Primary Surgical Considerations

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Outline

• Breast Cancer Diagnosis/Preoperative Local Staging

• Primary Surgical Management of Invasive/Non-Invasive BC
  – RCT of Lumpectomy vs. Mastectomy
  – Lumpectomy Indications/Contraindications
  – Technical Considerations/Margin Assessment
  – Contralateral Prophylactic and Nipple-Sparing Mastectomy

• Special Circumstances in Primary Surgical Management
  – Family History/BRCA 1 or 2 mutation carriers
  – Presence of EIC
  – Lobular Histology/Presence of LCIS
  – Occult Breast Cancer
  – Large Tumors/Neoadjuvant Chemotherapy
  – Management of Patients Presenting with Stage IV Disease
Breast Cancer
Diagnosis/
Preoperative
Local Staging
Breast Cancer Diagnosis

• Currently, *minimally invasive procedures* constitute the *standard of care* for diagnosis in the majority of patients.

• Needle biopsies can be *directed by whichever method assures easiest access and best accuracy* for obtaining a true positive or true negative result.

• *Core needle biopsy* is the *optimal method* for BC diagnosis and can be performed by palpation, ultrasound guidance or stereotactic guidance.
Core Needle Biopsy

**Advantages:**
- Differentiates between invasive and non-invasive cancer
- Leads to one-stage surgical procedures (including SNB before lumpectomy)
- Provides adequate material for biomarkers (ER/PR/HER2)
- Neoadjuvant chemo can be given with invasive ca on core

**Limitations:**
- False negative rate 1-2%
- With non-invasive cancer on core, invasive cancer may still be present in 10-25% of cases
- With atypical hyperplasia on core, invasive or non-invasive cancer may be present in 15-40% of cases and open biopsy should follow

MRI in Preoperative Local Staging

• Because of its high sensitivity in BC diagnosis and screening, MRI is being increasingly utilized in the preoperative local staging of BC
• Multiple studies (and a meta-analysis) have shown that MRI identifies additional cancer foci, otherwise undetected by clinical assessment and conventional imaging (in both breasts)
• No consensus on whether MRI improves patient outcomes in terms of rates of margin positivity, reoperation, IBTR or DFS and OS
• On the other hand there remains concern that MRI can increase unnecessary mastectomy rates

UK COMICE Randomized Trial: MRI Planning for Breast-Conserving Treatment

- 1623 women with biopsy-proven primary BC
- Scheduled for WLE based on triple assessment
- Randomized to receive MRI (n = 816) or no MRI (n = 807)

<table>
<thead>
<tr>
<th>Initial Surgery</th>
<th>MRI N (%)</th>
<th>No MRI N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>58 (7%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Pathologically</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidable Mastectomy</td>
<td>16 (2%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF/MC disease</td>
<td>101 (14%)</td>
<td>78 (11%)</td>
</tr>
</tbody>
</table>

- Change in management based on MRI = 50/816 (6%)
- Reoperation rates:
  - MRI: 18.75%
  - no MRI: 19.33%  $P = \text{NS}$
- No significant differences in DFS of QOL (distress/anxiety)

Turnbull L et al: Lancet 2009
MRI in Preoperative Local Staging
Potential Candidates

• Not necessary for all patients who undergo BCS
• Can be helpful in:
  • Patients with mammographically dense breasts and ill-defined tumors
  • Patients with invasive lobular carcinoma
  • Patients with multi-centric disease
  • Patients who are candidates for neoadjuvant chemotherapy
• MRI is essential in patients who present with axillary adenopathy and clinically and radiographically occult breast lesions
Primary Surgical Management in Patients with Invasive and Non-Invasive BC
Primary Surgical Management

• Evolution in the paradigm of surgical management over the past 30 years
• Trend towards increasing use of breast conserving procedures without compromising patient outcome
• Breast conserving surgery has become the preferred surgical treatment for the majority of early-stage BC patients
Invasive Breast Cancer
Breast Conserving Surgery vs. Mastectomy

- From 1973-1989, six randomized trials
- Two overview analyses
- Compared mastectomy to BCS ± XRT
- Maximum tumor size for entry: 2-5 cm
- No differences in overall survival
- XRT significantly reduced the rates of IBTR

Breast Conserving Surgery
Utilization

• 1990: NIH CDC Statement:
  – Breast Conservation Treatment is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is preferable because it provides survival equivalent to total mastectomy while preserving the breast.”

