What the surgeon wants from the radiologist before breast cancer surgery

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CAR, April 2013
Plan

- What is the role of MRI for breast cancer preoperative evaluation?

- How can radiology help in the evaluation of women treated with neoadjuvant chemotherapy?

- In the post-Z0011 era, does it remain relevant to evaluate the axillary region?
A few facts

- **Mastectomy** = local excision + radiation for lesions < 2cm

  - **YES**, in terms of **mortality** at 20 years:
    - 41.7% local excision vs 41.2% mastectomy
  
  - **NO**, in terms of **local recurrence**:
    - 30/352 (8.5%) local excision vs 8/349 (2.3%) mastectomy (p<0.001)
    - Prognosis worse in women with late recurrence
    - → Strive for complete excision of tumor with clean margins

- The local recurrence rate after conservative surgery is **significantly lower** than the rate of additional disease at MRI

  - 10-20% additional disease vs 1.8-4% recurrence rate at 8 years
A few more facts

**Positive margins**
- Not uncommon
- Frequency depends on definition

- 1648 ♀
  - 14% positive margins
  - 17% close (< 1 mm) margins
  - 17% re-excision → 33% residual tumor

- With **positive margins**, odds of local recurrence 2.4 X ↑ (p<0.01)

→ Strive for fewer interventions with positive margins and fewer re-excisions
First randomized prospective study evaluating preop breast MRI

1623 women eligible for breast-conserving surgery after triple assessment (clinical, mammo and US workup)
45 centers in the United Kingdom

<table>
<thead>
<tr>
<th></th>
<th>MRI group n = 816</th>
<th>No MRI group n = 807</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-intention mastectomy</td>
<td>58 (7%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Repeat tumorectomy within 6 mos</td>
<td>85 (10%)</td>
<td>90 (11 %)</td>
</tr>
<tr>
<td>Overall mastectomy rate</td>
<td>106 (13%)</td>
<td>71 (9%)</td>
</tr>
<tr>
<td>Overall reoperation rate at 6 mos</td>
<td>153 (19%)</td>
<td>156 (19%)</td>
</tr>
</tbody>
</table>
1. In COMICE, 38% of recommended mastectomies were false+
   - Suspicious lesions at MRI were not evaluated prior to surgery, surgery was widened without pathologic proof of disease.
2. The rate of re-intervention for + margins (10%) is quite low
   - Wider surgeries were performed, diminishing the potential benefit of MRI in precisely delineating multifocal disease.
3. 70% of women were menopausal and 77% were ≥ 50 yo
   - Likelihood of added benefit of MRI over MG-US is lower.
4. Radiologist-surgeon expertise issue
   - 14% of surgeons enrolled 1-2 patients per year
   - Rate of controlat cancer detection: 1.6%, half of expected value.

Long-term benefits on recurrence rate and mortality were not evaluated

Sardanelli: These results only reveal the performance of suboptimal MRI!
Preoperative Magnetic Resonance Imaging in Breast Cancer: Meta-Analysis of Surgical Outcomes


- 9 studies (2 randomized trials, 7 cohorts)

<table>
<thead>
<tr>
<th></th>
<th>Preop MRI</th>
<th>no MRI</th>
<th>Adjusted OR</th>
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<tbody>
<tr>
<td><strong>TOTAL n=3112</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial mastectomy</td>
<td>16.4%</td>
<td>8.1%</td>
<td>3.06 (p&lt;0.001)</td>
</tr>
<tr>
<td>Re-excision rate</td>
<td>11.6%</td>
<td>11.4%</td>
<td>0.95 (p=0.71)</td>
</tr>
<tr>
<td>Overall mastectomy</td>
<td>25.5%</td>
<td>18.2%</td>
<td>1.51 (p&lt;0.001)</td>
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</tbody>
</table>

| Inf Lobular CA n=766   |           |        |             |
| Initial Mastectomy     | 31.1%     | 24.9%  | 2.12 (p=0.008) |
| Re-excision rate       | 10.9%     | 18.0%  | 0.56 (p=0.09)  |
| Overall mastectomy     | 43.0%     | 40.2%  | 1.64 (p=0.034) |
Optimizing use of preop MRI

