Clinical Aspects of Breast Disease:

Cases

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March 2019

Better early detection
Better treatments
Less post-menopausal HRT

Case 1: DM

- DM is a 52 yo premenopausal female who underwent a routine screening mammogram which showed increasing calcifications in the L breast.
- Menarche: 11
- G3P3
- Age of first live birth: 21
- Mother: Breast, dx age 63, died age 65
- No masses are noted on PE
- Needle biopsy of calcifications shows atypical ductal hyperplasia (ADH)
- She undergoes a lumpectomy. Final pathology confirms ADH only.
- She presents to you for an opinion
Breast Cancer Risk Factors

- Increasing Age
- Female gender
- Family history of breast cancer
- Genetic predisposition
- Prior personal history of breast cancer
- Increased estrogen exposure
  - Early menarche (<12)
  - Late menopause (>50)
  - Hormone replacement therapy
- Nulliparity or 1st pregnancy after age 30
- Lack of breastfeeding
- Diet and lifestyle (obesity, excessive alcohol consumption)
- Radiation exposure before age 40
- Mammographic density
- Prior benign or premalignant breast changes
  - In situ cancer - Ductal carcinoma in situ (DCIS) or Lobular carcinoma in situ (LCIS)
  - Atypical hyperplasia - ductal (ADH) or lobular (ALH)

Hormonal Contraceptives & Risk of BC

- Prospective cohort study
- Current or recent hormonal contraception associ with a RR 1.20
- RR 1.09 for <1 yr of use to RR 1.38 with >10 yrs of use
- Overall absolute increase among current and recent users was 13/100,000 person years or 1 extra BC for every 7690 women using hormonal contraception x 1 year

Breast Cancer Risk Factors
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What breast cancer prevention options are available to her?

SERMS
Aromatase Inhibitors

Selective Estrogen Receptor Modulators (SERMS): Tamoxifen and Raloxifene

- FDA approved to reduce breast cancer risk
- Interact with the ER
- Estrogen agonistic and antagonistic properties based on specific tissue target and hormonal milieu
- Both can reduce risk of developing invasive breast cancer by 50% when taken daily x 5 years

Side Effects of Tamoxifen

- Hot flashes or sweats
- Anti-estrogenic against breast cancer
- Reduces cholesterol
- Uterine stimulation, bothersome GYN side effects
- Uterine Cancer
- Maintains bone density
- RALOXIFENE: LESS RISK OF UTERINE CA AND THROMBOEMBOLISM
- Increase risk of thromboembolism

Recommendations for Chemoprevention

- United States Preventative Services Task Force (USPSTF): Clinicians discuss chemoprevention with women at high risk of developing breast cancer who are at low risk for adverse effects
- Tamoxifen and Raloxifene are FDA-approved to reduce breast cancer risk in women at higher risk of developing breast cancer (LCIS, atypia, elevated Gail score)
- Raloxifene is approved in postmenopausal women only

Aromatase Inhibitors in Prevention

53-65% reduction in breast cancer incidence vs placebo
Not yet FDA approved
DM follow up

- DM agreed to tamoxifen use and tolerated 5 years of treatment well.
- She continues to monitored with yearly mammograms.

Bottom Line

- Breast cancer is the most commonly diagnosed cancer in American women; survival improving with time
- Know risk factors for breast cancer
- Atypical hyperplasia and in-situ cancers (DCIS, LCIS) are associated with increased risk of developing invasive breast cancer
- Tamoxifen and raloxifene are medications are FDA approved to reduce risk of developing breast cancer. The aromatase inhibitors may be approved in the future

Case 2: BU

- BU is a 61y female who underwent a routine yearly screening mammogram. She is ASYMPTOMATIC, does not have any palpable breast masses. Mammogram showed an area of architectural distortion in the L breast.
- A 0.9 X 1.0 X 0.6 CM corresponding lesion was seen on US.
- Menarche:12
- G3P3
- Age of first live birth:23
- Menopausal state: Post
- No FH
- +HRT on study at Rush, stopped 2002
- No palpable abnormalities were noted on exam
BU

- She undergoes a needle biopsy confirming cancer followed by a lumpectomy, SLN procedure.
- Final Pathology: Infiltrating Ductal Carcinoma*, grade 1, 0.9cm, 0/3 SLN involved, ER+ (Allred 8), PR+ (Allred 8), HER2 negative
- She receives adjuvant radiation therapy
- She is counseled about adjuvant chemotherapy and endocrine therapy.