• Despite this and the increase in detection of early-stage disease, BCS is underutilized as a surgical option

Optimal Lumpectomy Candidates

- Tumors < 5 cm in diameter
- Limited to one quadrant
- Breast size/tumor size ratio permitting lumpectomy with acceptable cosmetic result
- Patient is desirous of breast preservation
- Negative margins following resection
- No contraindications to breast XRT

Lumpectomy Contraindications

Absolute

- Multi-centric disease in more than one quadrant
- Diffuse suspicious microcalcifications
- Inability to obtain clear margins after multiple resections
- First or second trimester of pregnancy
- History of therapeutic radiation to the region

Lumpectomy Contraindications

Relative

- Large tumor size/breast size ratio for acceptable cosmesis
- History of collagen vascular disease (relative contraindication to XRT)
- Tumor location beneath nipple
- Unavailability of radiotherapy

Lumpectomy Technique
Choice of Incision

- Incision over mass
- Adequate length
- Always curvilinear
- Keep in mind possible future mastectomy
- Do not combine with axillary incision
Lumpectomy Technique
Excision and Specimen Orientation

• Thick flaps unless mass is superficial
• Keep in mind possible future PBI
• Remove piece of skin if mass is fixed
• Use sharp dissection
• Orient specimen and tag before removing

Sutures
Lumpectomy Technique
Intraoperative Margin Assessment

• Inking of specimen by pathologist
• Gross margin inspection
• Resection of additional tissue if necessary
What Constitutes Adequate Margin for IBC? 
Meta-Analysis: Effect of Margin Status on LR

- 21 studies
- 14,571 pts, 1,026 LRs
- LR by margin status
- LR by distance for (-) margins
- Odds of LR were significantly associated with margin status:
  - OR = 2.02 for (+)/close vs. (-) (P < 0.001)
  - OR = 1.80 for close vs. (-)
  - OR = 2.42 for (+) vs. (-) (both P < 0.001)
What Constitutes Adequate Margin for IBC?
Meta-Analysis: Effect of Margin Width on LR

• No significant association with margin width: 1 vs. 2 vs. 5 mm, $P > 0.10$

• Weak evidence that the OR of LR decreased as margin width increased:
  – OR for 1 mm, 2 mm, 5 mm: 1.0, 0.75, 0.51
  – $P = 0.097$ for trend in one model NS in another model

• Conclusions:
  – Margin status has a prognostic effect in women with IBC
  – Adoption of wider margins, relative to narrower is unlikely to have impact on LR

Houssami et al: Eur J Cancer 2010
What Constitutes Adequate Margin for DCIS?

Meta-Analysis: Effect of Margin Status on LR

- 4,660 patients from trials of BCS + XRT for DCIS
- Pts with (-) margins significantly less likely to experience IBTR than pts with (+) margins (OR 0.36)
- A (-) margin significantly reduced risk of IBTR compared with a close (OR 0.59) or unknown margin (OR 0.56)
What Constitutes Adequate Margin for DCIS?  
**Meta-Analysis: Effect of Margin Width on LR**

- **2-mm margin** was superior to a margin < 2 mm (OR 0.53)
- No significant difference in IBTR between 2 mm and more than 5 mm (OR 1.51; \( P \leq .05 \))
- A margin of 2 mm seems to be as good as a larger margin

<table>
<thead>
<tr>
<th>Negative Margin Width</th>
<th>No. of Patients</th>
<th>% of Patients With IBTR</th>
<th>Relapse vs &gt; 5 mm</th>
<th>OR</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cells on ink</td>
<td>914</td>
<td>9.4</td>
<td></td>
<td>2.56</td>
<td>1.1 to 7.3</td>
<td>&lt; .05</td>
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<tr>
<td>1-mm margin</td>
<td>1,239</td>
<td>10.4</td>
<td></td>
<td>2.89</td>
<td>1.3 to 8.1</td>
<td>&lt; .05</td>
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<td>2-mm margin</td>
<td>207</td>
<td>5.8</td>
<td></td>
<td>1.51</td>
<td>0.51 to 5.0</td>
<td>&gt; .05</td>
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<tr>
<td>( \geq ) 5-mm margin</td>
<td>154</td>
<td>3.9</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; IBTR, ipsilateral breast tumor recurrence; OR, odds ratio.