- Added value in women with dense breast parenchyma
  - 7% re-excision rate with preop MR vs 26% without
  - 17% positive margins with MRI vs 53% without

- Added value in women 39-49 yo
  - Re-excision rates were halved from 60% to 30% with MRI

Philpotts, RSNA 2011
Prospective study of 690 women undergoing breast MRI prior to surgery

- **141 additional lesions in 121 women (17.5%)**
  - 62 (44%) were pathology-proven malignant
  - 81 women had *Unidentified Bright Objects* without correlation at ultrasound (11.7% of population)
    - If within 3cm of the index cancer, margins were widened
      - 77.5% at surgery were malignant
    - If multicentric or contralateral, MRI follow-up (n=44)
      - No malignancies after mean follow-up of 57.1 months

*No change in surgical management should occur without pathologic proof*

Elshof, Br Ca Res Tr 2010
At the CHUM, preoperative MRI for:
- Clinico-radio-path discordance
- Young women
- Dense breast parenchyma
- Strong family Hx
- Candidates for neoadjuvant chemotherapy

Second-look ultrasounds/mag views as needed

MRI-guided biopsies
- In 2012, 88 lesions/1800 MRI (4.9%)
Shift in breast cancer

- Decrease in incidence of controlateral cancer since mid-80s
- Decrease in locoregional recurrence with targeted therapies

1985 marks introduction of Tamoxifen

EAPC = -3.07%/yr (95% CI, -3.5 to -2.7)

Introduction of Herceptin

The era of effective multimodality therapy obviates the need to surgically eradicate all microscopic disease in both the breast and the axillary nodes.

Outcome is largely determined by biology and the availability of targeted therapy.
Neoadjuvant chemotherapy

HOW CAN RADIOLOGY HELP THIS SUBGROUP OF WOMEN IN THE EVALUATION OF TREATMENT RESPONSE AND SURGICAL PLANNING?
Neoadjuvant chemotherapy is used increasingly preoperatively for women with breast cancer. With similar locoregional control and survival, decrease tumor bulk to allow for conservative surgery.

- More protocols are available
  - Not generally recommended for tumors <2cm, strongly expressing hormonal receptors, or of low-grade.
  - Not for ILC, DCIS

- Rate of complete pathologic response
  - As high as 40-67% in her2+ subpopulations

De Los Santos et al. Cancer 2013
Evaluation of tumor response

*Complete pathologic response* = no residual invasive CA (+- DCIS)

Must be able to **correctly assess response** to treatment, including DCIS, to limit the extent of surgery

- Clinical exam, mammo and US are imperfect for tumor assessment
  - Ultrasound still best for lymph node evaluation
  - Radiologic evaluation is opportunity to **deploy clip** at cancer site
    - Local control 98.6% with clip, vs 91.7% without

- **Highest sensitivity is MRI**, but with limitations

Assessing chemotherapy response at MRI

Pre-treatment

62 yo woman.
6.1 X 5.8 cm high-grade infiltrating ductal carcinoma with 5.5 cm axillary metastasis
ER- PR- her2- (Triple negative tumor).

Taxol X 12; FEC X 4
Assessing chemotherapy response at MRI

**Partial response** to treatment, with size decrease (4.6 down to 2.7 cm) for intramammary tumor, and axillary metastasis (5.8 down to 3 cm).