BU Questions

- Does screening mammography save lives?
- What impact did her HRT have on her risk of developing breast cancer?
- What treatment options are available for her?

Breast Cancer Screening:
Mammography
Do Screening mammograms save lives?

- No. Mammography in age 40-59 does not save lives and associated with over-diagnosis.
- Conflicting data, old studies, 30+ years
- Imaging techniques have improved; current estimates not accurate
- Breast cancer treatments have improved; early detection less important
- Benefits, harms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ages 40-49 years</th>
<th>Ages 50-59 years</th>
<th>Ages 60-69 years</th>
<th>Ages 70-74 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Deaths Avoided per 10,000</td>
<td>3 (0-9)</td>
<td>8 (2-17)</td>
<td>21 (11-32)</td>
<td>13 (0-32)</td>
</tr>
</tbody>
</table>

Screening mammography in women aged 40-74 years: Benefits

- Reduction in breast cancer mortality
  - women aged 40 to 49 years benefit the least
  - women aged 60 to 69 years benefit the most

Screening Harms:

- Overdiagnosis and overtreatment:
  - Finding a (non)invasive breast cancer that would otherwise not have become a threat to a woman’s health, or even apparent, during her lifetime
- False-positive results:
  - Increase medical, financial, psychological costs.
- False-negative results:
  - may provide false reassurance.
- Radiation-induced breast cancer (rare)
US Preventive Services Task Force (USPSTF) Recommendations 2016

<table>
<thead>
<tr>
<th>Population</th>
<th>Women aged 40-49 years</th>
<th>Women aged 50-74 years</th>
<th>Women aged ≥ 75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>The decision to start screening should be an individual one. Grade: C</td>
<td>Screen every 2 years. Grade: B</td>
<td>No recommendation. Grade: I statement (insufficient evidence)</td>
</tr>
</tbody>
</table>

Grade A: The USPSTF recommends the service. There is high certainty that the net benefit is substantial.

Grade B: The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is substantial.

Grade C: The USPSTF recommends selectively offering or providing the service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.

Grade D: The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

Grade I: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

2015 American Cancer Society (ACS) Update

- Screening mammogram starting at age 45 (strong recommendation)
- Women aged 45-54 should be screened annually (qualified recommendation)
- Women >55 should transition to biennial screening or continue annual screening (qualified)
- Women should have opportunity to begin annual screening between ages 40-44 (qualified)
- Women should continue screening as long as overall health is good and have a life expectancy of 10+ years (qualified)
- CBE not recommended (qualified)

ACS and USPSTF 2015 Breast Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>Mammography Screening Parameter</th>
<th>ACS Recommendation</th>
<th>USPSTF Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting age, years</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Screening frequency</td>
<td>Annually to age 54 years then biennially</td>
<td>Biennially</td>
</tr>
<tr>
<td>Stopping age, years</td>
<td>As long as healthy and with life expectancy of at least 10 years</td>
<td>75</td>
</tr>
<tr>
<td>Total lifetime mammograms if screening continued to age 74 years, number</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Lifetime risk of dying from breast cancer, %</td>
<td>1.9-2.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Lifetime risk of dying from breast cancer with no screening is 2.7%
Mammographic Screening

**Bottom Line:**
- Asymptomatic Women
- Frequency and when to start and stop screening are controversial
- At least biennial mammography between ages 55-74 is agreed upon by most health agencies

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What impact did her HRT have on her risk of developing breast cancer?

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Women’s Health Initiative: Continuous combined E + P vs placebo

- Study discontinued early (7/2002) because of increased risk of breast cancer, CHD, stroke, and VTE
- HR for breast cancer: 1.24 (95% CI 1.01-1.51)
- Cancers developed in E+P arm associated with larger primary and more LN positivity compared to placebo
- Reduced risk of colon cancer (HR 0.56, 95% CI 0.38 to 0.81) but cancers were more advanced
- Reduced rate of fractures

Rossouw JE et al., JAMA 2002
What treatment options are available for her?

