A Contemporary View of Lumpectomy Margin Evaluation

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Beth Israel Deaconess Medical Center
and Harvard Medical School
Boston, MA
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-excision 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
Limitations of Margin Assessment

- Technical and methodologic
- 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}
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Occurs even in the absence of compression for specimen radiography
The pancake phenomenon contributes to the inaccuracy of margin assessment in patients with breast cancer

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100 cases

Mean Height (cm)

By surgeon 2.6 (1.0-6.5)

By pathologist 1.4 (0.3-3.0) ▲46%

Independent of age, lesion type, breast density

Compression devices ▲54% vs ▲41% without (p = .003)
Technical and Methodologic Issues

• The “pancake phenomenon”
• Specimen orientation
In addition to orienting specimen using S and L sutures, a 3rd stich 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
• Experimental model using oriented, partially filled water balloon
• Three volunteers painted six surfaces
• Area of each color on surface quantitated by image analysis
• Area of some painted surfaces differed by as much as 100% between painters
• Last surface painted on average 18% larger than the rest
Where is the margin?
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

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<td>Green</td>
<td>100</td>
</tr>
<tr>
<td>Blue</td>
<td>96</td>
</tr>
<tr>
<td>Red</td>
<td>100</td>
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AJCP, 2014
# Recognition and Discrimination of Tissue-Marking Dye Color by Surgical Pathologists

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<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>
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</table>

AJCP, 2014
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
At many institutions

• Proscribed minimum required margin for breast conserving treatment based on:
  - data from retrospective studies
  - local lore/urban legend
  - how/where surgeons were trained

How “negative” does the margin really have to be?
What is an Adequate Margin?

- 25+ years after randomized trials, 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?
Surgeons (Azu, 2010)

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Margin Width</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not touching ink (%), 1</td>
</tr>
<tr>
<td>A 60 yr old, 0.8 cm Invasive ER/PR/HER2-, RT planned</td>
<td>11.2</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
  – Poor cosmesis
  – Morbidity
  – Cost
  – Patients opting for mastectomy
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
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 1 mm, 2 mm or >5 mm 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
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></th>
<th>No Systemic Therapy</th>
<th>Systemic Therapy</th>
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<tbody>
<tr>
<td><strong>NSABP B14</strong></td>
<td></td>
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<tr>
<td>ER+, N-</td>
<td>14.7%</td>
<td>4.3%</td>
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<td>(systemic Rx: none vs Tam)</td>
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<tr>
<td><strong>NSABP B13</strong></td>
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<tr>
<td>ER-, N-</td>
<td>13.4%</td>
<td>2.6%</td>
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<tr>
<td>(systemic Rx: none vs MF)</td>
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</table>

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

**EBCTCG Overview. Lancet 2005;365:1687**

#### TAMOXIFEN

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Tamoxifen events</th>
<th>Ratio of annual event rates</th>
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<tbody>
<tr>
<td><strong>Allocated tamoxifen</strong></td>
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<tr>
<td><strong>Control</strong></td>
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<td><strong>Logrank Variance of O-E</strong></td>
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### CHEMOTHERAPY

**EBCTCG Overview. Lancet 2005;365:1687**

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<th>Events/woman-years</th>
<th>Polychemo. events</th>
<th>Polychemo. : Control</th>
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<tr>
<td><strong>Allocated polychemo.</strong></td>
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<tr>
<td><strong>Adjusted control</strong></td>
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<td><strong>Logrank Variance of O-E</strong></td>
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<td><strong>Ratio of annual event rates</strong></td>
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(i) Site of first recurrence ($\chi^2 = 0.2; p > 0.1; NS$)

**Trials with data on isolated local and contralateral**

- **Isolated local**
  - TAMOXIFEN: 114/22257 (0.5%/y)
  - Chemotherapy: 208/18819 (1.1%/y)
  - Ratio: 0.47 (SE 0.08)

- **Contralateral**
  - TAMOXIFEN: 79/22257 (0.4%/y)
  - Chemotherapy: 120/18819 (0.6%/y)
  - Ratio: 0.56 (SE 0.01)

