San Antonio Breast Cancer Symposium Highlights 2016

A Surgeon’s Perspective

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Overview

- Genetic Risk and Guidelines
  - S2-01
  - ASBS Consensus Guideline on Hereditary Genetic Testing
- Genetic Risk and Breast Cancer Outcomes
  - S2-03
- Ductal Carcinoma In Situ
  - SSS-ASTRO-ASCO DCIS Margin Guidelines
  - S5-01
  - P1-11-03
- Staging the Regional Axilla after NCT
  - S2-07
  - P6-09-01
  - OT2-03-01
  - Alliance 11202
Genetic Risk and Guidelines

• Last 4 years drastic changes in the field of cancer genetics
  – Particularly this field now contains genetic panels that can have up to 50 genes
• What genes were included?
  – Known to drive breast cancer risk vs. minimal information but a possibility of involvement
• How do we handle giving a clinical risk estimate with the wide confidence intervals seen on many of these genes?
• What does a VUS mean for our patients?

Genetic Risk and Guidelines

Breast cancer risk estimates by panel gene

<table>
<thead>
<tr>
<th>Gene</th>
<th>Average Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>2.6 (90% C.I. 2.2-3.7)</td>
</tr>
<tr>
<td>BARD1</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>BRIP1</td>
<td>No evidence of association</td>
</tr>
<tr>
<td>CHEK2 (truncating)</td>
<td>3.0 (90% C.I. 2.6-3.5)</td>
</tr>
<tr>
<td>CHEK2 (missense)</td>
<td>1.58 (95% C.I. 1.42-1.75) for H157T</td>
</tr>
<tr>
<td>MRE11A</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>NBSN</td>
<td>2.7 (90% C.I. 1.9-3.7) for c.857del5</td>
</tr>
<tr>
<td>PALB2</td>
<td>5.3 (90% C.I. 3.0-9.4)</td>
</tr>
<tr>
<td>RAD50</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>RAD51/C/D</td>
<td>No evidence of association</td>
</tr>
<tr>
<td>XRCC2</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>SLX4</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>

Fergus Crouch in S2-01 summarizing Doug Eastman et al. NEJM. 2015.
Genetic Risk and Guidelines

Breast cancer risks associated with mutations in cancer predisposition genes identified by clinical genetic testing of 60,000 breast cancer patients


121,197 patients examined from the Ambry Genetics database from March 2012-June 2016
- 92.4% female
- 65% Caucasian

Mutations were detected in 9% of patients

12 genes showed a significant association with breast cancer

<table>
<thead>
<tr>
<th>High Risk</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>TP53</th>
<th>PTEN</th>
<th>CDH1</th>
<th>PALB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Risk</td>
<td>ATM</td>
<td>CHEK2</td>
<td>RAD51D</td>
<td>NF1</td>
<td>BARD1</td>
<td>MSH6</td>
</tr>
<tr>
<td>Low Risk</td>
<td>BRIP1</td>
<td>RAD50</td>
<td>RAD51c</td>
<td>MRE11A</td>
<td>NBN</td>
<td></td>
</tr>
</tbody>
</table>

http://discoverysedge.mayo.edu/2015/10/07/breast-cancer-predicting-individual-risk
## Genetic Risk and Guidelines

### ASBS Consensus Guidelines on Hereditary Genetic Testing

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cancer Types</th>
<th>Risk-Reducing Strategies</th>
</tr>
</thead>
</table>
| **BRCA1** | Breast cancer (up to 67%)  
Contralateral br cancer (up to 30%)  
Ovarian cancer (up to 45%) | Annual breast MRI (start age 25)  
Annual mammogram (start age 30)  
**Risk-reducing bilateral mastectomy** |
| **BRCA2** | Breast cancer (up to 66%)  
Contralateral br cancer (up to 30%)  
Ovarian cancer (up to 12%)  
Male breast cancer  
Prostate cancer | Annual breast MRI (start age 25)  
Annual mammogram (start age 30)  
Chemoprevention  
**Risk-reducing bilateral mastectomy** |
| **TP53** | Breast cancer  
Soft tissue sarcomas  
Osteosarcomas  
Brain tumors  
Adrenocortical carcinoma  
Multiple primary tumors | Annual breast MRI (start age 20)  
Annual mammogram (start age 30)  
**Risk-reducing bilateral mastectomy** |
| **PALB2** | Breast cancer (33%, but 58% with 2 first-degree relatives)  
Pancreatic cancer  
Male breast | Annual breast MRI (start age 25)  
Annual mammogram (start age 30)  
**Risk-reducing bilateral mastectomy** |
| **CDH1** | Breast cancer (39% of lobular carcinoma)  
Gastric cancer  
Colorectal cancer | Annual breast MRI (start age 30)  
Annual mammogram (start age 30)  
**Risk-reducing bilateral mastectomy**  
Gastric screening |
| **PTEN** | Breast cancer  
Thyroid cancer  
Endometrial cancer  
Colorectal cancer  
Kidney cancer | Annual breast MRI (start age 30)  
Annual mammogram (start age 30)  
**Risk-reducing bilateral mastectomy** |
| **ATM** | Breast cancer (rare mutations with a 40-60%) | Management recommendations have not been established |
### Genetic Risk and Guidelines

