Communication between Surgeon and Pathologist in Evaluating Adequacy of Lumpectomy for Breast Cancer

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Disclosures

• I have no financial disclosures
• Co-chair (with Tom Buchholz MD) of ASCO Endorsement Panel for Review of SSO/ASTRO Margin Consensus Guideline
Clinical Trials of Mastectomy vs. Breast Conservation Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th># Pts</th>
<th>Max tumor size</th>
<th>Overall Survival</th>
<th>Local Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mast</td>
<td>BCT</td>
</tr>
<tr>
<td>Milan Cancer Institute</td>
<td>701</td>
<td>2 cm</td>
<td>76%</td>
<td>79%</td>
</tr>
<tr>
<td>EORTC</td>
<td>868</td>
<td>5 cm</td>
<td>66%</td>
<td>65%</td>
</tr>
<tr>
<td>U.S. NCI</td>
<td>237</td>
<td>5 cm</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>NSABP B-06</td>
<td>1855</td>
<td>4 cm</td>
<td>71%</td>
<td>71%</td>
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</tbody>
</table>

**Outstanding Question:**
What is the optimal negative lumpectomy margin thickness?
Re-excision Lumpectomy for Margins: *How many is too many??*

  - 2,770 BCS pts from Fox Chase Cancer Center
  - No difference in 5- and 10-yr local recurrence rates for patients requiring no re-excisions vs. one re-excision vs two or more re-excisions

- Re-excisions to achieve optimal margin control potentially impair cosmetic result and increase costs of cancer care, but they do not correlate with higher risk of local failure

- **Outstanding Question:** What is the optimal negative lumpectomy margin thickness?
• Multidisciplinary panel of experts
  – Meta-analysis of margin width versus risk of ipsilateral breast tumor recurrence (IBTR) in Stage I/II breast cancer
    • 33 studies, 1965-2013
    • 28,162 patients
    • Median follow-up 6.6 years
    • IBTR in 1,506 (5.3%)
Key Findings/Recommendations

1. “Positive margins (ink on invasive carcinoma or DCIS) are associated with a 2-fold increase in the risk of IBTR compared with negative margins”

2. “This increased risk is not mitigated by favorable biology, endocrine therapy, or a radiation boost”

3. “More widely clear margins than no ink on tumor do not significantly decrease the rate of IBTR compared with no ink on tumor”

4. “There is no evidence that more widely clear margins reduce IBTR for young patients or for those with unfavorable biology, lobular cancers, or CA with EIC”
Key Findings: Importance of Systemic Therapy

• “The rates of IBTR are reduced with the use of systemic therapy”

• “In the uncommon circumstance of a patient not receiving adjuvant systemic therapy, there is no evidence suggesting that margins wider than no ink on tumor are needed”
Local Recurrence by Study Year & Margin Width: Effect of Advances in Systemic Therapy

Houssami N, Ann Surg Oncol 2014
Therefore...

• “The widespread use of systemic therapy today...increased the confidence of the MP that wider margins were unlikely to enhance local control in a clinically significant way in the current era”

• “Thus, although larger margin widths may have resulted in small reductions in local recurrence in the past, there is no evidence that they are important in the setting of current multimodality treatment”
Close Margins

• Limited data for Expert Panel to review regarding comparisons of “no ink on tumor” margin versus margin $\geq 1$ mm

• Dixon and Thomas, Int J Rad Onc Bio Phy 2014 editorial letter
  – “The consensus panel may be right that no ink on margin is sufficient, but the evidence that they present to support this is much less convincing than the evidence presented in the 2 meta-analyses that close margins increase ipsilateral breast tumor recurrence and that a margin width of 1 mm is optimal”
Importance of Clinical Judgment

• Consensus Guideline Expert Panel: “In addition, when an EIC is present, young age and *multiple close margins* are associated with an increased risk of IBTR and can be used to select patients who might benefit from re-excision”

• Multiple editorialists echoed importance of clinical judgement regarding considerations of re-excision lumpectomy, especially in the presence of close margins

  » Jagsi et al Int J Rad Onc Bio Phys 2014
  » Schnitt et al Arch Path Lab Med 2014
  » Hunt and Sahin JCO 2014
• Clinical judgment essential
  – Selected cases of positive margin might not warrant re-excision (rare)
  – Selected cases of negative/close margins might be considered for re-excision (not uncommon)
• Systemic therapy is essential in optimizing local as well as distant control of disease
  – Importance of cautious clinicopathologic correlation in confirming adequacy of data for selecting appropriate systemic therapy
Relevant Factors in Determining Re-excision and Systemic Therapy Needs

• Tumor location, size and diffuse versus focal pattern
• Correlation with preop breast imaging
  – Evidence of multiple tumors?
  – Concordance between imaging and pathology extent of disease?
  – Mammographically-detected microcalcifications: benign versus malignant calcifications on pathology
• Further evaluation of “close” margins (<2 mm)
  – how close; span of close margin; location; and multiple foci versus single focus of close margin
• How many re-excision lumpectomies are “acceptable”???
• Adequacy of molecular marker/Oncotype Dx testing
  – Similarity versus heterogeneity between multiple tumors
  – Extent of invasive disease resected with core biopsies
Are there any scenarios of a positive margin where reexcision is not warranted???

