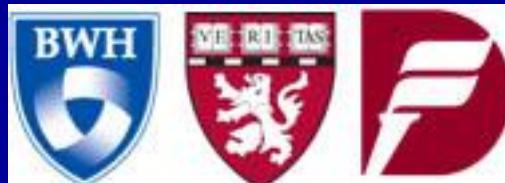


# **What is an Adequate Lumpectomy Margin in 2018?**

**Stuart J. Schnitt, M.D.**

**Brigham and Women's Hospital,  
Dana-Farber Cancer Institute, and  
Harvard Medical School**

**Boston, MA**



# Disclosures

- None

# Topics

- Current recommendations for lumpectomy margins for patients with *invasive breast cancer* treated with breast conserving surgery and whole breast irradiation
- Current recommendations for lumpectomy margins for patients with *DCIS* treated with breast conserving surgery and whole breast irradiation
- Evaluation of lumpectomy margins *post-NAST*

# Lumpectomy Margins 101

- 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 Lumpectomy Margin Evaluation

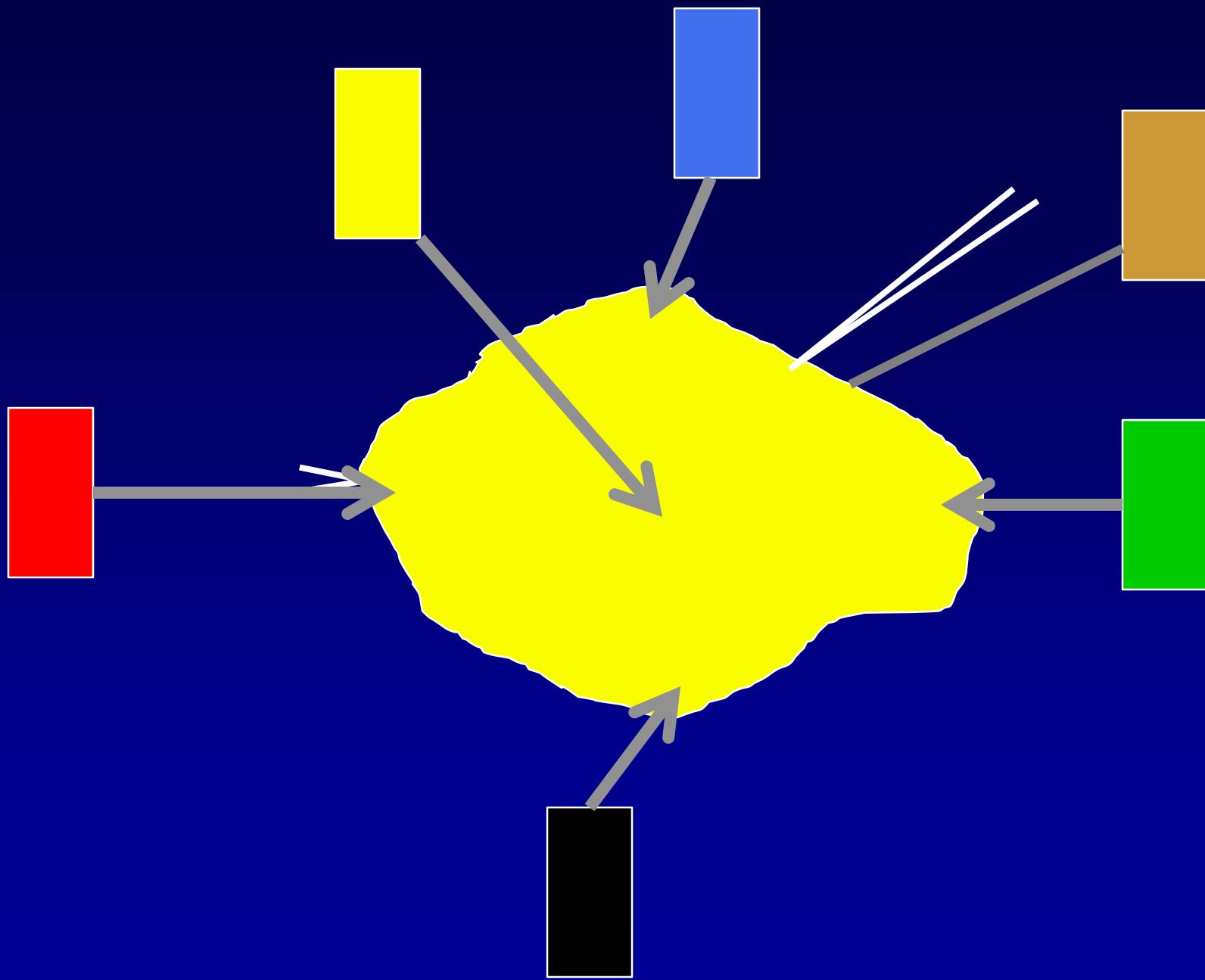
- IS NOT to ensure that there is no residual tumor in the breast