Dunne et al: J Clin Oncol, 2009
A Recently Observed Trend: Increase in the Incidence of Contralateral Prophylactic Mastectomy

Tuttle et al: J Clin Oncol 2007
Nipple-Sparing Mastectomy

Background

• In most mastectomy techniques the NAC is removed:
  • Contains terminal ducts
  • Centripetal lymphatic drainage towards the subareolar plexus of Sappey

• In early mastectomy studies the likelihood of occult NAC involvement was relatively high (8-50%)
  • Increased risk with tumor proximity to NAC, poorly differentiated tumors, lymph node positivity, size >2 cm

Nipple-Sparing Mastectomy

Rationale

- In more recent mastectomy series NAC involvement is seen in 6-11%.
- In the majority not appreciated preoperatively.
- Careful intraoperative evaluation of the NAC by FS or touch prep is necessary for NSM.
- Several series have demonstrated the feasibility of NSM but long term FU is needed.
- Main advantages: cosmesis and preservation of nipple sensation (variable).
- Potential concerns: nipple necrosis, long-term oncologic safety.

Nipple-Sparing Mastectomy
Appropriate Candidates

- Tumor size 3 cm or less
- Tumor location at least 2 cm from the nipple-areola complex
- Absence of multicentricity
- Absence of segmental malignant calcifications extending to the nipple-areola complex
- Clinically negative nodes
- Negative intraoperative biopsy of nipple-areola complex

Nipple-Sparing Mastectomy
Technique Aspects

- **Incisions:**
  - Peri-areolar with lateral extension
  - Trans-areolar, peri-nipple with lateral extension
  - Trans-areolar, trans-nipple with medial and lateral extensions
  - Inferior-lateral mammary crease incision
  - Nipple-sparing omega (mastopexy) incision
  - Vertical incision

Special Circumstances in Breast Cancer Primary Surgery
Family History/BRCA Status and IBTR

• Family history is not an independent predictor of IBTR in case-control studies

• Whether BRCA mutations increase IBTR rates after BCS is controversial:
  • Pierce et al: No significant increase in 10-year IBTR rate for BRCA+ pts (12%) vs. BRCA- pts (9%)
  • Robson et al: Non-significant increase in IBTR rate for BRCA+ Ashkenazi Jewish pts vs. BRCA- pts (RR=1.79; 95% CI=0.64-5.03)
  • Hafty et al: Significant increase in 12-year IBTR rate for BRCA+ pts (49%) vs. BRCA- pts (21%). No oophorectomy or tamoxifen used

Surgical Approach of BRCA+ Patients

- **Known Mutation Carriers:**
  - Discuss BCS vs. bilateral mastectomy
  - XRT is effective without excess toxicity
  - High rate of IBTR and CBC

- **Suspected Mutation Carrier:**
  - Proceed with surgery as planned based on tumor presentation (consider neoadjuvant Rx)
  - Proceed with genetic counseling and testing
  - Revisit the surgical management after systemic therapy is given and before XRT
Extensive Intraductal Component (EIC)

DCIS in ≥ 25% of the tumor area

- In early studies, EIC has been found to be associated with increase in IBTR rates after BCS
- Most of these studies included patients with involved margins and margin involvement generally correlates with the presence of EIC
- Subsequent studies that included patients with negative or focally positive margins, showed that presence of EIC does not significantly predict for IBTR
Presence of Lobular Histology

• Invasive lobular carcinoma can present in an insidious fashion making margin assessment often challenging

• Several studies have shown no significant differences in IBTR rates between pts presenting with lobular vs. ductal histology

• In one study, presence of LCIS increased IBTR rates at 10 but not at 5 years and mostly in younger women

Occult Breast Cancer
Incidence and Diagnosis

- 0.3%-1% of breast cancers present with clinical axillary adenopathy with an occult breast primary
- Breast MRI identifies the occult primary in 75-85% of the cases
- In the majority of cases with negative MRI, no tumor can be identified in the mastectomy specimen

