Update on the Surgical Management of Breast Cancer: What Happens After Imaging?

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MD Anderson Cancer Center
Outline

• Limiting and eliminating surgery for breast cancer – all exquisitely imaging dependent
  – Treatment vs active surveillance for DCIS
  – Targeted axillary dissection for node-positive breast cancer
  – Eliminating surgery for invasive breast cancer
MD Anderson Breast Imaging

2015-16
37 Faculty
125,000 MMGs
9,629 procedures
Ductal Carcinoma In Situ (DCIS)

- Incidence:
  - \( \approx 62,000 \) new cases US 2014
  - 20-25% of our Practice

- AKA:
  - Noninvasive Breast Cancer
  - Preinvasive Breast Cancer
  - Intraductal Carcinoma
  - “Precancer”
DCIS Has Increased 500 Fold Since the Advent of Mammographic Screening

Over Treatment!
### Natural History of Untreated DCIS

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>IBC (%)</th>
<th>Follow-up (yrs)</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>Rosen 1980</td>
<td>15</td>
<td>53</td>
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<td>Page 1982</td>
<td>28</td>
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<td>Collins 2005</td>
<td>13</td>
<td>46</td>
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<td>13.5</td>
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50-70% of women do not develop IBC, even at 20 years
But how to determine who will not progress?
Treatment of DCIS = Prevention of Invasive Cancer and death

Which patients will go on to develop invasive disease?
Breast Cancer Develops Over Time

- Breast cancer cells progress through changes over a period of years

Normal Duct → Ductal Hyperplasia → Ductal Hyperplasia with Atypia → Ductal Carcinoma In situ → Invasive Ductal Carcinoma

Reversible with Tamoxifen
Preoperative Systemic Therapy Window Studies

Biology of DCIS
UCSF Preoperative Endocrine Treatment for ER-positive DCIS

Exclusion criteria:
- palpable disease
- microinvasion
- not visible on MRI

Chen et al, *BMC Cancer*, 2009
Alteration of biomarker expression is associated with endocrine treatment for DCIS

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<thead>
<tr>
<th>baseline</th>
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<th>treated</th>
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<tr>
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<tr>
<td></td>
<td>Ki67</td>
<td>CD68</td>
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</tbody>
</table>
| Chen et al, *BMC Cancer*, 2009
Biomarker changes associated with endocrine treatment

Ki67, premenopausal

Ki67, postmenopausal

CD68, premenopausal

CD68, postmenopausal

Chen et al, *BMC Cancer*, 2009
Three-Month Pre-op Endocrine Therapy in DCIS

- Preoperative endocrine therapy of ER-positive DCIS
  - Safe
  - Histologic and radiologic changes are evident

- No long term data on efficacy

- What proportion of women might this therapy actually prevent the occurrence of invasive breast cancer?
Alliance-CALGB 40903
Phase II Single-Arm Study of Neoadjuvant letrozole for ER(+) postmenopausal DCIS

PI: Shelley Hwang

- 3 months Letrozole
- stable or responding
- progression

3 months Letrozole

Measure change Ki67, Imaging-path correlation, pCR

MMG MRI Surgery

ACCRUAL Completed 1/16: n=108
Observation?

Biopsy ONLY
No Surgery
No Radiation
+/- Hormonal
Atypical Ductal Hyperplasia

- Screen detected
  - 100,000/year
- Core biopsy
- Surgical excision recommended
- Upgrade rates
  - 10-30%
    - DCIS: 80%
    - Invasive: 20%

Underestimation of Invasive Breast Cancer at DCIS Diagnosis
‘DCIS’ at Core-needle Biopsy

• Meta-Analysis
  – 52 studies, 7350 patients
  – 25.9% occult invasive cancer at excision
  – Higher underestimation
    • Small gauge vs large VAB
      (30% vs 19%)
    • HG vs non-HG
      (32% vs 21%)
    • > 2 cm vs ≤ 2 cm
      (35% vs 20%)

Brennan et al, Radiology 2011
2009 NIH DCIS Consensus Conference
Recommendations

• Determine effectiveness of breast MRI in changing surgical management

• Improve MRI techniques to better discriminate which patients:
  – Need therapy
  – Could have **ACTIVE SURVEILLANCE**
Can breast MRI help to rule-out invasion in DCIS?

