A Contemporary View of Lumpectomy Margin Evaluation

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Disclosures

None
Local Treatment of Breast Cancer

• Breast conserving therapy now standard treatment for patients with invasive breast cancer
  – Breast conserving surgery and radiation therapy
  – Breast conserving surgery alone (for selected patients)
• Associated with high levels of local tumor control
Local Treatment of Breast Cancer

- Small proportion of patients develop local recurrence in the treated breast
- Minimizing local recurrence is important
  - Emotional distress
  - Adverse effect on survival
Risk Factors for Recurrence in the Conservatively Treated Breast

- **Clinical factors**
  - Young age

- **Treatment factors**
  - Extent of excision
  - Details of radiation therapy
  - Use of systemic therapy

- **Tumor factors**
  - Gross multicentric disease
  - Extensive intraductal component
  - Molecular subtype
  - Margins
Basics of Margin Evaluation

• Margin evaluation is an exercise in probabilities (not absolutes)

• Patients with positive margins are more likely to have residual disease at or near the primary site than those with negative margins

• But
  – A positive margin does guarantee residual disease
  – A negative margin does not preclude extensive residual disease
The Goal of Margin Evaluation

• *IS NOT* to ensure that there is no residual tumor in the breast
The Goal of Margin Evaluation

• To identify those patients more likely to have a large residual tumor burden and who, therefore, require further surgery (re-excison or mastectomy)

• To identify those patients unlikely to have a large residual tumor burden and who, therefore, are suitable candidates for breast conserving therapy without further surgery
Margins in Surgical Pathology

Colectomy

Lumpectomy

EASY

DIFFICULT!!
Limitations of Margin Assessment

• Technical and methodological
• Definition and interpretation
• Distribution of tumor in the breast
• Breast cancer biology
• Impact of systemic therapy
Technical and Methodologic Issues

• The “pancake phenomenon”
The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer

Roger A. Graham, M.D.\textsuperscript{a,c,*}, Marc J. Homer, M.D.\textsuperscript{b}, Judith Katz, M.D.\textsuperscript{b}, Janice Rothschild, M.D.\textsuperscript{a}, Homa Safaii, M.D.\textsuperscript{c}, Stacey Supran, M.A.\textsuperscript{d}

**Fig. 3.** Demonstration of typical specimen flattening and its impact on margin assessment.

Occurs even in the absence of compression for specimen radiography
Technical and Methodologic Issues

- The “pancake phenomenon”
- Specimen orientation
In addition to orienting specimen using S and L sutures, a 3rd stitch was randomly added to another margin.

Surgeon-pathologist discordance about 3rd margin location in 31% of cases.
Technical and Methodologic Issues

• The “pancake phenomenon”
• Specimen orientation
• Problems with ink
Inking of Specimen Margins

Unoriented Specimen

Oriented Specimen
Is this the orange margin or the blue margin?
# Recognition and Discrimination of Tissue-Marking Dye Color by Surgical Pathologists

**Recommendations to Avoid Errors in Margin Assessment**

Andrew S. Williams, MD, and Kelly Dakin Hache, MD, PhD

<table>
<thead>
<tr>
<th>Color</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>100</td>
</tr>
<tr>
<td>Green</td>
<td>100</td>
</tr>
<tr>
<td>Blue</td>
<td>96</td>
</tr>
<tr>
<td>Red</td>
<td>100</td>
</tr>
<tr>
<td>Violet</td>
<td>78</td>
</tr>
<tr>
<td>Orange</td>
<td>56</td>
</tr>
<tr>
<td>Yellow</td>
<td>50</td>
</tr>
</tbody>
</table>
Technical and Methodologic Issues

- The “pancake phenomenon”
- Specimen orientation
- Problems with ink
- No uniform sampling method; sampling error
Sampling of Lumpectomy Specimens

- Ranges from limited sectioning to total sequential embedding
- Even with total, sequential embedding, only a small proportion of the specimen is examined microscopically
How “Total” is Total Sequential Embedding?