A Multi-Disciplinary Approach

**Surgery**

**Modified Radical Mastectomy** vs. **Breast Conserving Surgery**

Likelihood of Cure is the Same !!!

**Sentinel Node Biopsy**

- Less invasive
- Fewer complications
- More accurate
Radiation Therapy

- Needed if breast conserving therapy has been performed
- Daily x 3-6 weeks
- Side effects: Short and long term

Medical Oncology

- Prognosis:
  - Tumor size
  - LN involvement*
  - Tumor grade
  - Lymphovascular invasion
  - ER status**, HER2 Neu status**
  - Other molecular tests – Oncotype, Mammaprint
- Treatment options: Endocrine Therapy, Chemotherapy

  * Single most important factor?
  **Also predictive of therapy benefit

Goals of Adjuvant Therapy

- Reduce burden of clinically undetectable, distant micrometastatic disease
- Improve relapse-free survival
- Improve overall survival
Adjuvant Endocrine Treatment

Tamoxifen

- Standard agent used in pre and post-menopausal women with ER/PR positive tumors
- Decreases risk of tumor recurrence by approximately 50%
- Risk of endometrial cancer and blood clots
- *Raloxifene is not FDA approved for breast cancer treatment, FDA approved for prevention and osteoporosis

Aromatase Inhibitors

- Anastrozole, Letrozole, Exemestane
- Blocks aromatase enzyme in the final step of estrogen biosynthesis (adipose tissue)
- Blocks conversion of androgens (androstenedione and testosterone) to estrogens (estrone and estradiol)
- Effective only in postmenopausal women
- Side effects: Arthralgias, bone loss
**Duration of Therapy**

- Tamoxifen: 5 vs 10 years
- Aromatase Inhibitor: 5 years vs 10 years

**Adjuvant Chemotherapy**
Absolute survival gain

- Short term toxicities: Hair loss, N/V
- Anemia, risk of infection
- Premature menopause, infertility
- Cognitive dysfunction
- Cardiac dysfunction
- Acute leukemia/MDS

 BENEFIT/HARM RATIO OF ADJUVANT CHEMOTHERAPY

Estimate Risk

Pop Culture Question

- What illness did this celebrity develop as a consequence of her adjuvant chemotherapy for breast cancer?
- Myelodysplastic Syndrome (MDS), BMT 2012

Adjuvant Chemotherapy

- Administration of chemotherapy reduces recurrence rates by 30%, decrease mortality by 20%
- Optimal duration of adjuvant chemo is 3 – 6 months
- Typical agents: Adriamycin, cyclophosphamide, taxanes, trastuzumab if HER2+
- Benefit is in addition to hormonal therapy
- Must weight potential benefits and side effects (short and long term)
BU Follow Up

• Her prognosis was determined to be excellent given the small tumor size without LN involvement, strong ER positivity, low grade.
• Because her tumor is ER+, she is being treated with adjuvant endocrine therapy only.
• She is doing well on anastrozole.

Bottom Line

• Treatment of early stage breast cancer requires a multi-disciplinary approach
• Treatment may include: surgery, radiation, hormonal therapy if the tumor is ER+, chemotherapy, trastuzumab if HER2+.
• Hormonal therapy:
  – AIs work only in postmenopausal women.
  – Tamoxifen works in pre- and postmenopausal women.
• Potential benefits and side effects of adjuvant treatment must be balanced.

TS

• TS is a 29 yo AAF who presents with a R breast mass
• She presents to you, her PCP
• What are the most common palpable masses in young women?
• What is the work up for a palpable breast mass?
Palpable masses in young women

• Fibroadenoma*
• Breast Cyst
• Intraductal papilloma
• Lipoma
• Abscess or mastitis
• Hematoma
• Fat necrosis
• Cancer

*most common

Work Up of a Breast Mass: History

• Location of mass
• How it was first noted (accidentally, by breast self-examination, clinical breast examination, or mammogram)
• How long it has been present? Change in size?
• Presence of nipple discharge? Character of discharge?
• Any change in breast appearance? Nipple inversion?
• Whether the lump waxes and wanes at times in the menstrual cycle
• Pt’s reproductive history, last menstrual cycle, history of HRT?
• Family history of breast cancer