- Northwestern
  - 217 with and 135 without MRI
  - No difference predicting invasive upgrade
  - 31% increase in pre-op biopsy rate, p<0.0001

- University Florence
  - 127 all with MRI
  - 27% upgrade
  - No MRI features correlated with invasive component, p=NS

LORIS Trial in UK
Watch and Wait: Active Surveillance

• Screen detected low/intermediate grade DCIS on VAB, > 46 years

• Randomize surgery versus no surgery
  – Non-inferiority trial 932 patients
  – Any size, no mass lesion
  – Primary endpoint: 5 year invasive disease
  – Secondary: Mastectomy rate, quality of life, biomarkers

CI: Adele Francis
LORIS Trial in UK 2014

Watch and Wait: Active Surveillance

• Both arms yearly mammograms

• Surveillance arm
  – No endocrine therapy permitted
  – No radiotherapy permitted

• Surgery arm
  – Any adjuvant therapy
  – Endocrine and radiotherapy as per local physician
Radiologic Monitoring
DCIS No-excision
Observation Only

What is the natural history of DCIS & micro-calcifications left in place?

Criteria for and how often: repeat biopsy?
Trial Schema

LORIS

932 Patients

CI: Adele Francis
An increase in the number, or size, of the microcalcification in the index lesion should not prompt routine patient recall. Neither should changes in the appearances/morphology, as casting type microcalcification is known to become more prevalent with increasing size.

RECALL

- A new cluster of microcalcification which is not definitively benign, out with the index lesion/quadrant or remote from the index lesion
- A new non-calcified lesion, asymmetry, or mass
LORIS: Recruitment on target and additional 40 sites to open July 2016
EORTC 1401; BOOG 2014-04

The LORD trial: A randomized non-inferiority trial between active surveillance and standard treatment in patients with low risk ductal carcinoma in situ
The LORD trial: N=1,240 Patients

- International multicenter, EORTC-Dutch Breast Cancer Group; PI: Jelle Wesseling
- Plan: open 2016
- Eligibility criteria
  - Women ≥45 years, microcalcifications detected by screening mammography
  - Unilateral, pure DCIS grade I based on multiple vacuum assisted biopsies
  - No prior history of IBC or DCIS
DCIS Grade: Predominantly Screen Detected

- Nuclear Grade
  - MD Anderson
    - Grade 1: 9%
    - Grade 2: 38%
    - Grade 3: 53%

- Histologic grade
  - NCDB
    - Grade 1: 15%
    - Grade 2: 38%
    - Grade 3: 46%

The COMET Trial
Comparison of Operative versus Medical Endocrine Therapy for Low Risk DCIS

- PI: Hwang - Duke
- Co-PIs: Partridge – DFCI; Thompson - MDACC
- Alliance for Clinical Trials In Oncology Foundation - PCORI
- Study sites planned: 100
**Endpoints:**
- 2-year invasive cancer dx
- 2-year OS, DSS
- PRO endpoints (QOL, fear of cancer recurrence, body image)

**Eligibility criteria:**
- Age $\geq$ 40
- Grade I/II DCIS without invasive cancer
- ER(+) and/or PR(+), HER2(-)
- No mass on PE or imaging
DCIS Treatment vs Observation

• Current imaging methods, clinical pathologic, and molecular factors are insufficient to reliably
  – Rule-out invasive cancer at initial pure DCIS diagnosis on VAB
  – Identify early invasive disease progression
  – Trials have begun
Limiting Axillary Surgery in US Guided Biopsy Proved Nodal Metastases

Targeted Axillary Dissection (TAD)
Eradication of Nodal Metastases

• Preoperative chemotherapy
  – Overall  40%
  – TN      50%
  – HER2+   70%+

Sentinel Node Biopsy after Preoperative Chemotherapy for Node Positive Breast Cancer ?
SLN after Preoperative Chemotherapy for Node Positive Breast Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Pts</th>
<th>FNR %</th>
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<tbody>
<tr>
<td>Mamounas</td>
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<td>Shen</td>
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<table>
<thead>
<tr>
<th>Retrospective Studies</th>
<th>Prospective Studies</th>
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<tbody>
<tr>
<td><strong>Trial Author</strong></td>
<td><strong>Year</strong></td>
</tr>
<tr>
<td>ACOSOG Z1071* Boughey</td>
<td>2013</td>
</tr>
<tr>
<td>SENTINA Kuehn**</td>
<td>2013</td>
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<tr>
<td>SN-FNAC Boileau</td>
<td>2015</td>
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* cN1 with at least 2 SLNs; FNR 8.7 if IHC used
** Most not biopsy proven, conversion from clinical pos to neg
# IHC used micromets and ITC considered ‘positive’
Axillary management after neoadjuvant chemotherapy