Occult Breast Cancer
Loco-Regional Management

- Traditionally, MRM followed by L-R XRT has been the standard approach
- Acceptable approaches with proven safety (in small series) include:
  - Axillary node dissection followed by breast XRT (and regional nodal XRT as appropriate)
  - Neoadjuvant chemotherapy followed by either one of the above options
- If mastectomy is not performed, omission of breast XRT increases the rates of IBTR (from about 12-33% to about 14-83%)

Neoadjuvant Chemotherapy
Loco-Regional Effects

• NC in operable breast cancer induces clinical response in 80-90% of the pts

• pCR rates range from 15-40%

• NC increases the rates of BCS without significantly increasing IBTR

• Potential to increase cosmetic result by decreasing the amount of breast tissue needed to be removed at lumpectomy
Challenges in Decreasing the Size of the Lumpectomy Specimen

• Sometimes difficult to define the extent of residual tumor and as a result the amount of breast tissue to be removed at lumpectomy

• Ideally one would want to remove less than originally required
How Do Tumors Shrink in Response to NC?
What is Adequate Surgical Resection after NC?
MRI Phenotypes

1: Single predominant mass with identifiable rim, displacing
2: Nodular pattern, irregular borders
3: Diffuse infiltrative pattern
4: Patchy enhancement
5: Septal spread

MRI Can Overestimate the Amount of Residual Disease

Before NC

After NC
Neoadjuvant Chemotherapy
Surgical Planning

- Identification of the exact tumor location in cases of cCR
  - Preoperative titanium clip placement
Ensuring Adequate Surgical Resection after NC

- Identify pattern of shrinkage and the extent of residual tumor preoperatively (mammogram, US, MRI)
- Accurately localize tumor bed area in cases of clinical/radiologic CR
- Thoroughly evaluate margins (intraoperatively and postoperatively)
- Perform additional resection if necessary

Invasive Lobular Carcinoma and NC

- Particular attention when planning BCS in pts with ILC after NC
- ILC often multicentric and can extensively involve the breast without significant clinical or mammographic findings
- MRI is useful in defining the extent in the breast (but not in the axilla)
- Very low pCR rates with ILC (0-3%)
- ILC predicts for ineligibility of BCS
- Unlikely that pts with extensive ILC will be converted to BCS candidates by NC

Conventional wisdom is that once metastases have occurred, aggressive local therapy provides no survival advantage and should not be pursued except to prevent local complications (bleeding, ulceration, infection).

Several retrospective studies have shown significantly better outcomes for women who had surgical removal of their tumor vs. those who did not (particularly for those who had negative margins).

Primary Surgical Therapy in Patients Presenting with Stage IV BC

• Most studies adjusted for imbalances in known prognostic factors (such as number of mets, location of mets, type of systemic therapy or use of radiotherapy)

• Most studies concluded that unrecognized selection bias may have accounted for the observed benefit of surgery and only a large prospective RCT could reliably answer the question (ECOG 2108)

Primary Surgical Therapy in Patients Presenting with Stage IV BC

- In the absence of RCT data, not removing the primary tumor remains the standard.
- Surgery can be entertained in selected cases (before or after systemic therapy) for local control if local manifestations are more likely to contribute to morbidity than distant ones.
- In such cases, breast conserving surgery is preferable if it can encompass the scope of the surgical resection.
- Axillary node surgery or breast XRT are generally not advisable.
Summary/Conclusions (1)

- Core needle biopsy is the standard diagnostic procedure for primary BC
- MRI is not indicated for all pts who undergo BCS
- Lumpectomy + breast XRT is the preferred surgical option in the absence of absolute contraindications
- An increase in the use of CPM has been recently reported
- Use of nipple-sparing mastectomy requires careful consideration and patient selection
Summary/Conclusions (2)

- Family history of breast cancer, presence of EIC (with negative margins), lobular histology and presence of LCIS do not increase the rates of IBTR and are not contraindications to BCS.

- In patients presenting with “occult” BC and axillary metastases, MRI plays an important role in identifying the primary in the breast. Breast XRT is an acceptable alternative to mastectomy, if MRI does not identify a distinct lesion.
In patients undergoing neoadjuvant chemotherapy, unique primary surgical issues relate to the assessment of the extent of residual disease and the exact location of residual tumor (or tumor bed) in patients with complete clinical and/or radiologic response.

There is currently no definitive evidence that the use of primary breast surgery in patients presenting with stage IV disease improves overall survival.