OVERVIEW OF BREAST CANCER AND IMAGING MODALITIES USED IN SCREENING AND DIAGNOSIS

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GOALS

1. Provide an overview of breast cancer including the types and stages of breast cancer.

2. Review current clinical breast imaging modalities.

3. Discuss the role of breast imaging in breast cancer screening, diagnosis, staging, and management.
**BREAST CANCER FACTS**

- In 2015, an estimated 231,840 new cases of invasive breast cancer will occur among US women.
- There will be an estimated 40,290 breast cancer deaths in the same year.
- 1 in 8 US women will develop breast cancer during their lifetime.

**BREAST CANCER FACTS**

- Excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women.
- While less than 5% of all breast cancers occur in women under 40, and 17% occur in women during their 40’s, breast cancer is the leading cause of cancer death among women ages 20 to 59.

**BREAST CANCER SURVIVAL**

- Over the past three decades breast cancer survival has been steadily improving.
- The decrease in breast cancer death rates represents progress in earlier detection, improved treatment, and decreasing incidence.
- Survival continues to be largely related to the stage at diagnosis.
- Early detection remains key in reducing mortality.
**BREAST CANCER SURVIVAL RATES**

5-year Relative Survival Rate by Stage

- 0 100%
- I 100%
- II 93%
- III 72%
- IV 22%

- National Cancer Institute’s SEER database

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**BREAST CANCER RISK FACTORS**

- Breast cancer risk increases with age
- 17% of invasive cancers occur in women 40-49
- 78% of invasive cancers occurs after age 50
- Breast cancer tends to be more aggressive in younger women with higher mortality
BREAST CANCER RISK FACTORS
• Approximately 20-30% of breast cancer patients have a family member with breast cancer.

• 70-80% of breast cancer patients have no family history of breast cancer.

• The two main risk factors for breast cancer are:
  • Being female
  • Getting older

RISK FACTORS FOR BREAST CANCER
Strong risk factors ( > 4x Relative risk)
• Age > 65 years
• Genetic mutation carriers BRCA 1 or BRCA 2
• Personal history of breast cancer at < 40 years
• High risk finding on breast biopsy
• Mammographically dense breasts
• More than 2 first degree relatives with premenopausal breast cancer

CANCER RISK WITH BRCA GENE MUTATION
• Women who have a BRCA1/2 gene mutation have an increased risk of breast and/or ovarian cancer at a younger age.

Breast cancer risk:
• 55-65% with BRCA1
• 45 % with BRCA2

Ovarian Cancer risk:
• 39% with BRCA 1
• 11-17% with BRCA2
Increasingly breast cancer is considered to be not one disease, but a group of related diseases distinguished by different molecular subtypes, risk factors, clinical behaviors, and responses to treatment.

Heterogeneity of the disease leads to variations in tumor histology and growth patterns which causes significant imaging challenges.

No single imaging tool is effective for the detection of all types and stages of breast cancers.

**BREAST PATHOLOGY**

- Benign Lesions
- Risk Lesions
- Locally Aggressive Lesions
- **Malignant Lesions**
RISK LESIONS

Proliferative Lesions With Atypia

- Atypical ductal hyperplasia (ADH) 4 – 5x RR
- Atypical lobular hyperplasia (ALH) 4 – 5x RR
- Lobular Carcinoma In Situ (LCIS) 6 – 12x RR

TYPES OF BREAST CANCER

- Noninvasive – Cancer cells restricted to the lining of milk ducts.
- Invasive - Cancer cells have invaded through the duct wall to adjacent tissues thereby gaining access to lymphatics and blood vessels.

BREAST CANCER DEVELOPMENT

[Diagram showing stages of breast cancer development: normal duct, ductal hyperplasia, atypical hyperplasia, DCIS, invasive ductal carcinoma]
TYPES OF BREAST CANCER

- NONINVASIVE
  - DCIS – DUCTAL CARCINOMA IN-SITU
  - LCIS – NOT CURRENTLY CONSIDERED A TRUE BREAST CANCER

- INVASIVE
  - DUCTAL CARCINOMA
  - LOBULAR CARCINOMA
  - MIXED DUCTAL/LOBULAR
  - OTHERS-

DUCTAL CARCINOMA

- DCIS - Non invasive ductal carcinoma insitu

- IDC – Infiltrating ductal carcinoma

- Special Forms
  - Tubular,
  - Medullary,
  - Mucinous
**DUCTAL CARCINOMA INSITU**

- Ductal carcinoma insitu (DCIS) is a spectrum of abnormal cellular changes that start in the lining the breast ducts.