# The Goal of Lumpectomy Margin Evaluation

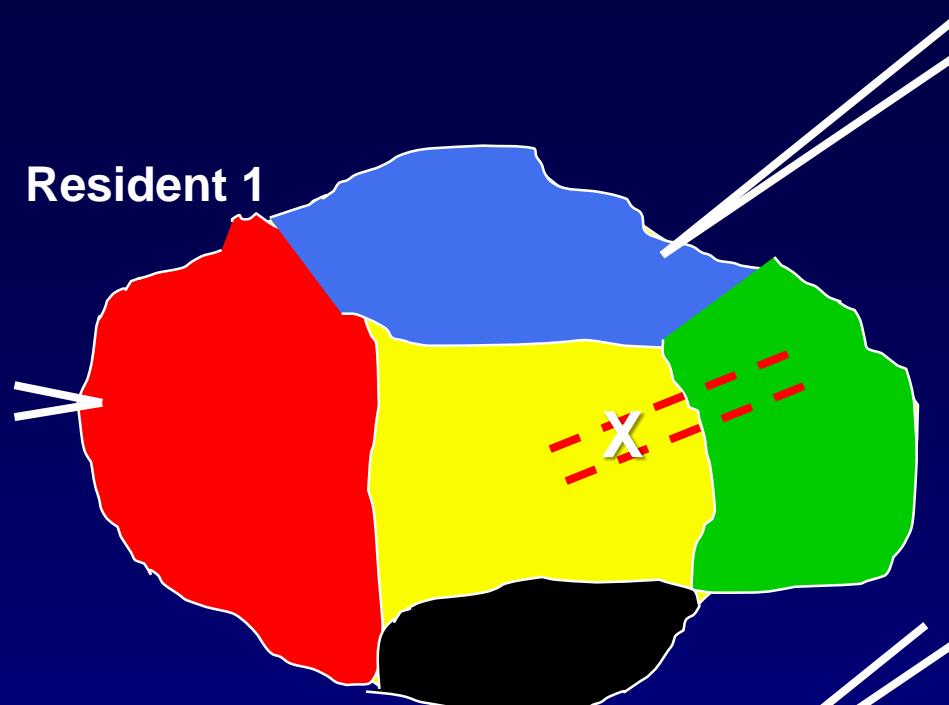
- To identify those patients more likely to have a large residual tumor burden and who, therefore, require further surgery (re-excision or mastectomy)
- To identify those patients unlikely to have a large residual tumor burden and who, therefore, are suitable candidates for breast conserving therapy without further surgery

# **Limitations of Lumpectomy Margin Assessment**

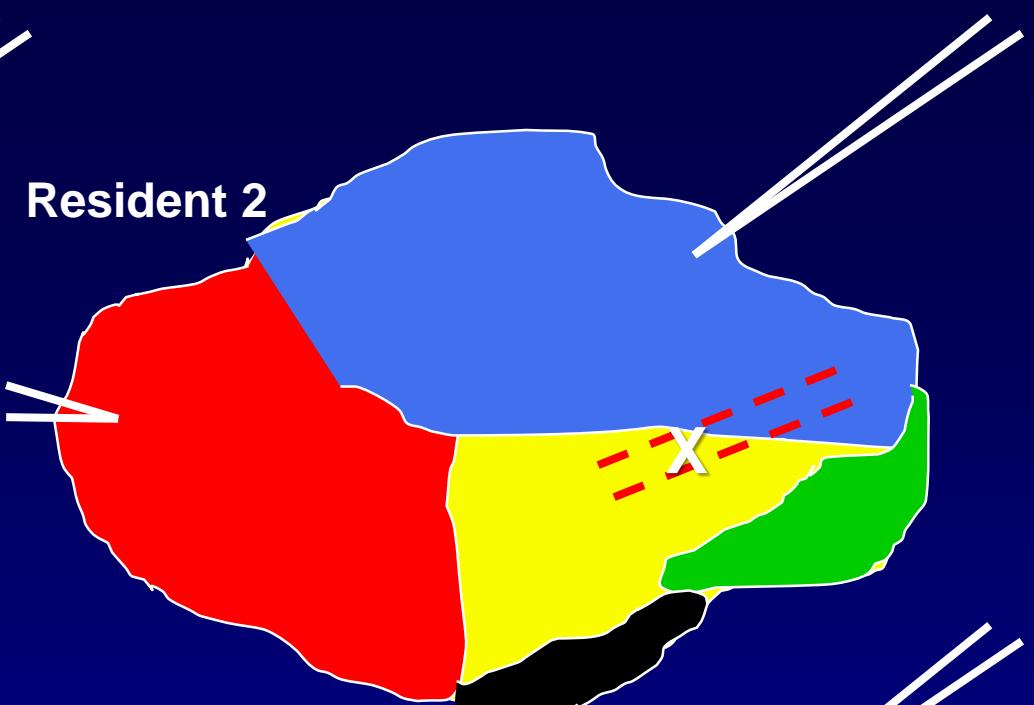
- Technical and methodologic
  - The “pancake phenomenon”
  - No uniform sampling method; sampling error
  - Specimen orientation
  - Problems with ink
    - »Running
    - »No landmarks