Work Up of a Breast Mass: Physical

• Inspection and palpation
• Breast exam includes the neck, supraclav, chest wall, both breasts, and axillae
• Examination supine and erect
• Characteristics of a malignant mass:
  – Single lesion
  – Hard
  – Immovable
  – Irregular borders
  – Size ≥2 cm
TS History

• Accidentally noted a R breast mass located UOQ x 1 year. Increase in size noted. There is no nipple discharge.
• Menarche: 13
• G8P3 (2 miscarriages, 3 abortions)
• Age of first live birth: 18

TS History

• Family History:
  • Maternal GM: Breast ca, dx 30s. Ovarian cancer
  • Mother: Breast ca, dx 40s
  • Sister: Breast ca, dx 46
  • First Cousin: Breast ca, ca age 34, BRCA1 mutation carrier
  • Maternal Uncle: Colon ca, dx age 52

PE

• PE: No asymmetry of breasts noted. No nipple retraction, erythema, skin thickening. A firm 2cm R breast mass was noted in the UOQ*. No palpable R axillary LN, no supraclav nodes.

*most common location for ca
What additional work up should be ordered?

Work Up of a Breast Mass

• DIAGNOSTIC Mammogram
• If patient <30 without FH, has exam clinically consistent with a benign lesion, may consider ultrasound
• Palpable masses should never be dismissed because imaging is negative, young age, male gender, or lack of risk factors if mass is discrete or suspicious
• Refer to breast surgeon for biopsy if any doubt

TS

• Diagnostic Mammogram shows a 2cm spiculated mass
• US confirmed a 1.7cm irregular hypoechoic mass
• What needs to be done now?
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TS

• Breast Biopsy:
• Positive for grade 3 infiltrating ductal carcinoma, ER-, PR-, Her2-.

TS: Is her FH concerning?

Pop Culture Question #2

• What celebrity revealed in a NY Times Op Ed on May 13, 2013 entitled “My Medical Choice” that she carried a BRCA1 gene mutation and underwent bilateral risk reducing mastectomy?

BRCA testing increased 64% after publication
Desai, S. BMJ 2016

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Genetics and Breast Cancer

BRCA1 and BRCA2

- Tumor suppressor genes; BRCA1 identified in 1994, BRCA2 identified in 1995
- Both men and women carry copies of these genes
- Autosomal dominant inheritance, passed via maternal or paternal allele
- Mutations in these genes (loss of function) increase cancer susceptibility. Cancer arises when both alleles are inactivated or defective.
- BRCA1 and BRCA2 encode proteins that are required for repair of certain kinds of DNA damage.

Features That Indicate Increased Likelihood of Having BRCA Mutations

- Multiple cases of early onset breast cancer (<50 years)
- Ovarian cancer (with family history of breast or ovarian cancer)
- Breast and ovarian cancer in the same woman
- Bilateral breast cancer
- Ashkenazi Jewish heritage
- Male breast cancer
BRCA1-Associated Cancers
Lifetime Risk

Breast cancer 50%-85% (often early age at onset)
Second primary breast cancer 40%-60%
Ovarian cancer 15%-45%
Possible increased risk of other cancers (eg, prostate, colon)

BRCA2-Associated Cancers
Lifetime Risk

Breast cancer (50%-70%)
Male breast cancer (6%)
Ovarian cancer (10%-20%)
Increased risk of pancreatic (6%), prostate, laryngeal, and other cancers

TS Follow Up
• TS tested positive for the BRCA1 mutation.
• She underwent bilateral mastectomy with reconstruction.
• She did not consider fertility preservation.
• She completed adjuvant chemotherapy.
• Because her tumor is ER−, she did not receive adjuvant hormonal therapy.
TS Follow Up

- Counseled about oophorectomy given BRCA mutation
- Pregnancy
- Agreed to oophorectomy at age 35, doing well 9 years post-diagnosis
- Survivorship
  - 2.6 million breast cancer survivors in the US
  - Focus on quality of life, fertility preservation, employment, access to healthcare

Bottom Line

- Know differential for a palpable breast mass
- Work up for a breast mass includes a good H&P, possible imaging (Mammography or US) and biopsy.
- Get a good FH and refer patients who you suspect of having a hereditary breast/ovarian ca syndrome for genetic counseling before testing.
- BRCA 1/2 are tumor suppressor genes; mutations in these genes are assoc with breast and ovarian ca. BRCA 2 also assoc with male breast ca and pancreatic ca. Mutations may be more prevalent in certain populations.