**Presentation**
- Asymptomatic (screening detected)
- Rarely bloody/clear nipple discharge or palpable lump
- Most often diagnosed because of microcalcifications detected on a screening mammogram.

**DUCTAL CARCINOMA INSITU**

- DCIS may or may not progress to invasive cancer, some tumors grow so slowly that even without treatment they would not affect a woman’s health.

- Studies suggest that at least one-third of DCIS cases will progress to invasive cancer if untreated.

- Identifying the subtypes of DCIS most likely to progress to invasive cancer is an active area of research.

**DUCTAL CARCINOMA IN SITU**

**SENSITIVITY**

- Mammography 70-80%
- Ultrasound <50%, more operator and scanner dependent
- MRI 88-95%
**INVASIVE DUCTAL CARCINOMA**

- Most common type of invasive breast cancer
- DCIS is nonobligate precursor
- Etiology unknown in the majority of cases
- 90% Sporadic, 10% Genetic (BRCA etc.)

**Clinical Issues**

- Suspect genetic/BRCA in < 40 y/o
- Tumor size and grade are predictors of mortality risk and of the risk of recurrence
- Screening significantly decreases stage at diagnosis
INVASIVE DUCTAL CARCINOMA NOS

LOBULAR CARCINOMA
- Noninvasive Lobular Neoplasia
  - ALH
  - LCIS
- Infiltrating Lobular Carcinoma
LCIS

- Lobular carcinoma insitu (LCIS) is not a true cancer or proven precancer, but an indicator of increased risk for developing invasive cancer.
- LCIS is associated with 6 – 12x increase in relative risk for future development of invasive breast cancer in either breast.
- No specific imaging findings, usually incidental finding on breast biopsy.

INFEKTITATING LOBULAR CARCINOMA

- ILC grows in linear "single file" fashion
- ILC is more clinically elusive because it may not incite a desmoplastic or inflammatory response.
- Early diagnosis may be difficult by physical exam and mammography
- Most common clinical presentation is a focal, hard, fixed mass.
- Often clinically occult until advanced
INVASIVE LOBULAR CARCINOMA

When compared to invasive ductal carcinoma (IDC):

- ILC has a higher tendency for multicentricity and bilaterality.
- Survival rates are similar between lobular and ductal cancers if detected at the same size and stage, however ILC tends to be diagnosed at more advanced stage than IDC.
- More likely to have positive surgical margins

INFLTRATING LOBULAR CARCINOMA

Mammographic Findings

- Spiculated mass
- Focal asymmetry
- Nearly 50% are missed by mammography at early stages
- Often underestimated in size
- Up to one third are bilateral requiring special attention to the contralateral breast

ULTRASOUND FINDINGS:

- 88% Sensitive, better than mammography
- Irregular mass with variable acoustic properties
- US may also significantly underestimate extent of disease
INFILTRATING LOBULAR CARCINOMA

MRI Findings:
• Most sensitive imaging modality for early detection of ILC
• Best tool for determining the extent of disease
• Best tool to identify multifocal, multicentric and bilateral disease

PET Imaging:
• High number false negative exams for both primary tumor and metastatic disease

INFILTRATING LOBULAR CARCINOMA

BREAST CANCER STAGING

Primary tumor (T):

Tis: Carcinoma in situ
T1: ≤ 2 cm
T2: >2 cm but ≤ 5 cm
T3: >5 cm
T4: Tumor of any size growing into the chest wall or skin including inflammatory breast cancer.
Lymph nodes (N)

N0: Negative lymph nodes.
N1: 1 to 3 positive AX LN, and/or IM LN
N2: 4 to 9 positive AX LN, and/or IM LN
N3: One of the following applies
   • >10 positive AX LN
   • Positive Infracavicular or Supraclavicular LN
   • Positive IM+AX LN

Metastasis (M):