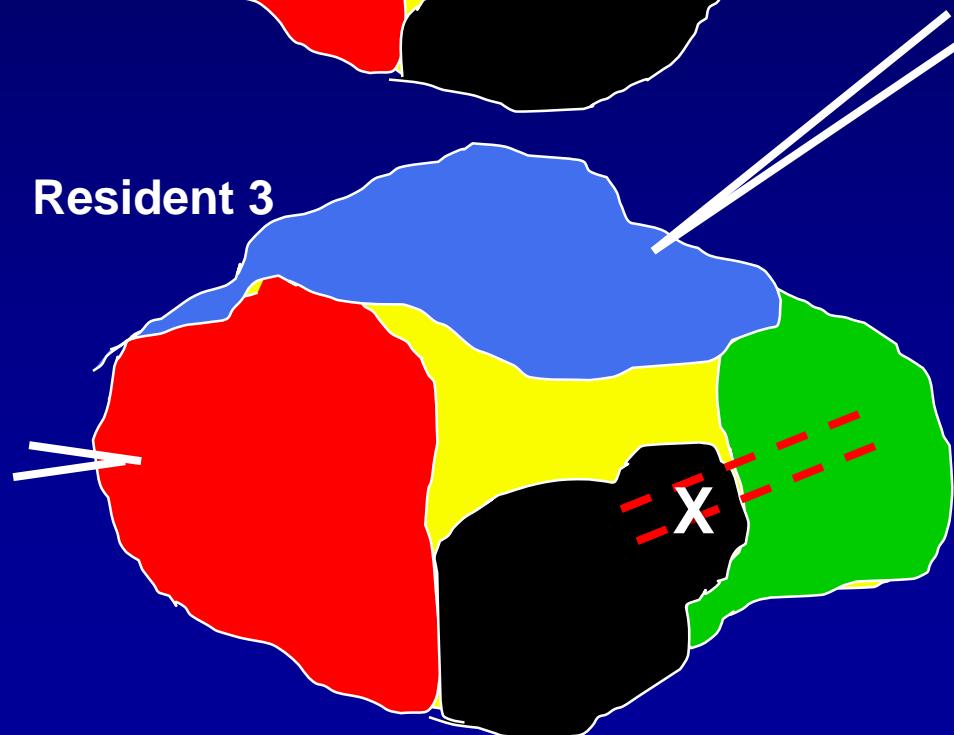
**Resident 1**



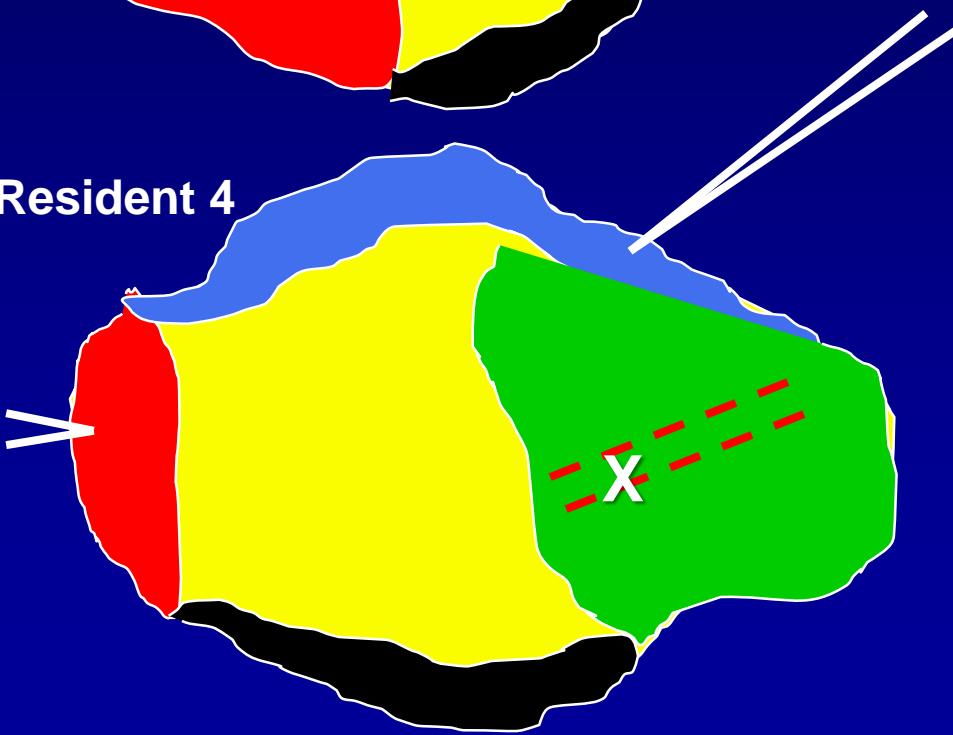
**Resident 2**



**Resident 3**



**Resident 4**



# **Limitations of Lumpectomy Margin Assessment**

- Technical and methodologic
  - The “pancake phenomenon”
  - Specimen orientation
  - Problems with ink
  - No uniform sampling method; sampling error
- Definition and interpretation

# **What is an Adequate Negative Margin?**

- Until recently no general agreement among surgeons or radiation oncologists as to what constitutes an adequate negative lumpectomy margin
- Widely varying rates of re-excision/re-operation
- Reducing rate of re-excision important
  - Patient anxiety
  - Morbidity
  - Cost
  - Adverse effect on cosmesis
  - Patients opting for mastectomy
  - Delayed start to systemic therapy

# **For Patients with Invasive Breast Cancer:**

- Lack of agreement on definition of an adequate negative margin
- Frequent use of re-excision (including in patients who already have negative margins)
- Declining rates of local recurrence over time
- Recognition of impact of systemic therapy on reducing local recurrence
- Better understanding of tumor biology



**SSO-ASTRO Consensus Guideline  
On Margins for Invasive Breast Ca**

# Feb. 10, 2014

Ann Surg Oncol  
DOI 10.1245/s10434-014-3481-4

Annals of  