• Approach with EXTREME caution!
• Potential case: Small, unifocal, screen-detected, deep-seated tumors adjacent to pectoralis AND…
  – Single focus of positive margin is at deep lumpectomy surface
  – Surgeon documents that resection extended to pectoralis fascia
  – Suspicion of margin distortion related to “pancake effect” of specimen mammography
  – Patient is committed to breast XRT
  – Re-excision will compromise cosmetic outcome
Scenarios where re-excision should be considered when margins are **negative but close**

- Multiple close margins, especially if...
  - Extensive DCIS
  - Cautery effect making margin evaluation more challenging
  - Clinical and radiographic extent of disease underestimates extent of disease identified by pathology (e.g. with invasive lobular histology)
  - Patient is young (<40 years)
    - Hunt and Sahin, JCO 2014
    - Buchholz and Newman, JCO 2014
    - Schnitt et al, Arch Pathol Lab Med 2014
    - Houssami and Morrow, J Surg Onc 2014
Scenarios where re-excision is determined by pattern of microcalcifications in addition to margin evaluation

• Multidisciplinary team should assess extent and level of suspicion regarding mammographically-detected calcs preoperatively
  – Guides planning for single/multiple wire localizations, even in the presence of a palpable tumor

• Pathology confirmation that calcs are benign versus malignant versus both

• Perform post-lumpectomy mammogram if any evidence of malignant calcs
  – Re-excision lumpectomy warranted for residual calcs, even if lumpectomy margins are widely negative
Managing Residual Microcalcifications
Clinicopathology Correlation to Optimize Systemic Therapy Needs

• Consider repeating IHC/biomarker evaluation on lumpectomy specimen if...
  – Extensive DCIS present on initial diagnostic cores with suspicion that markers represented in situ component
  – Suspicion of significant intratumoral heterogeneity
  – Initial markers suggest TNBC or borderline HER2

• Consider staging T/tumor diameter by extent of disease in cores if...
  – Lumpectomy specimen contains minimal residual invasive disease, especially when following vacuum-assisted core biopsy
Clinicopathology Correlation to Optimize Systemic Therapy Needs

• Cases of multiple tumors suspected by preoperative breast imaging
  – Confirm that all lesions are accounted for in resected breast specimen
  – May require post-lumpectomy imaging to rule out residual satellite lesions
  – Consider repeating IHC/biomarker studies and/or Oncotyping on separate lesions
    • Especially important where tumors have discordant morphology/histology and/or grade
## Expanded Eligibility for BCS

### Cases of Multifocal/Multicentric tumors

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>F/U</th>
<th>Margins</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leopold, 1989</td>
<td>10</td>
<td>64</td>
<td>“gross” exc</td>
<td>40%</td>
</tr>
<tr>
<td>Kurtz, 1990</td>
<td>61</td>
<td>71</td>
<td>Pos/uk: 39 Neg: 22</td>
<td>All: 25% Neg mar: 5%</td>
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<tr>
<td>Wilson, 1993</td>
<td>13</td>
<td>71</td>
<td>“gross” exc</td>
<td>23%</td>
</tr>
<tr>
<td>Hartsell, 1994</td>
<td>27</td>
<td>53</td>
<td>Grossly neg</td>
<td>3.7%</td>
</tr>
<tr>
<td>Cho, 2002</td>
<td>15</td>
<td>77</td>
<td>Micro neg</td>
<td>0%</td>
</tr>
<tr>
<td>Kaplan, 2003</td>
<td>36</td>
<td>98</td>
<td>Micro neg</td>
<td>2.8%</td>
</tr>
<tr>
<td>Okumura, 2004</td>
<td>34</td>
<td>45</td>
<td>&gt;2mm in 21 cases</td>
<td>2.9%</td>
</tr>
</tbody>
</table>
Clinicopathology Correlation to Optimize Systemic Therapy Needs

- Cases of multiple tumors suspected by preoperative breast imaging
  - Confirm that all lesions are accounted for in resected breast specimen
  - May require post-lumpectomy imaging to rule out residual satellite lesions
  - Consider repeating IHC/biomarker studies and/or Oncotyping on separate lesions
    - Especially important where tumors have discordant morphology/histology and/or grade
Multiple Tumors
Guideline not relevant for...