- 4.2 cm lumpectomy specimen
- Cut at 3mm intervals resulting in 14 slices
- Each slice embedded in paraffin and cut at five microns
- Results in 14 five micron sections
- 70 microns of tissue examined from a 4.2cm specimen = 0.2% of specimen
Complete Histologic Examination of this 4.2 cm Lumpectomy Specimen Would Require

84000 slides
Definitions and Interpretive Issues
Defintions

• No general agreement among surgeons or radiation oncologists as to what constitutes an adequate negative margin
  – No margin width about which >50% of surgeons or radiation oncologists agree is “adequate” or “negative”
  – All available data from retrospective studies
  – Issue never addressed in randomized trials
What is an Adequate Margin? Surveys (Azu, 2010)

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Not touching ink (%)(^1)</th>
<th>&gt;1–2 mm (%)</th>
<th>&gt;5 mm (%)</th>
<th>&gt;1 cm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 60 yr old, 0.8 cm Invasive ER/PR/HER2-, RT planned</td>
<td>11.2</td>
<td>42.0</td>
<td>27.9</td>
<td>18.9</td>
</tr>
</tbody>
</table>

\(^1\) Percentage of surgeon respondents who selected a given margin width for each clinical scenario, N=318
What is an Adequate Margin?
Radiation Oncologists (Taghian, 2005)

FIGURE 1. Responses regarding the definition of negative margins in North America (United States and Canada). Results from 702 respondents. The question asked was: “How do you define negative margins after local excision?”
Variability in Reexcision Following Breast Conservation Surgery

48% of re-excisions performed on patients with negative margins
Why does it matter?

- Extent of surgical resection most important determinant of cosmetic outcome
Why does it matter?

• Re-excisions associated with
  – Patient anxiety
  – Morbidity
  – Cost
  – Patients opting for mastectomy
How Well Does Any Given Margin Measurement Reflect Reality?
Distribution of Tumor in the Breast
Histologic Multifocality of Tis, T1-2 Breast Carcinomas

Implications for Clinical Trials of Breast-Conserving Surgery

ROLAND HOLLAND, MD,* SOLKE H. J. VELING, MSc,† MARCEL MRAVUNAC, MD§
AND JAN H. C. L. HENDRIKS, MD‡

Cancer, 1985
Negative Margin Width and Local Recurrence

If this is the case, do millimeters really matter?
• 14,571 patients from 21 studies

• No significant difference in LR rates associated with threshold margin widths of 1mm, 2mm or >5mm when adjusted for use of radiation boost or endocrine therapy
Breast Cancer Biology
Impact of Breast Cancer Biology on Local Recurrence

• More biologically aggressive types (e.g., triple negative breast cancer) associated with higher local recurrence rates regardless of margin width
Local recurrence by breast cancer subtype: DFCI / BWH / MGH experience

Nguyen P L et al. JCO 2008;26:2373-2378
Impact of Breast Cancer Biology on Local Recurrence

- More biologically aggressive types (e.g., triple negative breast cancer) associated with higher local recurrence rates regardless of margin width

- OncotypeDX recurrence score (developed to predict likelihood of distant recurrence) also predicts loco-regional recurrence \((Mamounas, 2010)\)
Impact of Breast Cancer Biology on Local Recurrence

• More biologically aggressive types (e.g., triple negative breast cancer) associated with higher local recurrence rates regardless of margin width

• OncotypeDX recurrence score (developed to predict likelihood of distant recurrence) also predicts loco-regional recurrence (Mamounas, 2010)

• Wider margins don’t overcome bad biology
Impact of Systemic Therapy
Effective Systemic Therapy Reduces Local Recurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>No Systemic Therapy</th>
<th>Systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+, N-</td>
<td>14.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>(systemic Rx: none vs Tam)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-, N-</td>
<td>13.4%</td>
<td>2.6%</td>
</tr>
<tr>
<td>(systemic Rx: none vs MF)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients in both studies had NSABP-defined negative margins (i.e., no tumor touching ink)
TAMOXIFEN CHEMOTHERAPY

Overview.

EBCTCG Overview. Lancet 2005;365:1687

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Polychemo. events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated polychemo.</td>
<td>Adjusted</td>
<td>Logrank Variance</td>
</tr>
<tr>
<td>(i) Site of first recurrence ($\chi^2 = 0.2; p &gt; 0.1; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials with data on isolated local and contralateral*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated local</td>
<td>206/15684</td>
<td>268/12271</td>
<td>-48.8</td>
</tr>
<tr>
<td>Contralateral*</td>
<td>55/15684</td>
<td>60/12271</td>
<td>-9.8</td>
</tr>
<tr>
<td>Distant/multi.</td>
<td>528/15684</td>
<td>613/12271</td>
<td>-104.2</td>
</tr>
<tr>
<td></td>
<td>(1.3%/y)</td>
<td>(2.2%/y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.4%/y)</td>
<td>(0.5%/y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3.4%/y)</td>
<td>(5.0%/y)</td>
<td></td>
</tr>
</tbody>
</table>