M0: No distant metastasis
M1: distant metastasis

Stage 0: Tis, N0, M0
Stage I: T1, N0, M0
Stage IIA: T0, N1, M0 / T1, N1, M0 / T2, N0, M0
Stage IIB: T2, N1, M0 / T3, N0, M0
Stage IIIA: T0-2, N2, M0 / T3, N1-2, M0
Stage IIIB: T4, N0-2, M0
Stage IIIC: T0-4, N3, M0
Stage IV: T0-4, N0-3, M1
### Breast Cancer Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-Year Relative Survival Rate</th>
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<tbody>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>I</td>
<td>100%</td>
</tr>
<tr>
<td>IIA</td>
<td>92%</td>
</tr>
<tr>
<td>IIB</td>
<td>81%</td>
</tr>
<tr>
<td>IIIA</td>
<td>67%</td>
</tr>
<tr>
<td>IIIB</td>
<td>54%</td>
</tr>
<tr>
<td>IV</td>
<td>20%</td>
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### Breast Cancer Screening

**Justification for Screening**

- The cause of breast cancer is unknown and wide scale prevention is not currently an option.
- Current evidence strongly supports that breast cancer is confined to the breast for a period of time prior to the development of systemic disease.
JUSTIFICATION FOR SCREENING

- Breast Cancer has a preclinical phase (Sojourn time) before the cancer can be detected by physical exam or causes symptoms.

- If detected during this Sojourn time there is a high probability of complete cure.

- Breast cancer in younger women has a shorter sojourn time, therefore screening intervals must be appropriate to provide optimal benefit.

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BREAST IMAGING MODALITIES

**Screening**
- Mammography
- Ultrasound
- MRI
- Nuclear (BSGl)

**Diagnosis/Staging**
- Mammography
- Ultrasound
- MRI
- CT/PET
- Nuclear Sentinel node localization
- Galactography
- Nuclear (BSGl)
RADIOGRAPHIC DENSITY OF THE BREAST
BI-RADS LEXICON

1. The breast is almost entirely fat
2. There are scattered fibroglandular densities that could obscure a lesion on mammography
3. The breast is heterogeneously dense which may lower the sensitivity of mammography
4. The breast is extremely dense, which significantly lowers the sensitivity of mammography

SENSITIVITY OF SCREENING MAMMOGRAPHY

<table>
<thead>
<tr>
<th></th>
<th>SFM</th>
<th>FFDM</th>
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<tbody>
<tr>
<td>Fatty Breast</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Dense Breast</td>
<td>&lt;50%</td>
<td>65%</td>
</tr>
</tbody>
</table>

* FFDM has approximately 15% increased sensitivity in dense breast
THE EFFECT OF BREAST DENSITY ON IMAGING STUDIES

Most effected
• Mammography

Less effected
• Sonography
• MRI
• BSGI/MBI

SCREENING MAMMOGRAPHY GUIDELINES

• Current recommendations from the American Cancer Society (ACS), Society of Breast Imaging (SBI) and the American College of Radiology (ACR) on breast cancer screening:
  • Annual breast cancer screening should begin at age 40 and earlier in high-risk patients.
  • Recommend appropriate utilization of additional medical imaging modalities such as magnetic resonance imaging (MRI), and ultrasound for breast cancer screening.
ACR/SBI RECOMMENDATIONS FOR SCREENING PRIOR TO AGE 40

- BRCA1 or BRCA2 mutation carriers
- Women with mothers or sisters with pre-menopausal breast cancer
- Women with a greater than 20 percent lifetime risk for breast cancer on the basis of family history (both maternal and paternal)
- Women with histories of chest radiation prior to age 30
- Women with biopsy-proven ALH, ADH, DCIS, invasive breast cancer, or ovarian cancer regardless of age.

*Initiate screening by age 30 but not before age 25

MAMMOGRAPHY

- Only imaging modality currently approved for general population screening
- Sensitivity 98% in fatty breast, < 50% in dense breast
- 10-15% of palpable breast cancers occult on mammogram

CHARACTERISTICS OF MALIGNANCY

Mammography
- Spiculated or ill-defined mass
- Round to oval masses with variable margin types
- Malignant microcalcifications
- Architectural distortion
- Neodensity
- Parenchymal Asymmetries
ACCURACY OF MAMMOGRAPHY

- Sensitivity 80-90%
- False negative rate in patients with a palpable mass (Diagnostic setting) 10-15%
- False negative rate of 8-10% in screening setting with an average delay in diagnosis of 45 weeks
- Positive predictive value 25-45%