**SURGICAL ONCOLOGY**  
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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<sup>1</sup>, Stuart J. Schnitt, MD<sup>2</sup>, Armando E. Giuliano, MD<sup>3</sup>, Jay R. Harris, MD<sup>4</sup>, Seema A. Khan, MD<sup>5</sup>, Janet Horton, MD<sup>6</sup>, Suzanne Klimberg, MD<sup>7</sup>, Mariana Chavez-MacGregor, MD<sup>8</sup>, Gary Freedman, MD<sup>9</sup>, Nehmat Houssami, MD, PhD<sup>10</sup>, Peggy L. Johnson<sup>11</sup>, and Monica Morrow, MD<sup>12</sup>

## *Annals of Surgical Oncology* Article Most Cited in 2014-2015

International Journal of  
Radiation Oncology  
biology • physics  
[www.redjournal.org](http://www.redjournal.org)

Clinical Investigation: Breast Cancer

## 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,<sup>\*</sup> Stuart J. Schnitt, MD,<sup>†</sup> Armando E. Giuliano, MD,<sup>‡</sup>  
Jay R. Harris, MD,<sup>§</sup> Seema A. Khan, MD,<sup>||</sup> Janet Horton, MD,<sup>¶</sup> Suzanne Klimberg, MD,<sup>#</sup>  
Mariana Chavez-MacGregor, MD,<sup>\*\*</sup> Gary Freedman, MD,<sup>||</sup>  
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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Society of Surgical Oncology–American Society for  
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and Monica Morrow

# SSO-ASTRO Consensus

## Primary Evidence Base

### 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, PhD<sup>1</sup>, Petra Macaskill, PhD<sup>1</sup>, M. Luke Marinovich, MPH<sup>1</sup>, and Monica Morrow, MD<sup>2</sup>