#### ASBS Consensus Guidelines on Hereditary Genetic Testing

<table>
<thead>
<tr>
<th>Gene</th>
<th>Condition</th>
<th>Prevention Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHEK2</td>
<td>Breast cancer (20% but increases with 44% with 1st &amp; 2nd-degree relatives) 30% risk of contralateral breast cancer Male breast cancer Colorectal cancer Thyroid cancer Kidney cancer</td>
<td>MRI Chemoprevention Risk-reducing bilateral mastectomy</td>
</tr>
<tr>
<td>STK-11</td>
<td>Breast cancer Ovarian cancer Colorectal cancer Duodenal cancer Pancreatic cancer</td>
<td>Annual breast MRI (start age 30) Annual mammogram (start age 30)</td>
</tr>
<tr>
<td>BRIP 1</td>
<td>Breast cancer (2- to 3.5-fold) Ovarian cancer (8-fold)</td>
<td>MRI Chemoprevention Consider BSO</td>
</tr>
</tbody>
</table>

### Genetic Risk & Breast Cancer Outcomes

**Does BRCA status affect outcome in young breast cancer patients? Results from the prospective study of outcomes in sporadic and hereditary breast cancer (POSH)**


3053 patients examined from the UK 2000-2008
- All had Invasive Breast Cancer
- ≤ 40 years old

Blood samples were tested for BRCA1 & 2 in 2016
Mutations were found in 379/2759 (~14%)
Genetic Risk & Breast Cancer Outcomes

- Looked at the molecular subgroups
  - TNBC survival favored BRCA gene carriers (~11% at 10 years)

Ductal Carcinoma In Situ

Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma In Situ

- Literature review which included 20 studies of 7883 women
- 2mm margins were adequate
  - Larger margins did not decrease the RR
  - Positive margins have a much higher RR
Ductal Carcinoma In Situ

- Treatment with surgery alone is linked to a higher RR compared to treatment with surgery and WBRT.
- Treatment with HT can reduce the RR, but no data has shown a link between HT and the width of clean margins.
- The width of the clean margins shouldn’t affect the type of WBRT a woman receives.
- DCIS with microinvasion should be considered DCIS when deciding on optimal margin width.

DCIS biological risk profile predicts risk of recurrence after breast conserving surgery in a Kaiser Permanente NW population


Validation study of a new prognostic indicator
- 0-10 (Low ≤3, High >3)
- Goal to identify the 72% that are not helped by RT

Comma et al. Natl Cancer Inst Monographs. 2010
Ductal Carcinoma In Situ

DCIS
BCS (1990-2007)
N=608

Prospective Biological Risk Signature Testing
N=455

RT
N=377

No RT
N=78

10 year IBE
Risk

Ductal Carcinoma In Situ

Overall
Low (≤3)
Elevated (>3)

20% 10% 10%
30% 8%
15% 5%
Ductal Carcinoma In Situ

Rates of ipsilateral breast tumor recurrence (IBTR) following breast conserving surgery (BCS) and hypofractionated radiotherapy for ductal carcinoma in situ (DCIS)

Dumitru D, Benson J, Wishart G, Provenzano E. (P1-11-03)

- 8.3% developed recurrence (n=9 with RT and n=5 no RT, p=0.534) at 10.5 years
- Similar IBTR rates seen in with Traditional WBRT (approx. 1% per year)
Staging the Regional Axilla after NCT

- Degree of pathologic response after NCT correlates with both DFS and OS in both the breast and axilla
- Likelihood of pCR is predicted by molecular subtype

<table>
<thead>
<tr>
<th></th>
<th>~40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER/PR +</td>
<td>21.1%</td>
</tr>
<tr>
<td>Her-2 +</td>
<td>64.7%</td>
</tr>
<tr>
<td>Triple Negative</td>
<td>49.4%</td>
</tr>
</tbody>
</table>

- Overall pCR is a prognostic factor, which differs slightly by molecular subtype

Bear et al. JCO. 2003.