**Surgery**: partial mastectomy and axillary dissection - T2 N1 disease.

MRI correlates well with **pathology size** for enhancing **masses**. MRI’s ability to evaluate for complete response better for **high grade** lesions.
Assessing chemotherapy response at MRI

30 yo woman, no family history
Multifocal Grade 2 infiltrating ductal carcinoma
ER+ PR+ Her2- (Luminal A subtype)

T1 gado before treatment

Taxol X 12; FEC X 4
Assessing chemotherapy response at MRI

Clinically, residual 3.1 X 2.6 cm mass; no palp node. At MRI: enhancing masses have resolved, spiculated mass and distortion remain.

Surgery: modified radical mastectomy with skin preservation and DIEP flap. Surgical pathology revealed partial response, with discontinuous residual disease (largest IDC measuring 2 cm); 7/12 nodes +.
Assessing chemotherapy response at MRI

43 yo woman with 3.5 x 1.3 cm Grade 3 IDC; ER+ PR- Her2+ (Her2-enriched tumor)
Treated with AC X 4, T + H

MRI reveals no residual enhancement, suggestive of complete response. Partial mastectomy and sentinel node performed. Final pathology revealed 2 mm residual focus of ductal carcinoma in situ, 0/3 lymph nodes

MRI is limited in cases of DCIS, and for multifocal disease
MRI as predictor of tumor response

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spec</th>
<th>NPV</th>
<th>PPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>83%</td>
<td>47%</td>
<td>47%</td>
<td>83%</td>
<td>74%</td>
</tr>
</tbody>
</table>

567 women, reported by De Los Santos et al. Cancer 2013.

- MRI’s predictive ability depends on cancer subtype, reflecting
  - Type and Frequency of response to chemotherapy
  - MRI appearance of tumour
    - Radiologic complete response for NME and low-grade cancers should be interpreted with caution
- Management changes based on MRI will require further improvements in our ability to correctly assess for pathologic complete response at imaging
  - Diffusion-weighted imaging
  - Tumour bed biopsy?
Once Imaging Complete
Individualizing surgery for each woman

Optimal **Lumpectomy** Candidates:

- Tumors < 5 cm, limited to one quadrant
- Breast size/tumor size ratio permitting lumpectomy with acceptable cosmetic result
- No contraindications to breast XRT

Golshan M. Diseases of the Breast 2009
Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised


Nottingham City Hospital Breast Unit, Nottingham, UK
Surgical considerations after partial mastectomy

Which women are candidates for oncoplastic reconstruction:

- Excision of more than 20% of breast volume
- Non favorable localisation (central, inferior, medial)
- Large breasts or important ptosis and desire reduction
When more than 20% excised...

- The goal is to **obliterate the residual cavity** to avoid a seroma by remodeling with **displacement of adjacent breast tissue**
- Undermining of skin and separation of breast tissue from pectoral muscle & **reapproximation** of breast tissue
Musculocutaneous flap post partial mastectomy

- If not enough residual breast tissue available a musculocutaneous flap may be used
- Latissimus dorsi most frequent
- **Preoperative imaging essential** because if positive margins....very difficult problem
Non favorable location (Inferior)
Non favorable location (Inferior)
Partial mastectomy with reduction

Images from S. Willey
Partial mastectomy with reduction

Images from S. Willey
Immediate Reconstruction post Mastectomy
With or without neoadjuvant chemotherapy

Delayed Reconstruction
Immediate Reconstruction post Mastectomy
The main advantage is skin preservation
Skin sparing mastectomy & Immediate reconstruction with expander
Preservation of the nipple-areola complex is becoming more widespread.
Nipple Sparing Criteria
Not Typically Performed after Neoadjuvant Chemotherapy

Optimal **Nipple-sparing mastectomy** Candidates:

- Tumor < 3 cm
- Tumour at least 2 cm from the nipple-areola complex
- Absence of multicentricity
- No malignant calcifications extending to nipple-areola complex
- Negative intraoperative biopsy of nipple-areola complex

Golshan M. Diseases of the Breast 2009
Does it remain relevant to evaluate the axillary region after the results from the ACOSOG Z11 trial have been released?
Until recently...