MAMMOGRAPHY

Advantages:
- Widely available
- Relative low cost
- Proven mortality reduction
  - 44% reduction in mortality Swedish Trial
  - 40% reduction in mortality Canadian trial

Disadvantages:
- Radiation Exposure
- Compression
- False positives/negatives
- Patient recalls
- Sensitivity decreases with increased breast density
LIMITATIONS OF MAMMOGRAPHY

- 1000 SCREENED
- 70-100 RECALLED
- 20 BIOPSIED
- 12-15 BENIGN FALSE POSITIVE
- 5-8 CANCERS FOUND
- 1 CANCER MISSED

3D TOMOSYNTHESIS COMPARED TO 2D MAMMOGRAPHY

- 15% decrease in recall rate
- 21% increase in PPV for biopsy
- 29% increase in breast cancer detection
- 41% increase in detection of invasive cancer
- No change in DCIS detection rate


ULTRASOUND

- Primary adjunctive test to diagnostic mammography
- Not significantly limited by breast density
- Operator dependent modality requiring significant experience, optimal technique and equipment
- Physicians performing breast ultrasound must have good mammography skills in order to correlate findings
**DIAGNOSTIC BREAST ULTRASOUND PERFORMANCE**

- IDC – 96% sensitive vs. 84% for mammography
- ILC – 88% sensitive vs. 52% for mammography
- DCIS – less sensitive than mammography, < 50% sensitivity if compared to MRI

**ULTRASOUND**

**Advantages:**
- No radiation
- Widely available
- Low cost

**Disadvantages:**
- Operator dependent
- Less reproducible

**SCREENING BREAST SONOGRAPHY**

- Meta-analysis of 7 studies using supplemental screening US in high risk women with dense breasts
  - 60-100% increase in cancer detection rate
  - 3-4 cancers per 1000 average risk women
  - 4-13 cancers per 1000 high risk women
  - 3% risk of US induced biopsy
  - 8-11% PPV of biopsy recommendation
  - 4x more false positive exams
DYNAMIC CONTRAST ENHANCED BREAST MRI
MRI CHARACTERISTICS OF MALIGNANCY

Morphology
• Mass enhancement
  • Evaluation of shape, margins and internal enhancement characteristics
• Nonmass enhancement
  • Focal, linear, ductal

Contrast Enhancement Kinetics
• Rate of initial rise and washout
• 90% of IDC have rapid, and intense contrast enhancement with variable degrees of washout
• Low grade cancers demonstrate slower less intense enhancement with slower washout

ENHANCEMENT CURVE ANALYSIS
BREAST MRI

Advantages:
- Nearly 100% sensitive for invasive cancer
- 40-90% Sensitive for DCIS depending on grade
- High specificity for invasive cancer, lower for DCIS

Disadvantages:
- High cost requiring dedicated coils and software
- Contrast risks including rare allergic RXN or Renal function limitations

MRI INDICATIONS

PREOPERATIVE INDICATIONS

- Best imaging modality for determining local extent of disease.
- Preoperative MRI reduces reexcision and recurrence rates
- Most effective evaluation for synchronous multifocal, multicentric (11-31%) or bilateral cancer 3-10%
- Evaluate for skin or nipple/areolar involvement
- Pectoral or chest wall involvement
- Evaluation of pathologic nipple discharge
MRI INDICATIONS

POSTOPERATIVE INDICATIONS

• Localize residual disease with positive surgical margins
• Recurrence surveillance after breast conserving surgery, differentiation of scar vs. recurrent tumor

MAGNETIC RESONANCE IMAGING

OTHER INDICATIONS

• High Risk Screening
  • BRCA 1/2 mutation carriers
  • Following high risk biopsy ADH/ALH/LCIS
  • High risk patients > 20% lifetime risk
  • Monitoring neoadjuvant chemotherapeutic response

ACRIN 6666

Breast MRI performed following 3 rounds of annual Mammographic and US screening

Round 1: Mammo found 7.5/1000, US found 5.3/1000 additional cancers

Round 2+3: Mammo found 8.1/1000, US found 3.7/1000 additional cancers

MR performed after round 3 found 14.7/1000 cancers. 4X more than adding US to to annual Mammogram

Berg, WA et al JAMA 2012;307(13):1394-1404
SENSITIVITY OF BREAST IMAGING MODALITIES USED FOR SCREENING HIGH RISK PATIENTS


<table>
<thead>
<tr>
<th>MODALITY</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>MAMMOGRAPHY</td>
<td>13-40%</td>
</tr>
<tr>
<td>ULTRASOUND</td>
<td>13-33%</td>
</tr>
<tr>
<td>MRI</td>
<td>71-100%</td>
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MRI finds 2-3 times more cancers than Mammography or US

PET/CT

- FDG PET is not indicated or approved by Medicare for use in the initial diagnosis of primary breast cancer.