• **Node negative**
  - SLND (after neoadjuvant chemotherapy)
  - ALND if SLN +

• **Node positive-biopsy proved**
  - 2014 NCCN guidelines → ALND
  - 2015 NCCN guidelines → Emerging role for targeted axillary dissection (TAD)
  - 2016 NCCN → SLN if clinically negative, marking of nodes to ensure removal, dual-tracer, at least 2 SLN
Nodal FNA and Placement of Clip Marker When Metastatic Disease Identified

Bruno Fornage, MD
Hypothesis

Identification and Removal of the Clipped Node with Biopsy Proven Mets Prior to Chemo will Increase Accuracy of the SLN Procedure after Pre-Op Chemo
Prospective Registry of Breast Cancer Patients with Axillary Nodal Metastases Identified During Ultrasound Staging at MD Anderson Cancer Center: Protocol 11-1087

• Eligibility:
  – Abnormal axillary nodes on US metastases documented by cytology
• Marker clip placed in node with metastases
• Preoperative chemotherapy
• Routine axillary node dissection to determine the false-negative rate
Prospective Registry of Breast Cancer Patients with Axillary Nodal Metastases Identified During Ultrasound Staging at MD Anderson Cancer Center: Protocol 11-1087

Routine ALND, identification of marked node, pathologic correlation (disease presence and size) with compared with other nodes
Technically successful with SLND (100%)

- $^{125}$I seed does not interfere with Tc99M lymphoscintigraphy

MD Anderson Experience with TAD

- Clipped node not retrieved as a SLN in 23% of cases
  - Not related to the presence or absence of residual disease ($P = 0.66$)
Targeted Axillary Dissection (TAD)

1-5 Days Before Surgery
Breast Imaging
$^{125}$I seed placed in marked node

Day of Surgery
Node containing $^{125}$I seed
selectively removed

Nuclear Medicine
Radioisotope injection for SLND

SLNs removed

212 patients with completion dissection

Tumor stage
- T0/T1: 9.5%
- T2: 65%
- T3: 23%
- T4: 2%

Biopsy proved axillary node mets

# Abnormal nodes on US
- 1  36%
- 2  20%
- 3  17%
- ≥ 4 28%

Pathologic Evaluation of Clipped Node

Biopsy Node Positive N=230
  Neoadjuvant therapy

No ALND
N=18

Path Node Negative
N=78 (37%)

Evaleuable Patients*
N=212

Path Node Positive
N=134 (63%)

False Negative Results**
7/134

False Negative Rate
5.2% (95% CI 2.1 - 10.5)

*Update, +21 patients

**Clipped node showed no disease but other nodes in axillary specimen contained metastases
Patients Undergoing TAD

TAD Performed After NCT
N=109

No ALND
N=12

Evaluable Patients*
N=97

Path Node Negative
N=40 (41%)

Path Node Positive
N=57 (59%)

SLN negative = 5/54
SLN not identified = 3

Clipped node and SLN negative
N=2/57

False Negative Rate
SLND Alone = 9.3% (95% CI 3.1 – 20.3)
TAD (SLNs + Clipped Node) = 3.5% (95% CI 0.4-12.1)

*Updated, +1 patients
How often are residual nodes positive when SLN/Clip Node Positive?