- 99% or ←→ 95% confidence intervals

Treatment effect 2p < 0.00001

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Tamoxifen events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated tamoxifen</td>
<td>Adjusted</td>
<td>Logrank Variance</td>
</tr>
<tr>
<td>(j) Site of first recurrence ($\chi^2 = 5.4; p = 0.07; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials with data on isolated local and contralateral*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated local</td>
<td>114/22257</td>
<td>208/18819</td>
<td>-57.9</td>
</tr>
<tr>
<td>Contralateral*</td>
<td>79/22257</td>
<td>120/18819</td>
<td>-26.9</td>
</tr>
<tr>
<td>Distant/multi.</td>
<td>507/22257</td>
<td>631/18819</td>
<td>-116.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>69/22257</td>
<td>56/18819</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>(0.5%/y)</td>
<td>(1.1%/y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.4%/y)</td>
<td>(0.6%/y)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2.3%/y)</td>
<td>(3.4%/y)</td>
<td></td>
</tr>
</tbody>
</table>

- 99% or ←→ 95% confidence intervals

Treatment effect 2p < 0.00001
Lack of agreement regarding definition of a negative margin

Common use of re-excision (including in pts already with no ink on tumor)

Recognition of impact of contemporary systemic therapies on reducing LR rates

Better understanding of tumor biology

Joint SSO-ASTRO Consensus on Margins in Invasive Breast Cancer
# Joint SSO-ASTRO Consensus on Margins in Invasive Breast Cancer

**July 12-13, 2013**

**Co-chairs:**
- Monica Morrow, SSO
- Meena Moran, ASTRO

**Participants:**
- ASBS: Suzanne Klimberg
- ASCO: Marina Chavez MacGregor
- ASTRO: Jay Harris, Gary Freedman, Janet Horton
- CAP: Stuart Schnitt
- SSO: Armando Giuliano, Seema Khan
- Advocate: Peggy Johnson
- Methodologist: Nehmat Houssami

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*Funded by a grant from Susan G. Komen*
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Funded by a grant from Susan G. Komen
February 10, 2014

Original Article - Breast Oncology - Special Article

Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

Meena S. Moran, MD, Stuart J. Schnitt, MD, Armando E. Giuliano, MD, Jay R. Harris, MD, Seema A. Khan, MD, Janet Horton, MD, Suzanne Klimberg, MD, Mariana Chavez-MacGregor, MD, Gary Freedman, MD, Nehmat Houssami, MD, PhD, Peggy L. Johnson, and Monica Morrow, MD

Clinical Investigation: Breast Cancer

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SSO-ASTRO Consensus

- Applies only to patients with invasive breast cancer treated with breast conserving surgery and whole breast irradiation
- Does not apply to:
  - Patients treated with partial breast irradiation
  - Patients treated with lumpectomy without radiation
  - Patients treated with neoadjuvant chemotherapy
  - Patients with DCIS
The Association of Surgical Margins and Local Recurrence in Women with Early-Stage Invasive Breast Cancer Treated with Breast-Conserving Therapy: A Meta-Analysis

Nehmat Houssami, MD, PhD¹, Petra Macaskill, PhD¹, M. Luke Marinovich, MPH¹, and Monica Morrow, MD²

Study-level meta-analysis of 33 studies (870 abstracts screened): 28,162 patients
1,506 local recurrences

Study eligibility: > 90% Stage I+II
Minimum mean/median f/u 4 yrs
LR in relation to margin status
Whole breast RT
## Margins Meta-analysis: Results

Median Prevalence of LR: 5.3% (2.3-7.6%)

<table>
<thead>
<tr>
<th>Margin status</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1.0</td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Positive/Close</td>
<td>1.96</td>
<td>1.72-2.24</td>
<td></td>
</tr>
</tbody>
</table>

- Adjusting for age, yr of recruitment, endocrine rx did not change results
- Increased local recurrence rate associated with positive margins not nullified by radiation boost, systemic therapy, or favorable biology
## Margins Meta-analysis: Results

<table>
<thead>
<tr>
<th>Margin status</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close</td>
<td>1.74</td>
<td>1.42-2.15</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Positive</td>
<td>2.44</td>
<td>1.97-3.03</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
1. Heterogeneity in definitions of positive and close margins
2. Panel felt that analysis of specific margin widths supersedes this
# Margins Meta-analysis: Results

Relationship Between LR and Threshold Margin Distance

<table>
<thead>
<tr>
<th>Threshold Distance</th>
<th># studies</th>
<th># subjects/# LRs</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mm</td>
<td>6</td>
<td>2376/235</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2 mm</td>
<td>10</td>
<td>8350/414</td>
<td>0.91</td>
<td>0.46-1.80</td>
</tr>
<tr>
<td>5 mm</td>
<td>3</td>
<td>2355/103</td>
<td>0.77</td>
<td>0.32-1.88</td>
</tr>
</tbody>
</table>

\[ p \text{ (association)} = 0.90 \]
\[ p \text{ (trend)} = 0.58 \]