Staging the Regional Axilla after NCT

Predictors of locoregional recurrence after neoadjuvant chemotherapy and surgery for node positive breast cancer: Results from ACOSOG Z1071 (Alliance)

Boughey JC, Ballman KV, McCall LM, Mittendorf EA, Hunt KK (P6-09-01)

[Bar chart showing pCR and no pCR percentages for HR+, Her-2+, and TN categories with 5 year LRR]
Staging the Regional Axilla after NCT

Clinically Negative Axilla → NCT → SLNB

Sentinel node detection after neoadjuvant chemotherapy in patient without previous axillary node involvement (GANE A 2 trial): Follow-up of a prospective multi-institutional cohort


Useful, feasible, safe
- 92.4% female
- 65% Caucasian

Cohort of 15 Institutions
Staging the Regional Axilla after NCT

**T1-4 Br Ca**
Ax Ultrasound
N=608

**+LN**

SLNB + ALND
n=307
79.8% identified
FNR ~20%

**- LN**

SLNB ± ALND
n=509
97% identified

**+ SLN**
24%
N=139

**- SLN**
75%

ALND
pN- = 73% (n=88)
pN+ = 24%
(15 Macro=15)

SLN alone
N=418

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Staging the Regional Axilla after NCT

<table>
<thead>
<tr>
<th>3 year survival</th>
<th>N=418</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>97.8%</td>
</tr>
<tr>
<td>Disease Free Survival</td>
<td>94.8%</td>
</tr>
</tbody>
</table>

**Recurrence**

<table>
<thead>
<tr>
<th></th>
<th>N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>3</td>
</tr>
<tr>
<td>Ipsilateral Breast</td>
<td>3</td>
</tr>
<tr>
<td>Contralateral Breast</td>
<td>3</td>
</tr>
<tr>
<td>Lymph Node</td>
<td>1</td>
</tr>
</tbody>
</table>
Staging the Regional Axilla after NCT

Clinically Negative Axilla → NCT → SLNB

Clinically Positive Axilla → NCT

Complete Response → ?

No Complete Response → ALND

Staging the Regional Axilla after NCT

Predictor of LRR after NCT in NSABP B-18 & B-27

E. Mamounas. JCO. 2012
Staging the Regional Axilla after NCT

ACOSOG (Alliance) z1071 Trial

- T1-4, N1-2, M0
- With Bx proven LN disease
- N=663

NCT

SLN IDed (≤2), then followed with ALND
- N=525 (79%)

FNR 12.6%
Goal 10%

J. Boughey et al. JAMA. 2013

Number of SLN Removed

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>False Negative Rate</td>
<td>32%</td>
<td>21.1%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>12.6%</td>
</tr>
</tbody>
</table>

J. Boughey et al. JAMA. 2013
Staging the Regional Axilla after NCT

Targeted Axillary Lymph Node Dissection (TAD)

<table>
<thead>
<tr>
<th>Node</th>
<th>+LN</th>
<th>Total LN</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clipped</td>
<td>115</td>
<td>120</td>
<td>4.2%</td>
</tr>
<tr>
<td>SLNB</td>
<td>62</td>
<td>69</td>
<td>10.1%</td>
</tr>
<tr>
<td>SLNB + Clipped</td>
<td>73</td>
<td>74</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

A Caudle et al. JCO. 2016

Staging the Regional Axilla after NCT

- Normal Exam after chemotherapy
  - ± axillary imaging
- Remove ≥ 3LNs
- Dual Mapping
- Remove Targeted/Clipped Node
- Count all remaining disease as a positive node
  - Even IHC detected (FNR 8.4%)
NSABP B-51/RTOG 1304 (NRG 9353)

Clinical T1-T3 N1 M0 breast cancer

Axillary nodal involvement (FNA or core-needle biopsy)

NACT (plus anti-HER2 therapy for HER2+ patients)

Definitive surgery with histological documentation of negative axillary nodes (either by axillary dissection or by SLNB ± axillary dissection)

Stratification
- By type of surgery (mastectomy vs lumpectomy)
- ER status (+ vs -), HER2 status (+ vs -), pCR in breast (yes vs no)

Randomization

No regional nodal XRT
- Breast XRT if breast-conserving surgery, but no chest-wall XRT if mastectomy

Regional nodal XRT
- With breast XRT if breast-conserving surgery, or chest-wall XRT if mastectomy

Nature Reviews | Clinical Oncology

Alliance for Clinical Trials in Oncology A11202

Clinical T1–T3 N1 M0 breast cancer

NACT

Breast-conserving surgery or mastectomy and sentinel lymph-node surgery

SLN negative

SLN positive

Randomization

ALND plus breast/chest wall and nodal XRT (without XRT to dissected axilla)

No further axillary surgery, but breast/chest wall and nodal XRT

Nature Reviews | Clinical Oncology

Thank You.