- **Meta-analysis of 33 studies:**
  - **28,162 patients**
  - **1,506 local recurrences**

# Meta-Analysis Results

## Impact of Margin Width on Local Recurrence Adjusted for Treatment Covariates

		Margin Width: OR			
Treatment Covariate	# studies	1mm	2mm	5mm	p-value
Endocrine Rx	16	1.0	0.98	0.90	0.95
Radiation Boost	18	1.0	0.82	0.92	0.86

# 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*

# **Consensus Guideline Reviewed and Endorsed By:**

- Society of Surgical Oncology
- American Society of Breast Surgeons
- American Society of Radiation Oncology
- American Society of Clinical Oncology

# **Tailoring therapies – improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015**

A. S. Coates<sup>1</sup>, E. P. Winer<sup>2</sup>, A. Goldhirsch<sup>3\*</sup>, R. D. Gelber<sup>4</sup>, M. Gnant<sup>5</sup>, M. Piccart-Gebhart<sup>6</sup>,  
B. Thürlimann<sup>7</sup>, H.-J. Senn<sup>8</sup> & Panel Members<sup>†</sup>

*Ann Oncol 2015*

The Panel strongly endorsed recent findings that the minimal acceptable surgical margin was ‘no ink on invasive tumor or DCIS’.

**Re-iterated in 2017 Consensus**

# NCCN Guidelines, 2016



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 1.2016 Invasive Breast Cancer

[NCCN Guidelines Index](#)  
[Breast Cancer Table of Contents](#)  
[Discussion](#)

### MARGIN STATUS IN INFILTRATING 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.<sup>1</sup> 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.

# Impact of SSO-ASTRO Guideline on Re-Excision Rates

# Impact of SSO-ASTRO Guideline on Re-Excision Rates

	n	Before Guideline	After Guideline	Absolute Reduction	Proportional Reduction	p
Chung (2015)	846	19.3%	12.9%	6.4%	33%	0.03
Rosenberger (2016)	1205	21.4%	15.1%	6.3%	29%	0.006
Drohan (2017)	599	13.8%	7.8%	6.0%	43%	0.02
Schulman (2017)	26,102*	20.2%	16.5%	3.7%	18%	0.004

\*cases from 252 surgeons in ASBS Mastery Database

# Impact of SSO-ASTRO Guideline on Re-Excision Rates

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Schulman (2017)	26,102*	20.2%	16.5%	3.7%	18%	0.004

\*cases from 252 surgeons in ASBS Mastery Database

## Caveats:

*Baseline re-excision rates relatively low in all studies (~20%)*  
*All studies conducted relatively soon after guideline publication*

# Trends in Reoperation After Initial Lumpectomy for Breast Cancer

## Addressing Overtreatment in Surgical Management

Monica Morrow, MD; Paul Abrahamse, MA; Timothy P. Hofer, MD; Kevin C. Ward, PhD, MPH;

Ann S. Hamilton, PhD; Allison W. Kurian, MD, MSc; Steven J. Katz, MD, MPH; Reshma Jaggi, MD, DPhil *JAMA Oncol, 2017*

- **Population-based sample of 3729 women who underwent lumpectomy 2013-2015 (immediately before and immediately after publication of consensus guideline)**
- **Re-excision rates and conversion to mastectomy declined by 16% ( $p<0.001$ )**
- **Final rates of breast conserving surgery increased 13% with a decrease in both unilateral and bilateral mastectomy ( $p=0.0002$ )**

# **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 systemic therapy
  - Patients with DCIS

# Topics

- Current recommendations for lumpectomy margins for patients with *invasive breast cancer* treated with breast conserving surgery and whole breast irradiation
- Current recommendations for lumpectomy margins for patients with **DCIS** treated with breast conserving surgery and whole breast irradiation
- Evaluation of lumpectomy margins *post-NAST*

# Why Re-Think Margins in DCIS?

- Declining rates of local recurrence over time
  - Better imaging
  - More comprehensive pathologic examination
  - Endocrine therapy
- Lack of agreement among surgeons and radiation oncologists on optimal adequate margin width
  - ~1/3 of patients undergo re-excision with associated morbidity, cost, compromise in cosmesis, and conversion to mastectomy

# Why Re-Think Margins in DCIS?

- Recognition of limitations of microscopic margin evaluation
- 2014 SSO-ASTRO consensus guideline on margins for invasive breast cancer (no ink on tumor) not directly applicable to DCIS