*Adjusted for length of f/u*
## Impact of Margin Width on LR
### Treatment Covariates

<table>
<thead>
<tr>
<th>Treatment Covariate</th>
<th># studies</th>
<th>1mm</th>
<th>2mm</th>
<th>5mm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine Rx</td>
<td>16</td>
<td>1.0</td>
<td>0.98</td>
<td>0.90</td>
<td>0.95</td>
</tr>
<tr>
<td>Radiation Boost</td>
<td>18</td>
<td>1.0</td>
<td>0.82</td>
<td>0.92</td>
<td>0.86</td>
</tr>
</tbody>
</table>

*Adjusted for length of f/u
Risk of Local Recurrence Related to Margin Width Over Time
SSO-ASTRO Consensus

The Bottom Line

• A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a 2-fold increase in local recurrence

• This increased risk is not nullified by delivery of a boost dose of radiation, delivery of systemic therapy (endocrine therapy, chemotherapy, or biologic therapy), or favorable biology
SSO-ASTRO Consensus
The Bottom Line

• Negative margins (no ink on tumor) optimize local control
• Wider margin widths do not significantly improve local control
• The routine practice of obtaining margins more widely clear than no ink on tumor is not indicated
Do These Statements Apply to Patient Subsets?

- Lobular carcinoma
- Unfavorable biologic subtypes
- Age < 40
- Extensive intraductal component (EIC)
An EIC identifies cases that may have a large residual DCIS burden after lumpectomy.
Residual DCIS Related to Presence of EIC

Holland R, J Clin Oncol 1990;8:113
An EIC identifies cases that may have a large residual DCIS burden after lumpectomy.

There is no evidence of an association between EIC and an increased risk of LR when margins are negative.

Margins wider than no ink on tumor are not routinely indicated.
Consensus Statement

EIC

- Given the potential for considerable residual DCIS in EIC+ patients, consider
  - Post excision mammography to document complete removal of calcifications
  - Other high-risk features, such as young age, multiple close margins

  to identify patients likely to benefit from re-excision.
Practical Implications

• Consensus guidelines are intended to help standardize practice; not a substitute for clinical judgment
Practical Implications

• Guideline intent
  – To convey the view of the panelists that in current clinical practice where the vast majority of patients receive some form of systemic treatment, the frequent practice of routine re-excisions for arbitrary margin widths (2mm, 5mm, 10mm, etc) intended to diminish local recurrence in the breast conservation therapy setting may not be evidence-based
Practical Implications

• Provides the prospect for liberation from rules mandating re-excisions based merely on margin widths alone

• Suggests reserving re-excisions for individuals likely to be at high risk for local recurrence when all relevant risk factors are considered together
SSO-ASTRO Consensus

Endorsed By

• Society for Surgical Oncology (SSO)
• American Society of Radiation Oncology (ASTRO)
• American Society of Breast Surgeons (ASBS)
• American Society of Clinical Oncology (ASCO)
Criticisms of SSO-ASTRO Consensus

• Study-level rather than patient-level meta-analysis used as primary evidence base
  – Largely retrospective studies

• Unable to compare margins of “no ink on tumor” to 1mm or more
Counter Arguments

• NSABP B-06 (negative margin = no ink on tumor)
  – 5% 12-yr local recurrence rate in N+ patients receiving chemotherapy

• Lack of evidence showing a significant difference in local recurrence rates for margins of 1, 2 and 5mm makes it unlikely that a difference between no ink on tumor and 1mm would be significant
Counter Arguments

• Even more effective systemic therapy today than in cohorts of patients included in meta-analysis
• Variability and technical problems in margin assessment
• If the discussion has now become “is no ink on tumor as good as 1mm?” instead of “is 2mm better than 1mm, or is 5mm better than 2mm?”, many patients will be spared unnecessary surgery
The use of no ink on tumor as the standard for an adequate margin in invasive cancer in the era of multidisciplinary therapy is associated with low rates of local recurrence and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease healthcare costs.
Breast Conservation Surgery and the Definition of Adequate Margins
More Is Not Better...It’s Just More

Julie A. Margenthaler, MD; Aislinn Vaughan, MD

JAMA Surgery, 2014
What Does This Mean for Pathology Reporting of Margins?

• Consensus guidelines should influence how clinicians interpret our reports rather than how pathologists report margins

• Continue to report margins per CAP guidelines
  – Positive margin = ink on invasive cancer or DCIS
  – Report distance to negative margins in mm or fractions thereof for both invasive cancer and associated DCIS
Coming in later this year……

SSO-ASTRO
Consensus Guidelines on Margins for DCIS