OVER-DIAGNOSIS OF BREAST CANCER

Hannah W. Hazard, MD FACS
Department of Surgery Grand Rounds
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OVERVIEW

• Introduction
• Screening Practices and Recommendations
• Treatment of Breast Cancer
• Over-diagnosis of breast cancer
• Next steps?
IMPACT

• 1 in 8 women diagnosed with breast cancer (12%)
• 2.8 million breast cancer survivors
• 2014 estimates from the ACS
  – 232,670 new cancers
    • 62,570 will be in situ
  – 40,000 will die from breast cancer
• 2\textsuperscript{nd} leading cause of cancer death
  – 1 in 36 women
SCREENING PRACTICES

- Various screening modalities make it all more confusing
  - Digital mammogram
  - Tomosynthesis
  - MRI
  - Screening US

- Variable depending on the organization making the recommendation

- Confusion for patients and physicians
CURRENT GUIDELINES

Group
• American Cancer Society
• American College of Surgeons
• USTF

Recommendation
• Yearly starting at 40
• Supports ACS
• Biennial between 50-74 yo

Average Sensitivity-80% (variability based on age, density, etc) Thus a 20% false negative mammography rate
CURRENT TREATMENT RECOMMENDATIONS - SYSTEMIC

- Duration from 6 months to 5 (10) years – The longer the therapy the better
- Recommendations are dependent on various factors
  - Estrogen receptors / Progesterone receptors
  - Her-2/neu (0-3+)
  - Stage
  - Age and comorbid conditions
  - Genetic profile of the tumor (Oncotype, Mammoprint, etc)
CURRENT TREATMENT RECOMMENDATIONS - SYSTEMIC

• Chemotherapy
  – Usually Adriamycin based
  – 4-8 cycles depending on regime

• Anti-hormonal therapy (ER/PR)
  – ER/PR positive tumors only
  – SERM vs. AI
    • SERM only possibility for pre-menopausal women (Tamoxifen)
    • AI for pre or postmenopausal women with invasive cancers only

• Biologic agents (Her-2)
  – Invasive cancers only
  – Duration of one year
CURRENT TREATMENT RECOMMENDATIONS – SURGICAL

Primary Tumor
• Breast Conservation v. Mastectomy
  – Stage (ie no T4)
  – Tumor/breast ratio
  – Patient preference
  – Will they get XRT?
  – Cosmesis

Nodal Evaluation
• No SLN / SLN / ALND
  – DCIS v. Invasive cancers
  – Overall pt comorbidities
  – Known axillary disease?
• SLN
  – Invasive cancers
  – DCIS only if getting a mastectomy or discordant path
• ALND
  – Known disease in axilla that is bulky
  – Positive frozen SLN on mastectomy
CURRENT TREATMENT RECOMMENDATIONS - RADIATION

• Indications
  – Post Lumpectomy
    • Almost always – should be though of hand and hand
    • May avoid in the very elderly, significant pulmonary disease, severe co-morbidities
  – Post Mastectomy
    • Tumors ≥ 5cm (T3) or inflammatory BCA/chest wall invasion (T4)
    • ≥ 4 nodes positive (N2) – moving target with great indication for 1-3 nodes
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• Whole Breast
  – Standard
    • About 6 weeks
  – Hypofraction (Canadian)
    • About 2.5-3 weeks

• Partial Breast
  – Mammosite
  – External beam

• Intra-operative
  – Coming soon to the OR
  – One time dose lasting 25-45 minutes
    • Done before closing
OVER-DIAGNOSIS

• Defined as the diagnosis of a neoplasm that never would have clinical significance
  – Could be DCIS in the healthy?
  – Could be invasive in those with poor health and limited survival due to co-morbid conditions?