**SSO-ASTRO-ASCO Consensus Guideline  
On Margins for DCIS**

**Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ**

**August, 2016**

Monica Morrow, MD<sup>1</sup>, Kimberly J. Van Zee, MD<sup>1</sup> , Lawrence J. Solin, MD<sup>2</sup>, Nehmat Houssami, MBBS, PhD<sup>3</sup>, Mariana Chavez-MacGregor, MD<sup>4</sup>, Jay R. Harris, MD<sup>5</sup>, Janet Horton, MD<sup>6</sup>, Shelley Hwang, MD<sup>7</sup>, Peggy L. Johnson, MD<sup>8</sup>, M. Luke Marinovich, PhD<sup>3</sup>, Stuart J. Schnitt, MD<sup>9</sup>, Irene Wapnir, MD<sup>10</sup>, and Meena S. Moran, MD<sup>11</sup>

*Ann Surg Oncol, 2016*

**Society of Surgical Oncology–American Society for Radiation Oncology–American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma In Situ**

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*JCO, 2016*

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Monica Morrow MD <sup>a,\*</sup>, Kimberly J. Van Zee MD <sup>a</sup>, Lawrence J. Solin MD <sup>b</sup>, Nehmat Houssami MBBS, PhD <sup>c</sup>, Mariana Chavez-MacGregor MD <sup>d</sup>, Jay R. Harris MD <sup>e</sup>, Janet Horton MD <sup>f</sup>, Shelley Hwang MD <sup>g</sup>, Peggy L. Johnson <sup>h</sup>, M. Luke Marinovich PhD <sup>i</sup>, Stuart J. Schnitt MD <sup>j</sup>, Irene Wapnir MD <sup>k</sup>, Meena S. Moran MD <sup>l</sup> *Pract Radiat Oncol, 2016*

# **SSO-ASTRO-ASCO Consensus on Margins in DCIS**

## **Primary Evidence Base**

- **Meta-analysis of 20 studies:**
  - 7883 patients
  - 865 local recurrences (50% invasive)
- **Analysis**
  - Random-effects logistic meta-regression (frequentist analysis); single margin cut point/study
  - Network meta-analysis (Bayesian model); multiple margin cut points/study

# Negative Margins Reduce Local Recurrence Rate

- Local recurrence significantly less frequent with negative vs positive/close margins
  - Logistic OR: 0.53 for negative vs positive/close
  - Bayesian OR: 0.45 for negative vs positive

Adjusted for age, grade, WBRT, endocrine therapy, median recruitment year, follow-up

# What Margin Width Minimizes the Risk of LR in Patients Receiving WBRT?

## Logistic Analysis

	> 0 or 1 mm	2 mm	3 mm	10 mm
n	1533	4902	470	978
Odds Ratio	referent	0.51	0.42	0.60
95% CI		0.31–0.85	0.18–0.97	0.33–1.08
p value		.01	.04	.09
Predicted 10 yr LR	18.1%	10.1%	8.5%	11.7%

- Comparable reductions in OR for LR for margins of 2, 3, and 10 mm relative to >0 or 1mm
- Pairwise comparisons found no differences between 2, 3 and 10 mm thresholds (all p > 0.40)

# What Margin Width Minimizes the Risk of LR in Patients Receiving WBRT?

## Bayesian Analysis

	Threshold Negative Margin Distance			
	> 0 or 1 mm	2 mm	3 mm	10 mm
n	2230	2412	289	1963
Odds Ratio	0.45	0.32	0.30	0.32
95% CrI	0.32–0.61	0.21–0.48	0.12–0.76	0.19–0.49

- Similar reductions in OR for LR for margins of 2, 3 and 10mm that were all greater than for >0 or 1mm

# What Margin Width Minimizes the Risk of LR in Patients Receiving WBRT?

## Bayesian Analysis

Relative OR for 2mm vs 10mm

0.99 (95% CI 0.61-1.64)

No significant difference

# **SSO-ASTRO-ASCO Consensus on Margins in DCIS**

## **The Bottom Line**

- **For patients with DCIS treated with BCS + WBRT**
  - A positive margin is associated with a significant increase in local recurrence; not nullified by WBRT
  - Margins of at least 2mm are associated with a reduced risk of local recurrence relative to narrower margin widths in patients receiving WBRT
  - The routine practice of obtaining negative margin widths wider than 2mm is not supported by the evidence