- FDG PET is an adjunct to standard imaging modalities for staging patients with distant metastasis, or restaging patients with locoregional recurrence or metastasis.

- Monitoring treatment of a breast cancer when a change in therapy is contemplated as an adjunct to other imaging modalities.
PET/CT

Advantages:
• Sensitive in the evaluation of advanced locoregional and metastatic breast cancer and evaluation of response to treatment of advanced breast cancer

Disadvantages:
• Not appropriate for use initial diagnosis of breast cancer
• Cost
• Radiation exposure

MOLECULAR BREAST IMAGING

Molecular breast imaging (MBI) also referred to as Breast Specific Gamma Imaging (SBGI) is a nuclear medicine examination utilizing IV injection of Tc-99m Sestamibi and imaging of the breasts using a high resolution gamma camera.
**MBI Procedure Overview**

- Patient receives a low dose injection of a radiotracer (e.g. Tc-99m Sestamibi)
- The tracer preferentially accumulates in cancer cells and is not influenced by breast density
- The breast is minimally compressed between two digital gamma cameras
- Imaging starts minutes post injection; acquires standard CC and MLO views of each breast (same as mammography)
- Images are presented in the same format as mammography making it easy to compare.

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**2 Commercial Dual-Head MBI Systems**

- Both are FDA 510(k) cleared
- Both are dual head & use CZT detectors

- **Gamma Medica LumaGEM**
- **GE Healthcare Discovery NM750b**

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**Cadmium Zinc Telluride CZT SEMICONDUCTOR DETECTORS**

- Gamma energy directly converted to electron hole pairs.
- Electron hole pairs channeled to electronics by applying external voltage.

- CZT + ASIC detector module
  - 1" square detector
  - 16 x 16 independent pixels

- Application specific integrated (ASIC) circuit electronics process each pixel independently.

Courtesy: Gamma Medica Inc.
CLINICAL CASE

• 53 y/o female with dense mammogram presented for additional screening
• Mammogram is dense but interpreted as negative
• MBI shows intense focal tracer accumulation at 2 o’clock
• Targeted ultrasound reveals a correlative suspicious solid mass
• Subsequent US guided biopsy shows invasive ductal carcinoma
• MBI, ultrasound and biopsy all done at the same visit
MBI STUDY ( AJR 2015, N=1585): LOW-DOSE SCREENING

- Prospective screening study comparing MBI and mammography
- Criteria for inclusion: Breast density alone
- 21 cancers found in 1585 women
- MBI identified 17 while mammography only visualized 5
  - Of 14 cancers detected on MBI alone, 11 were invasive
  - Of the 11 invasive cancers only seen on MBI, 9 were node-negative
- Additional 8.8 cancers per 1000
  - CDR for mamm= 3.2 per 1000
  - CDR for MBI + mamm= 12.0 per 1000


MBI STUDY ( AJR 2015, N=1585): LOW-DOSE SCREENING

- False Positive Rate = 6.5%

- 4 False Negatives (0.25% FN rate, 0.13% combined with mammography):
  - 2 detected on Mammo (DCIS, 5mm & IDC 3mm);
  - 2 interval cancers (Both multifocal ILC under 1 cm)
    * one found at mastectomy
    * one found on MRI


AJR 2015: TRUE POSITIVE CASE

Mammographically occult invasive lobular carcinoma

- 54-year-old woman
- Screening mammography interpreted as negative.
- MBI image interpreted as multifocal area of radiotracer uptake
- Pathology was multifocal node-negative grade I invasive lobular carcinoma more than 4 cm in extent
### MBI

**Advantages:**
- High sensitivity 90%
- High specificity 85%
- High negative predictive value 98%
- Low false positive

**Disadvantages:**
- Requires new capital purchase
- Radiation exposure
- Integration into existing breast centers
- Image guided biopsy