• Trick is how to tell and how often it really occurs……
ASSESSING FOR OVER-DIAGNOSIS

• Ideally we would compare two populations that only differed by screening v. no screening
  – Does not exist
  – Estimated range in literature 0-54%

• Autopsy studies

• Population based studies
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Invasive (%)</th>
<th>In situ (%)</th>
<th>Age 40-70</th>
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<tbody>
<tr>
<td>VA, 1973</td>
<td>70</td>
<td>1.4</td>
<td>4.3</td>
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<tr>
<td>CA, 1975</td>
<td>67</td>
<td>0</td>
<td>4.5</td>
<td>10 % (DCIS)</td>
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<tr>
<td>Denmark, 1984</td>
<td>77</td>
<td>1.3</td>
<td>14.3</td>
<td>n/a</td>
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<tr>
<td>CA, 1985</td>
<td>101</td>
<td>0</td>
<td>8.9</td>
<td>13 % (DCIS)</td>
</tr>
<tr>
<td>Australia, 1985</td>
<td>207</td>
<td>1.4</td>
<td>12.1</td>
<td>n/a</td>
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<tr>
<td>NM, 1987</td>
<td>221</td>
<td>1.8</td>
<td>0</td>
<td>7% (IBC)</td>
</tr>
<tr>
<td>Denmark, 1987</td>
<td>109</td>
<td>0.9</td>
<td>14.7</td>
<td>39% (DCIS)</td>
</tr>
</tbody>
</table>

Median Prevalence: IBC 1.3%; Median DCIS 8.9%

Modified from Welch, et al Annals of Internal Medicine Vol 127:11; p 1023-1028
POPULATION-BASED STUDIES

• Prospective evaluation of incidence
  – Initial spike in cancer followed by a fall of incidence to below initiation levels
  – Cumulative incidence should be the same between screened and non-screened

• What we do see is not that!
  – Initial spike without a return to pre-screen incidence
POPULATION-BASED STUDIES – SWEDISH STUDY

• 1985 beginning of screening program
  – Intervals of 18-27 months

• Prevalence period and stabilized period

• In all age groups, there was the expected spike in diagnosis
  – However, 70-74yo returned to expected incidence

• Lead time?
POPULATION-BASED STUDIES - MALMO

• 10 year duration (1976)
• Women age 55-69 randomly assigned to invitation to screen (21,088) versus no invitation (21,195)
• Women age 45-54 eventually invited to screen
• 15 years after trial ended, 10% increase in incidence of breast cancer (7% for invasive only)
COCHRAN REVIEW, 2013

• RCT of mammographic screening with no mammographic screening
• 8 trials with 600,000 women age 39-74
• 3 trials with no reduction in mortality (good randomization)
• 4 trials with 25% risk reduction (suboptimal randomization)
• Overall RR is 0.81
• For every 2,000 treated – 1 woman will avoid dying of BCA and 10 women will be treated unnecessarily
• How do we interpret?
• How do we talk to patients?
• Target DCIS?
• Target pathologist’s diagnostic criteria
DUCTAL CARCINOMA IN SITU (DCIS)

• About 20-25% of new cancer diagnosis

• Proliferation of abnormal epithelial cells within the confines of the basement membrane of the duct without stromal invasion

• Stage 0 breast cancer – 98-99% survival
PROGRESSION

J Clin Invest. 2007 November 1; 117(11): 3155–3163
PROGRESSION

J Clin Invest. 2007 November 1; 117(11): 3155–3163
MYOEPITHELIAL CELLS

• Myoepithelial cells important in progression from non-invasive to invasive
  – Changes in coding of secreted proteins that include basement membrane components

• Decreased CD10 (myoepithelial-cell specific marker) associated with lower Disease Free Survival (DFS)
MOLECULAR MARKERS IN DCIS

Protein – coding genes
• COX-2 and Ki67
  – High expression correlates with high risk of recurrence of invasive and non-invasive
• Rb pathway abnormalities
  – Contribute to invasive?
• ERBB2 and 14-3-3ζ
  – Contribute to invasive by promoting transition from epithelial to mesenchymal cells

microRNA
• miR-21
  – Targets PTEN, PDCD4, TMI
  – Increase with tumor progression
• miR-145
  – Increase in DCIS compared to ADH
INTRA-TUMOR HETEROGENEITY