JV

- JV is a 62 yo who noted a red rash on her R breast
- She was admitted with R breast swelling, warmth and redness
- Menarche:11
- G3P3
- Age of first live birth:23
- On examination, there was marked ulceration of the R breast with a palpable LN in the R axilla.
- Questions:
  - What’s the differential?
  - What imaging would you order?
DDx: Red Breast

- Mastitis
  - Breastfeeding
  - S. Aureus
- Paget’s Disease of the Breast
- Inflammatory breast cancer

DDx: Red Breast

- Mastitis
- Paget’s Disease of the Breast
  - Eczematous patch on nipple
  - Suggests underlying cancer
- Inflammatory breast cancer

DDx: Red Breast

- Mastitis
- Paget’s Disease of the Breast
- Inflammatory breast cancer
  - Peau d’orange
  - Neoplastic cells block lymphatic drainage
**Inflammatory Breast Cancer**

- Swollen erythematous breast
- Underlying invasive carcinoma is generally poorly differentiated, obstructs dermal lymphatic spaces
- Many are metastatic at diagnosis; the overall 5-year survival is less than 50%, lower in those with metastatic disease at diagnosis.
- About half express ER and 40% to 60% overexpress HER2.

**JV**

- Mammogram was unable to be performed
- US showed a 3.5cm mass at 7 o'clock with a prominent LN
- CT scan showed bilateral lung nodules, mediastinal, hilar and axillary adenopathy, and liver lesions
- Bone scan showed rib and scapular lesions
- What additional test would you order?

**JV**

- Breast biopsy was positive for Infiltrating Ductal Carcinoma, grade 3, ER-, PR-, HER2+ (overexpressed).
- Skin biopsy positive for dermal lymphatic infiltration.
- Physical exam and pathology suggestive of Inflammatory Breast Carcinoma
- She is seen for a second opinion, wondering if she should be treated at all. She is c/o breast pain requiring opioids, swelling. Exam notable for ulceration of skin with oozing of serosanginous fluid.
Metastatic Breast Cancer

• MBC is incurable
• *Bone, lungs, liver, brain are common sites of metastasis
• Median survival of pts with metastatic disease is over 2 years!
• 22% of metastatic breast ca patients are alive at 5 years
• Goals: Palliate or delay symptoms, increase survival
• Balance toxicity of therapy with its benefits
• Enroll onto clinical trials if possible

BENEFIT/HARM RATIO OF PALLIATIVE CHEMOTHERAPY FOR METASTATIC DISEASE

- Improved PFS, OS
- Improvement of breast wound and pain

- Estimate Risk
- Fatigue, hair loss
- Risk of Infection, anemia
- Travel to and from treatment
HER2Neu+ Breast Cancer

- HER2Neu amplified breast cancer are more aggressive, carry worse prognosis
- Trastuzumab (Herceptin): Monoclonal antibody targets the HER2 Neu protein
- Improves survival in patients with metastatic and early stage disease
- Well tolerated, CHF in 1-4% of patients

JV Follow-Up

- Because JV's tumor is ER-, she was encouraged to consider palliative treatment with paclitaxel chemotherapy and trastuzumab
- Breast pain disappeared after first treatment with paclitaxel and trastuzumab.
- Pt had an excellent response to chemo/trastuzumab. Lung, liver, adenopathy disappeared. Maintained on trastuzumab only.
- Developed CNS metastasis 1 yr after diagnosis.
- Palliative whole brain radiation therapy.
- Died 17 mo after diagnosis of metastatic disease

HER2Neu+ Breast Cancer

- New agents:
  - Lapatinib, FDA approved 2007
  - Pertuzumab, FDA approved 2012
  - Ado-trastuzumab, FDA approved 2013
  - Neratinib, FDA approved 2017
Bottom Line

• Metastatic breast cancer is incurable
• Goals of treatment are to palliate, improve QOL, improve survival
• Cytotoxic treatment can be palliative
• Need to know ER, PR and HER2Neu status to help guide breast cancer therapy
• New treatments – enroll patients onto clinical trials

Special thanks to Dr. Kamran Mirza for his histological pictures.