at time of surgery
  - Does not apply to those who received neoadjuvant systemic therapy
- Clinical Stage
  - Abbreviated as (c)
  - Based on physical exam and imaging findings
  - Used to provide guidance for sequence of treatment recommendations
- Response to Neoadjuvant Systemic Therapy
  - Clinical Response abbreviated a ycT, ycN
  - Surgical pathology findings following systemic therapy are abbreviated as ypT, ypN
Multigene Genomic Profile Assays

• Stage 1A
  – T1 or T2
  – N0
  – M0
  – ER +, HER2 negative
  – OncotypeDX RS <11

• Results of other genomic profiles currently not assigned pathologic prognosis stage
  – More limited level 1 evidence
  – Shorter interval updates planned

AJCC Breast 2018

Tumor Size Measured to the Nearest Millimeter

• If multiple areas, the sum of the areas is not added together
  – TX: Primary tumor can not be assessed
  – T0: No evidence of the primary tumor
  – Tis: in situ
    • Tis (DCIS)
    • Tis (Paget)
      – Only if not associated with invasive disease or DCIS
      – Rare

• For invasive disease, only the invasive component is measured
  – T1: 2 cm or less in size
    • T1mi- microinvasion 1 mm or smaller
  – T2: 2 cm to 5 cm in size
  – T3: > 5 cm in size only the invasive component is measured
  – T4: Any size tumor invading the chest wall or skin
    • Inflammatory breast cancer
    • Involvement of the pectoralis muscle without invasion into chest wall structures (ribs, intercostal muscle, serratus anterior muscle) is based on tumor size

AJCC Breast 2018
Nodal Anatomy

- Breast drains via three major pathways
  - Axillary
    - Infra mammary nodes are within the breast tissue. Considered axillary nodes for staging purposes
  - Interpectoral
  - Internal mammary
- Supraclavicular nodes
  - Considered regional nodes for purpose of staging
- Cervical or contralateral nodes are considered metastatic
  - Internal mammary or axillary nodes on the opposite side (M1)

Lymph Nodes
Nodal Involvement Further Defined

- **Macrometastasis**
  - Area of cancer involvement measures > 2 mm
- **Micrometastasis**
  - Area of cancer involvement measures between 0.2 mm (200 cells) to 2 mm
- **Isolated tumor cells**
  - Fewer than 200 cells, less than a 0.2 mm area of involvement
  - Does not change the cancer stage
    - Excluded from the total positive nodal count
    - Are included in the total number of nodes evaluated
  - Is recorded as i+ or mol+

Nodal Involvement

<table>
<thead>
<tr>
<th>NX:</th>
<th>Lymph nodes can not be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No longer a valid category unless nodes have been removed and can not be examined by imaging or physical exam</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N0:</th>
<th>Cancer has not spread to the Lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N0(i+): less than 200 cells were seen with routine stains or immunohistochemistry staining</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N1:</th>
<th>1 to 3 Lymph nodes are involved with cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N1mi: Micro metastasis in axillary LN 0.2 mm – 2 mm</td>
</tr>
</tbody>
</table>

| N2: | 4 to 9 axillary lymph nodes or involvement of internal mammary node |

| N3: | 10 or more positive axillary nodes OR involvement of other nodes infraclavicular, supraclavicular, internal mammary node |

AJCC Breast 2018
Metastasis (M)

- Cancer has spread to distant sites
- Spread via lymphatics and vascular system
- Most common sites in breast cancer
  - Bone, lung, liver, brain

Biopsy for Confirmation of Metastasis

- Should be performed whenever possible
- ER/PR/HER2 should be repeated
- Caution needs to be taken with bone biopsies and potential false negative results
Metastatic Disease

- Initial diagnosis
  - Metastatic classification does not change regardless of response to neoadjuvant treatment
  - Development of metastatic disease after the start of treatment is considered disease progression

- Recurrent
  - Development of metastatic sites after original diagnosis does not change the original stage
  - If develop metastatic sites after original diagnosis considered recurrent Stage IV disease

AJCC Breast 2018

Metastases

- cM0
  - Radiologic evaluation (CT scan/bone scan/PET/CT) not necessary
    - Not warranted in asymptomatic T1/T2 N0 disease
  - Radiologic work varies by T and N
    - Mixed recommendations for T2N1 disease
  - Radiologic work should be based on level of suspicion
    - History, physical examination and labs

- M1
  - cM1
    - Clinical and/or radiologic evidence
  - pM1
    - Biopsy proven metastatic disease
    - Circulating Tumor Cells (CTC) are not considered M1 disease
Pathologic Response to Neoadjuvant Therapy

- Pathologic complete response (pCR) = improved disease free survival
- Pathologic complete response (pCR) = improved overall survival
- The pathologist measures the largest single focus of disease in breast and/or lymph node but should not include areas of fibrous tissue
- A “y” will be placed in front of the pathologic findings to indicate the patient received systemic treatment before surgery
- Example: ypT0 ypN0 = complete response (pCR)
- Example: ypT1 ypN1 = the amount of remaining disease in the breast/LN

Posttreatment Pathologic Stage

- If evidence of metastatic disease before systemic therapy remains as M1 if proceeds to surgery following systemic therapy
- If develops metastatic disease after the start of neoadjuvant therapy this is disease progression
For further details, the updated Breast Chapter for the 8th edition AJCC Cancer Staging Manual is available for download

https://cancerstaging.org/references-tools/deskreferences/Pages/Breast-Cancer-Staging.aspx
References


References


Continuing Education Credit

• For a listing of upcoming webinars:
  – Nurse.com/Webinars
  – ContinuingEducation.com
  – Search by your profession for webinars

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