<table>
<thead>
<tr>
<th></th>
<th>0 positive nodes</th>
<th>1 positive node</th>
<th>2 positive nodes</th>
<th>≥ 3 positive nodes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>51.4%</td>
<td>17.6%</td>
<td>5.3%</td>
<td>25.7%</td>
</tr>
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Positive Nodes after Pre-op Chemo

Alliance A11202

N=2,918

Clinical T1-T3, N1 Breast Cancer

Neoadjuvant Chemotherapy; Clinically Node-Negative on Physical Exam after Treatment

Surgery with SLND and Intraoperative Pathologic Evaluation

No SLN identified

No Registration, Randomization

Positive SLN

Intraoperative Registration, Randomization

Arm 1: ALND + Nodal RT
Arm 2: Axillary and Nodal RT

Negative SLN

Await Final Pathology

Negative

No Registration, Randomization

Primary aim: Determine whether axillary radiation alone is not inferior to ALND + radiation

Chair: Judy Boughey
Alternative Methods For Localization of Biopsy Proven Node

- Netherlands Cancer Institute-Amsterdam
  - Place $^{125}$I-seed and leave in for 4+ months during neoadjuvant chemo

- Stanford
  - Biopsy node then place India black ink into node for later localization

Donker et al. *Ann Surg* 2014

US Guided Wire-localization of Biopsy Proven Node

• Case Western Reserve
• Retrospective review 73 patients w clip placed in metastatic node and localized with wire after NCT
  – Clipped node was successfully localized in 97% of cases
  – 22% of cases clipped node not retrieved as a SLN

Plecha et al, Ann Surg Onc, EPUB 2015
Other Factors to Consider

• True multidisciplinary practice
• Type of clip to place
• Localization method
• Technical issues
  – Clip not placed within node, seed/wire not in clipped node, clip not found in specimen (MDA n=5)
• Radiation fields among nodal pCR cases
Targeted Axillary Dissection

- Technique requires extreme close collaboration between surgeon and radiologist.
- Ensuring removal of the node with biopsy proven metastatic disease after NCT is a more accurate method to stage the axilla compared with SLN alone.
- Outcome studies of TAD alone among patients with a nodal pCR are underway.
Feasibility Trial for Eliminating Breast Cancer Surgery in Exceptional Responders with Invasive Breast Cancer
Neoadjuvant Systemic Therapy

J Clin Oncol 1999, 17(2):460-469
Complete Pathologic Response
Neoadjuvant Chemotherapy

• Dependent on approximated biologic subtype and therapy

• pCR Breast
  – TN  48%
  – HER2-Positive  50%
  – HR-positive  16%

MD Anderson Local Regional Recurrence Among Patients with pCR

- Breast conserving therapy, n = 751
  - 2005-2012, with trastuzumab

- Five-year local-regional recurrence
  - HER2+ pCR vs not
    - 2.6% vs 13.3%
  - TN pCR vs not
    - 1.4% vs 10.1%

Swisher et al, Ann Surg Onc 2015
How will we safely select patients for avoidance of breast surgery after neoadjuvant therapy?
## Prior Attempts: Avoidance of Surgery after Neoadjuvant Therapy

<table>
<thead>
<tr>
<th>Author/Year</th>
<th># XRT alone</th>
<th>5-year LRR Surgery</th>
<th>5-year LRR XRT Alone</th>
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<tr>
<td>deLena et al 1981*</td>
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<td>31%</td>
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<td>Perloff et al 1988*</td>
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<td>Scholl et al 1984</td>
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<td>Touboul et al 1996*</td>
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<td>Ring et al 2003</td>
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<tr>
<td>Daveau et al 2011</td>
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<td>12%</td>
<td>23%</td>
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*prospective study
Prior Attempts: Avoidance of Surgery after Neoadjuvant Therapy

- **Major issues**
- Selection based on clinical response only, most
- Limited use of breast imaging
- One study did utilize random biopsy, without image guidance (Clouth *et al* 2007)
- Prior to understanding of subtype response, best available regimens, and optimized breast imaging

van la Parra and Kuerer, *BCR*, 2016
Breast Imaging and Predicting Pathologic Response

• Summary:
  – MRI, MMG, US, PET/CT, MBI breast lack sufficient sensitivity/specificity predict pCR

• Radiologic complete response in only 20% yet 50+% have pCR TN/HER2+

van la Parra and Kuerer, BCR, 2016
MRI Detection of Residual Disease

• TBCRC Trial 017
• N=746 patients
• Patients categorized by subtype
• Accuracy of preop MRI in predicting pCR
  • \textit{rCR} = \textit{resolution of all areas of abnormal enhancement, mass or distortion}
  • \textit{pCR} = \textit{no residual invasive disease or DCIS}