# **SSO-ASTRO-ASCO Consensus on Margins in DCIS**

- Approved by leadership of
  - SSO**
  - ASTRO**
  - ASCO**
  - ASBS**

# De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

G. Curigliano<sup>1\*</sup>, H. J. Burstein<sup>2†</sup>, E. P. Winer<sup>2</sup>, M. Gnant<sup>3</sup>, P. Dubsky<sup>3,4</sup>, S. Loibl<sup>5</sup>, M. Colleoni<sup>1</sup>, M. M. Regan<sup>6</sup>, M. Piccart-Gebhart<sup>7</sup>, H.-J. Senn<sup>8</sup> & B. Thürlimann<sup>9</sup>, on behalf of the Panel Members of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017 **Annals Oncol 2017**

## Ductal carcinoma *in situ*

Breast conserving surgery followed by radiation therapy remains the standard of care for ductal carcinoma *in situ* (DCIS) [1, 2] assuming adequate margins can be obtained. The majority of panel endorsed recent Surgical Society of Oncology (SSO), American Society of Clinical Oncology (ASCO) and American Society for Radiation Oncology (ASTRO) guidelines that recommended that a margin  $\geq 2$  mm is sufficient to avoid re-excision [3]. A substantial minority of the panel would accept narrower margins in individual cases, including ‘no ink on DCIS’. The Panel acknowledged the recent trials showing that either aromatase inhibitors (AIs) or tamoxifen can be an effective adjuvant treatment options to lower the risk of recurrent DCIS [4, 5].

# Margins in Patients with DCIS Treated with BCS Alone

- **Excision alone, regardless of margin width, associated with higher LR rates than treatment with excision and WBRT**
- Optimal margin width unknown; conflicting evidence
- Margin should be at least 2mm
- Some evidence suggests more widely clear margins than 2mm are beneficial

# **Summary: Margins for DCIS**

- Among patients with DCIS treated with BCS + WBRT
  - Negative lumpectomy margins reduce the risk of LR by ~50%
  - However, minimum margin distances above 2mm are not significantly associated with further reduction in risk of LR in women receiving WBRT

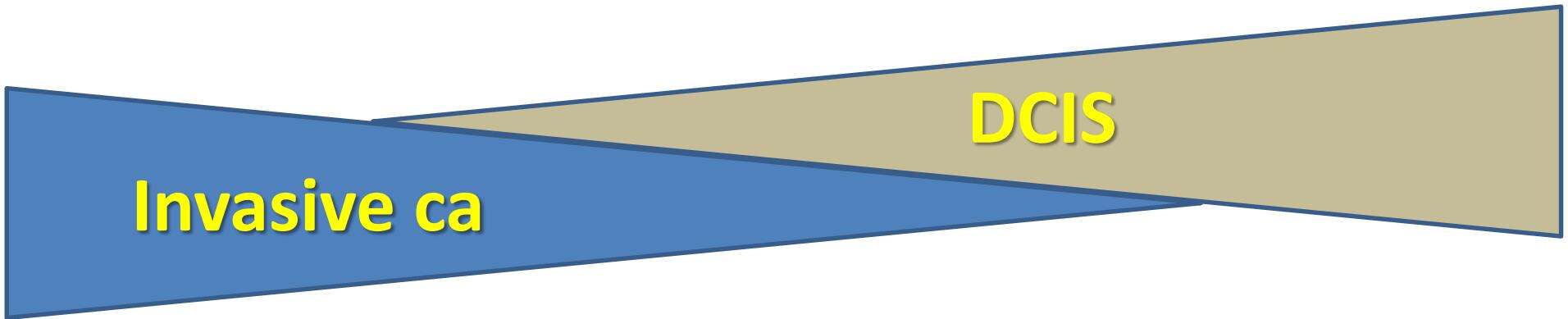
# **Summary: Margins for DCIS**

- Among patients with DCIS treated with BCS + WBRT
  - Negative lumpectomy margins reduce the risk of LR by ~50%
  - However, minimum margin distances above 2mm are not significantly associated with further reduction in risk of LR in women receiving WBRT
  - The use of 2mm as the standard for an adequate margin in DCIS treated with BCS + WBRT is associated with low rates of local recurrence and has the potential to decrease re-excision rates, improve cosmetic outcome and decrease health care costs