Abnormal lymph node on U/S ➔ FNA &
axillary dissection if +

Normal lymph nodes on U/S ➔ sentinel lymph node biopsy &
axillary dissection if +
Now

- **Radiologists** not sure when to biopsy abnormal lymph nodes
- **Surgeons** not sure when to ask for a frozen section and when to do axillary dissection
- **Radio-oncologists** now see patients with positive sentinel nodes without dissections
- **Patients** have to make important decisions based on a widely criticised trial
ACOSOG Z0011
Phase 3 non-inferiority trial conducted at 115 sites
<table>
<thead>
<tr>
<th>Eligible</th>
<th>Ineligible</th>
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<tbody>
<tr>
<td>- Clinical T1 T2 N0 breast cancer</td>
<td>- Clinical N1 or T3</td>
</tr>
<tr>
<td>- H&amp;E-detected metastases in SN</td>
<td>- Extracapsular extension</td>
</tr>
<tr>
<td>- Lumpectomy with whole breast irradiation</td>
<td>- Bilateral breast cancer</td>
</tr>
<tr>
<td>- Adjuvant systemic therapy by choice</td>
<td>- Total mastectomy</td>
</tr>
<tr>
<td></td>
<td>- Preoperative chemotherapy</td>
</tr>
<tr>
<td></td>
<td>- Nodal irradiation or PBI</td>
</tr>
<tr>
<td></td>
<td>- Metastases in SN detected by IHC</td>
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</tbody>
</table>
Patient Characteristics Z11

- Median age: 55 years
- 70% T1 tumors
- HR (+) >80% in both groups
- Equal number of patients with systemic therapy (96-7%)
  - 58% chemotherapy & 46% hormone therapy
Patient Characteristics Z11

- 70% had only one positive node
- 40% with micrometastases and 60% macrometastases
Results

- No significant difference in **Locoregional Recurrence** between patients treated with SLN (2.8%) or ALND (4.1%)

- No significant difference in **Disease-Free Survival** between patients treated with SLN (83.9%) or ALND (82.2%)

- No significant difference in **Overall Survival** between patients treated with SLN (92.5%) or ALND (91.8%)
Criticisms

- Mainly older ER positive patients with very favorable prognosis (how many 5 cm tumors?)
- 70% had only one + lymph node
- Don’t know HER 2 status of patients
- How many patients HER 2+ or triple – which confer a worse prognosis?
Methodological Shortcomings

- Targeted enrollment of 1900 with final analysis after 500 deaths
- 891 (47%) patients accrued
- Trial closed early because mortality rate (94 deaths) lower than expected
- Protocol violations (no radiotherapy in 11%, no lymph node metastasis (7% vs 11% in SNB only))

- Analysis based on *intent to treat* in a trial of noninferiority
Methodological Shortcomings

• Missing data
  - Histological grade 25%
  - Lymphovascular invasion 25%
  - Size of metastasis 15%
  - Hormone receptor status 9%
  - Lost to followup 19% (22% vs 17%)
Radiotherapy

- Details of the radiation not in database
- The degree to which the radiation oncologists biased the field edge superiorly to cover more of the axilla is currently undocumented
- It is probable that the majority of patients received adequate dose to the Level I and a portion of Level II to control microscopic disease
Conclusions of INESS (Institute of Excellence in Health and Social Services)

- Z11 does not provide sound statistical proof that omission of axillary dissection after positive sentinel node biopsy is not inferior to axillary dissection
- Prudence has to be applied when applying the results to patients with a more aggressive tumor who are underrepresented in z11
  - Young patients
  - T2
  - More than 1 LN with a macrometastasis
  - Grade 3
  - HER 2+ or triple –
What we do in the CHUM (mostly)…
Should radiologists continue to perform FNA of suspicious nodes?