De Los Santos et al. Cancer 2013
Overall accuracy of MRI for predicting pCR was 74%
• Practice implications:
  
  - NPV < 50% of MRI overall following NEO lacks the accuracy necessary to obviate surgical resection
  
  - NPV MRI in the TN and Her2 amplified groups marginally better in 60% range
MRI Detection of Residual Disease

- MRI is sensitive for detecting residual disease
- Supports role in prospective trial to evaluate omission of surgery
- NRG (Basik, De Los Santos, Umphrey)

De Los Santos et al. *Cancer* 2013
• TN and HER2-Pos; T1/T2
  – Powered for pCR rate 40% and NPV of 90%; n=22/40 total
  – *Partial and complete imaging response*
  – 9G minimum of 6 cores, clip removed and replaced
  – Endpoints: VAB vs FNA and combination compared with surgical pathology excision
Hypothesis: Image Guided Tissue sampling key to selection of patients

68 TN s/p paclitaxel + AC; pCR
Key: Image Guided Tissue Sampling

rCR

43 TN s/p paclitaxel + AC; pCR
German Breast Group Multicenter Biopsy Trial

*Prediction of pCR*

- 164 patients, 2009 to 2013
- NCT, cCR (PE or/and imaging)
- False-negative rate: 49.3%
- NPV for correct diagnosis of pCR: 71%

Heil et al, *BJC*, 2015
German Breast Group Multicenter Biopsy Trial

Potential Issues with Accurate Prediction of pCR

• Inclusion of all subtypes
• No tumor stage/size criteria
• No strict imaging selection criteria
  – Biopsy could be done under US in OR
  – 37% did not have an initial clip at tumor site
• Biopsy method (sampling error) size/number not available in
  55% 30% VAB; 70% smaller gauge core cutting
• 16 cases stereotactic/mammographic
  – FNR 0%, NPV:100%

Heil et al, BJC, epub 2015
Development of Selection Criteria for Definitive Biopsy Alone Trial

MD Anderson Protocol 2016-046
Eliminating Breast Cancer Surgery in Exceptional Responders with Neoadjuvant Therapy
MDA PA 2016-046
Eliminating Breast Cancer Surgery in Exceptional Responders with Neoadjuvant Therapy

• Eligibility
  – T1/T2 unicentric TN and HER2+
  – Clinical (ultrasound) N0 at presentation
  – Neoadjuvant chemotherapy w anti-HER2
    • Imaging cCR or near cCR
      – Microcalcifications
  – pCR VAB minimum 9G 12 cores
  – Standard WB radiotherapy with low axilla
Eliminating Nodal Surgery?

- Selection of N0 versus N1 with conversion?
- MD Anderson, n=527, 2009-14, T1T2 TN and HER2 NCT (+ trastuzumab)
- pCR in breast (no invasive or in situ)
  - When initial US node negative
    - 98.3% pathologic node negative
  - When initial US & path node positive
    - 22.7% remain pathologic node positive

Kuerer et al, pre-publication data, 2016
Field is changing: better systemic therapies

Targeted imaging and biopsy has potential for selective elimination of surgery

Ensure safety and efficacy
Conclusions

• *Breast cancer patient care advancements are intimately related and dependent on the exquisite and meticulous collaborative involvement and care by dedicated breast radiologists*
Patients Undergoing SLND

Biopsy Node Positive Patients
N=230

- No SLND
  N=79
- No ALND
  N=17

Neoadjuvant therapy

SLND Performed
N=151

- Evaluable Patients*
  N=134

  Path Node Negative
  N=50 (37%)

  Path Node Positive
  N=84 (63%)

  SLN negative= 8/79
  SLN not identified = 5

  Clipped node and SLN negative N=2/84

False Negative Rate

- SLND Alone = 10.1% (95% CI 4.5 – 19.0)
- SLND + Evaluation of Clipped Node = 2.4% (95% CI 0.3-8.3)

*Updated, +16 patients
Nodal Imaging for Predicting Nodal Pathologic Response

• Ultrasound, MRI, PET-CT, MBI lacks sufficient sensitivity and specificity to accurately predict nodal pCR after neoadjuvant chemotherapy

• NPV 29-81%


van la Parra and Kuerer, BCR, 2016