- **Distant/multi.**
  - TAMOXIFEN: 507/22257 (2.3%/y)
  - Chemotherapy: 631/18819 (3.4%/y)
  - Ratio: 0.64 (SE 0.05)

- **Unknown**
  - TAMOXIFEN: 69/22257 (0.3%/y)
  - Chemotherapy: 56/18819 (0.3%/y)
  - Ratio: 0.6 (16.7)

- **99% or 95% confidence intervals**

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

Recognition of impact of contemporary systemic therapies on reducing LR rates

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

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

Funded by a grant from Susan G. Komen
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
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
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
Meta-Analysis Results

• Positive margins associated with at least a 2-fold increase in risk of local recurrence

• Increased local recurrence rate associated with positive margins not nullified by radiation boost, systemic therapy, or favorable biology
## Meta-Analysis Results

### Impact of Margin Width on Local Recurrence

Adjusted for Treatment Covariates

<table>
<thead>
<tr>
<th>Treatment Covariate</th>
<th># studies</th>
<th>Margin Width: OR</th>
<th>1mm</th>
<th>2mm</th>
<th>5mm</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Endocrine Rx</td>
<td>16</td>
<td></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></td>
<td>1.0</td>
<td>0.82</td>
<td>0.92</td>
<td>0.86</td>
</tr>
</tbody>
</table>
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.
- 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.
SSO-ASTRO Consensus
The Bottom Line

• The use of *no ink on tumor* as the standard for an adequate margin in invasive cancer in the era of multimodality therapy (which includes systemic therapy in most patients)
  – is associated with low rates of local recurrence
  – has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease healthcare costs
Do These Statements Apply to Patient Subsets?

• Lobular carcinoma
• Age < 40
• Unfavorable biologic subtypes
• Extensive intraductal component (EIC)
Do These Statements Apply to Patient Subsets?

- Lobular carcinoma
- Age < 40
- Unfavorable biologic subtypes
- Extensive intraductal component (EIC)
Consensus Statement

EIC

- An EIC identifies cases that may have a large residual DCIS burden after lumpectomy.
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 (2 mm, 5 mm, 10 mm, 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)
surgery of the primary

The Panel strongly endorsed recent findings that the minimal acceptable surgical margin was ‘no ink on invasive tumour or DCIS’.
MARGIN STATUS IN INFITRATING CARCINOMA

The use of breast-conserving therapy is predicated on achieving a pathologically negative margin of resection. The NCCN Panel accepts the definition of a negative margin as "No ink on the tumor," from the 2014 Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guidelines on Margins. Cases where there is a positive margin should generally undergo further surgery, either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for breast-conserving therapy, this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity.
EDITORIAL

Individualized, Patient-Centered Application of Consensus Guidelines to Improve the Quality of Breast Cancer Care

Reshma Jagsi, MD, DPhil,* Benjamin D. Smith, MD, † Michael Sabel, MD, ‡ and Lori Pierce, MD*

*Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan; † Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; and ‡ Department of Surgery, University of Michigan, Ann Arbor, Michigan

This guideline statement has the potential to substantially reduce the number of operations required of patients who pursue breast-conserving therapy, thereby reducing both cost and burden, and perhaps also improving ultimate cosmetic outcomes.
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 for both invasive cancer and associated DCIS
The Future of Lumpectomy Margin Evaluation

- RF Spectroscopy/Response (MarginProbe)
- Spectral imaging
- Optical imaging
- High frequency ultrasound
- Molecular margins

NONE READY FOR PRIME TIME
Conclusions

• While wider margins may have conveyed a small benefit in the past, multimodality therapy obviates the need for wider margins in contemporary practice
Conclusions

• The use of no ink on tumor as the standard for an adequate margin in invasive cancer in the era of multimodality 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
SNEAK PREVIEW

SSO-ASTRO-ASCO Consensus Guideline on Margins for DCIS
For pts with DCIS treated with excision and WBRT, the magic number is......

2 mm