- Yes, almost all of the time...to avoid SNB
- Not only for T3 or N1

- How do you know if the surgeon will use z11 criteria?
- How do you predict that patient will not request or require mastectomy (if additional foci found)?
- How do you predict whether the patient will not receive preoperative chemotherapy?
Always Follow Z11 Criteria

Axillary dissection:

– Total mastectomy
– Neoadjuvant chemotherapy
– Partial breast radiotherapy
We often follow Z11 Criteria

No dissection:
– T1/T2
– One or two positive SLNs without extracapsular extension
– Whole-breast radiotherapy
– Receiving systemic therapy

*Almost always when older patient with hormone receptor + disease
In the CHUM...

In patients at higher risk of locoregional recurrence the complexities of z11 are explained and informed decision is obtained

« Risk-benefit ratio is patient specific »
What about regional node irradiation??

TRADING ONE TREATMENT FOR ANOTHER
Radiooncologists generally include level 1 and 2 in their fields of treatment if no axillary dissection
### Table 1. Suggested Approach for Radiation Field Design in Patients With Sentinel Node–Positive Disease Not Undergoing Axillary Lymph Node Dissection

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>No. of Positive Sentinel Nodes</th>
<th>Total No. of Sentinel Nodes Sampled</th>
<th>Probability of Additional Nodes* (%)</th>
<th>Probability of Additional Nodes† (%)</th>
<th>Probability of Four or More Nodes Involved‡ (%)</th>
<th>Field Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC, 1.0 cm, ER positive, LVI negative</td>
<td>1 (IHC only)</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>&lt; 1</td>
<td>Tangents only</td>
</tr>
<tr>
<td>IDC, 1.8 cm, G3, ER positive, LVI negative, unifocal</td>
<td>1 (macro)</td>
<td>2</td>
<td>27</td>
<td>24</td>
<td>2</td>
<td>High tangents</td>
</tr>
<tr>
<td>IDC, 2.0 cm, ER negative, LVI positive</td>
<td>2 (macro)</td>
<td>2</td>
<td>63</td>
<td>66</td>
<td>30</td>
<td>High tangents/consider full nodal treatment</td>
</tr>
<tr>
<td>ILC, 4.0 cm, ER positive, multifocal, LVI negative</td>
<td>2 (macro)</td>
<td>2</td>
<td>77</td>
<td>64</td>
<td>40</td>
<td>High tangents/consider full nodal treatment</td>
</tr>
<tr>
<td>IDC, 3 cm, ER negative, LVI positive, multifocal</td>
<td>3 (macro with ENE)</td>
<td>3</td>
<td>78</td>
<td>95</td>
<td>90</td>
<td>Full nodal treatment</td>
</tr>
</tbody>
</table>

Abbreviations: ENE, extranodal extension; ER, estrogen receptor; G, grade; IDC, infiltrating ductal carcinoma; IHC, immunohistochemistry; ILC, infiltrating lobular carcinoma; LVI, lymphovascular invasion; macro, macroscopic.

*On the basis of the Memorial Sloan-Kettering Cancer Center nomogram.\(^9\)
†On the basis of the MD Anderson Cancer Center nomogram.\(^10\)
‡Katz et al.\(^22\)
AMAROS EORTC 10981
(After Mapping of the Axilla Radiotherapy or Surgery)

- 4827 Total Patients
- Tumor < 5 cm
- Mastectomy or BCS
- Opened in 2001-ongoing
- SLN-Positive randomized to RT vs ALND
- **Main objective**: prove equivalent locoregional control and reduced morbidity for ART

New Trials

?Abandoning SLN

- Sentinel node vs. Observation after axillary Ultrasound (SOUND)
- N=1,560
- European Institute of Oncology, Milan
- Eligibility: <2 cm, negative preop axillary US, breast conservation

Gentilini & Veronesi, Breast 2012
Photomosaic of 32,000 Barbies
Chris Jordan, « Close encounters: facing the future »
Katzen art centre, Massachusetts.