• DCIS heterogeneity – positive for p53 and thus mutation in TP53 (Allred, et al)

• Heterogeneity seen in cell lines with expression of CD44 and CD 24 (Park et al)
  – Basal-like tumors high diversity
  – Luminal and Her2 low diversity
  – Intra-tumoral diversity a predictor of invasive progression like in Barrett’s esophagus?
MOLECULAR DIVERSITY IN DCIS AND EARLY INVASIVE CANCER

• Gene expression patterns
  – 31 pure DCIS; 36 pure IC; 42 mixed; 6 controls
  – 22% luminal A; 28% luminal B; 15% Her2; 18% basal-like

• Subset of DCIS with gene expressions more similar to invasive cancers than DCIS
  – ER/PR negative; high proliferation; high-grade; Her2 positive (7)

• High levels of EMT-related genes
  – CXCL1, SNAI1, S100A7, MMP1

Muggerud, et al
BIOMARKERS?

• P16/cyclooxygenase 2 (COX-2)/Ki-67
  – 2x increase risk of invasive recurrence

• ER-/Her2+/Ki67+
  – Increase risk of noninvasive recurrence

• Her2
  – May be associated with a higher risk of recurrence but not invasive recurrence
ST GALLEN CLASSIFICATION?

- 458 women with DCIS
- ER/PR positive if greater than 1%; Ki67 high if greater than 14%
- No one had endocrine or chemo post-op
  - Luminal A: 186 pts
  - Luminal B (Her2-): 33 pts
  - Luminal B (Her2+): 74 pts
  - Her2+/ER: 61 pts
  - Triple Negative: 27 pts
- No statistically significant difference between subtypes for local, regional or distant recurrences

Zhou et al BMC Cancer 2013, 13:512
• At this point in time, there is no clear-cut way to distinguish which DCIS will become clinically significant and which will not.
DO WE TARGET OVER-SCREENING ANOTHER WAY?

• Pathologic diagnosis
• When should we stop screening mammograms?
PATHOLOGY

Atypical Ductal Hyperplasia

ductal carcinoma in situ
PATHOLOGY

- The fine line between ADH and DCIS
- Do we change the nomenclature?
  - Ideally would help distinguish high risk and low risk DCIS
  - Test DCIS only then you discount the environment which may be equally as important
- Myoepithelial cell changes, etc
WHEN TO STOP SCREENING MAMMOGRAPHY?

• What are the recommendations?

• How do you tell a patient in a kind way?
MAMMOGRAPHY IN THE ELDERLY

• Randomized trials did not include women older than 74
• Observational studies indicate extending it past 74 for women who are expected to live longer than 10 years
• Modeling studies
  – 2 fewer BC deaths/1000 with biennial screening in 70s
  – 200 false positives/1000
  – 13 over-diagnosis/1000
EXAMPLE

• 74 yo woman
• Co-morbidities:
  – HTN
  – Afib
  – GERD
  – Severe obesity BMI 46
  – Asthma
  – OSA
  – SOB with any exertion
  – h/o “enlarged heart”

• Screening mammogram?
• What is her life expectancy?
• How do you tell her not to screen?

• Bx DCIS – OR for lumpectomy
CONCLUSION

• We likely over-diagnose

• Particularly true with the implementation of screening mammography programs
  – Increase in DCIS diagnosis has not resulted in a decrease in the number of invasive cancers

• May also be because of the persistence of screening mammography in patients whose life expectancy is shortened secondary to co-morbid conditions

• Limited understanding on the progression to clinically significant disease as in DCIS
CONCLUSION

• There are markers that show promise but are not conclusive
• Can not use current grade or classification system to predict those that go on to invasive cancers
• Until we can predict, will need to continue to treat as if clinically significant
THANK YOU