- Pure DCIS
- Neoadjuvant Chemotherapy
- Partial breast irradiation/No irradiation
Optimal Margins for Pure DCIS

  - Sparse data, but many c/w adequacy of “no ink on tumor” approach
  - Consider more aggressive approach because of intraluminal/intraductal extension that can appear to “skip” over segments of normal tissue
- Existing Consensus Guidelines:
  - American Soc of Breast Surgeons: No ink on tumor
  - NCCN: > 1 mm
  - NICE: 2 mm
  - New Zealand Guidelines Group: 2 mm
Margins and Lumpectomy Following Neoadjuvant CTX

CTX Effect on Primary Tumor

Primary Tumor

- Invasive
- Invasive + DCIS

Following CTX

- Smaller Tumor
- Smaller Tumor with Satellites
- Tumor Less Well Defined
- Intralucial Residual Only
- Smaller Tumor-No Change in Intralucial Component
- Intralucial Residual Only
Cases where adjuvant XRT is either minimized or omitted

- Usually elder patients with hormone receptor-positive, HER2/neu-negative breast cancer
  - CALGB 9343
  - PRIME Study
Enrollment: 1994-1999
Age at least 70 yrs
T1, ER-positive breast CA
All clinically-neg axillae:
- *ALND encouraged but not required*
- *2/3 had no surgical staging of axilla*

Median f/u: 12 years

*Hughes K S et al.*
*JCO 2013;31:2382-2387*
S2-01
The PRIME 2 trial: Wide local excision and adjuvant hormonal therapy ± postoperative whole breast irradiation in women ≥ 65 years with early breast cancer managed by breast conservation

Dr. Kunkler: Nothing to disclose.
Dr. Williams: Nothing to disclose.
Dr. Jack: Nothing to disclose.
Dr. Canney: Nothing to disclose.
Dr. Prescott: Nothing to disclose.
Dr. Dixon: Nothing to disclose.
Eligibility and Follow-Up

- Age ≥ 65 years
- Histologically confirmed Unilateral Invasive breast cancer
- Pathology size ≤ 3cm
- Breast conserving surgery
- **Excision margin of ≥1mm on histological assessment**
- ER and/or PR-positive
- Treated with adjuvant endocrine therapy
  - 9% received neoadjuvant endocrine therapy
- Multicenter study: 98 sites; 6 countries
- Median Follow-up: 5 years
Design

1326

WBI*, N=658

No WBI, n=668

* 40 - 50Gy in 15 – 25 #
## Local control

<table>
<thead>
<tr>
<th></th>
<th>Local recurrence</th>
<th>5 yr actuarial rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT (n=668)</td>
<td>26</td>
<td>4.1%</td>
</tr>
<tr>
<td>RT (n=658)</td>
<td>6</td>
<td>1.3%</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

**Graph:**
- **Cumulative failure (%)**
- **Time to first local recurrence**
- **Time (years) vs. Cumulative failure (%)**
- **RT**
- **No RT**
- **p=0.002**
# Multivariate LR

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T size (ref 0-10mm)</strong></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10.1-20mm</td>
<td>0.53 (0.23, 1.22)</td>
<td>0.14</td>
</tr>
<tr>
<td>20.1-30mm</td>
<td>1.17 (0.43, 3.20)</td>
<td>0.76</td>
</tr>
<tr>
<td>Margins (ref &gt;5mm)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&lt;1mm</td>
<td>1.99 (0.25, 16.04)</td>
<td>0.52</td>
</tr>
<tr>
<td>1-5mm</td>
<td>0.89 (0.40, 1.98)</td>
<td>0.78</td>
</tr>
<tr>
<td>Re-excision</td>
<td>1.05 (0.38, 2.89)</td>
<td>0.92</td>
</tr>
<tr>
<td>Radiotherapy (ref Yes)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>5.08 (1.95, 13.24)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (ref 65-69)</strong></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>70+</td>
<td>2.08 (0.95, 4.55)</td>
<td>0.07</td>
</tr>
<tr>
<td>Grade (ref G1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>1.31 (0.59, 2.90)</td>
<td>0.51</td>
</tr>
<tr>
<td>G3</td>
<td>3.48 (0.89, 13.65)</td>
<td>0.07</td>
</tr>
<tr>
<td>LVI (ref No)</td>
<td>1</td>
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<tr>
<td>Yes</td>
<td>1.28 (0.29, 5.59)</td>
<td>0.75</td>
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<tr>
<td>ER status (ref High)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2.84 (1.21, 6.65)</td>
<td>0.02</td>
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</table>
More widely negative margins should be considered in cases where XRT fields will be modified or omitted.
Summary and Conclusions

• Adequacy of lumpectomy in breast conserving surgery requires multidisciplinary attention to several factors related to both local and distant control of disease
  – No ink on tumor is an acceptable margin for most Stage I/II lumpectomy cases
  – Consider re-excision for cases of close margins
    • Span/multiplicity of close margin; pt age; extent of DCIS
  – Where relevant, document absence of residual calcifications and/or satellite lesions with post-lumpectomy mammogram
• Confirm adequacy of tumor evaluation(s) for appropriate selection of systemic therapy
THANK YOU!!!!!!!!