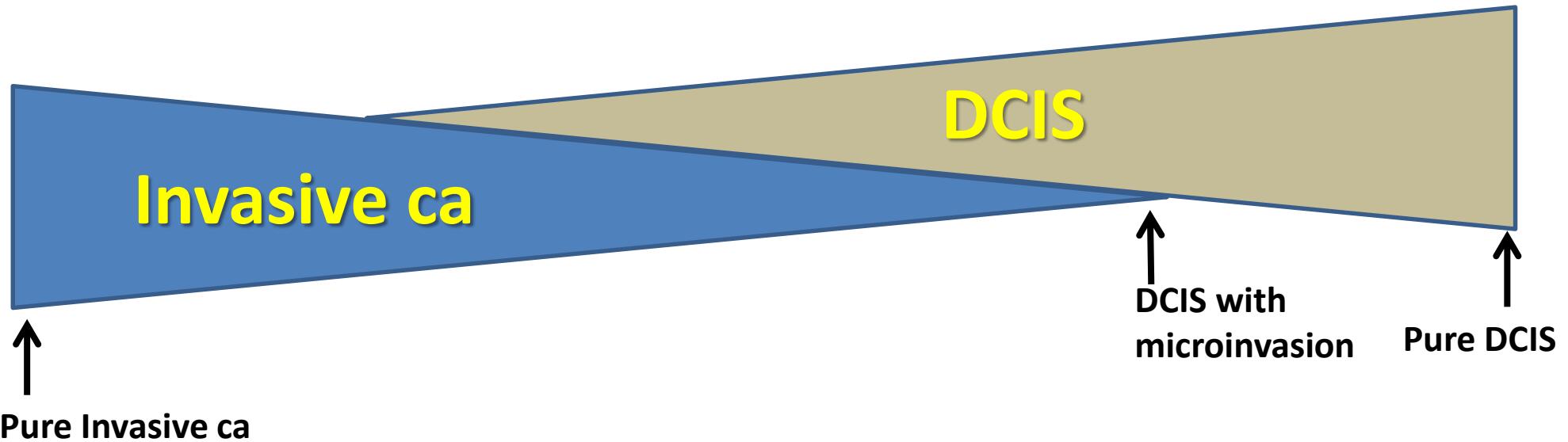
# **Practical Implications of Consensus Guidelines**

- Consensus guidelines are intended to help standardize practice; not a substitute for clinical judgment
- Situations in which margins wider than no ink on tumor may be preferable for invasive breast cancer
- Situations in which margins <2mm are acceptable for patients with DCIS

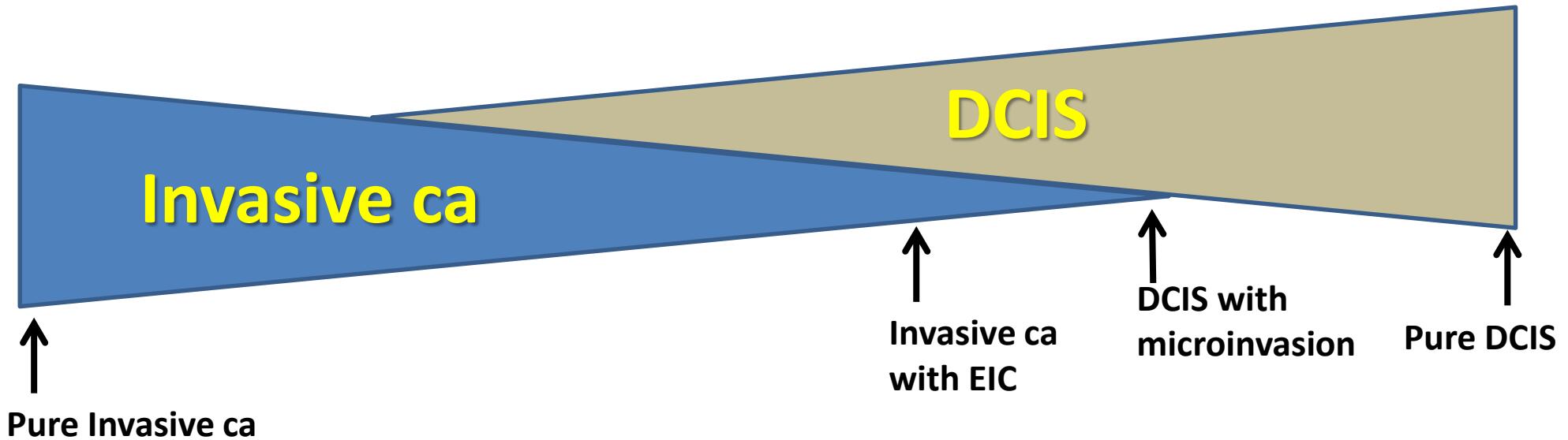
# Which Margins Guideline to Use?



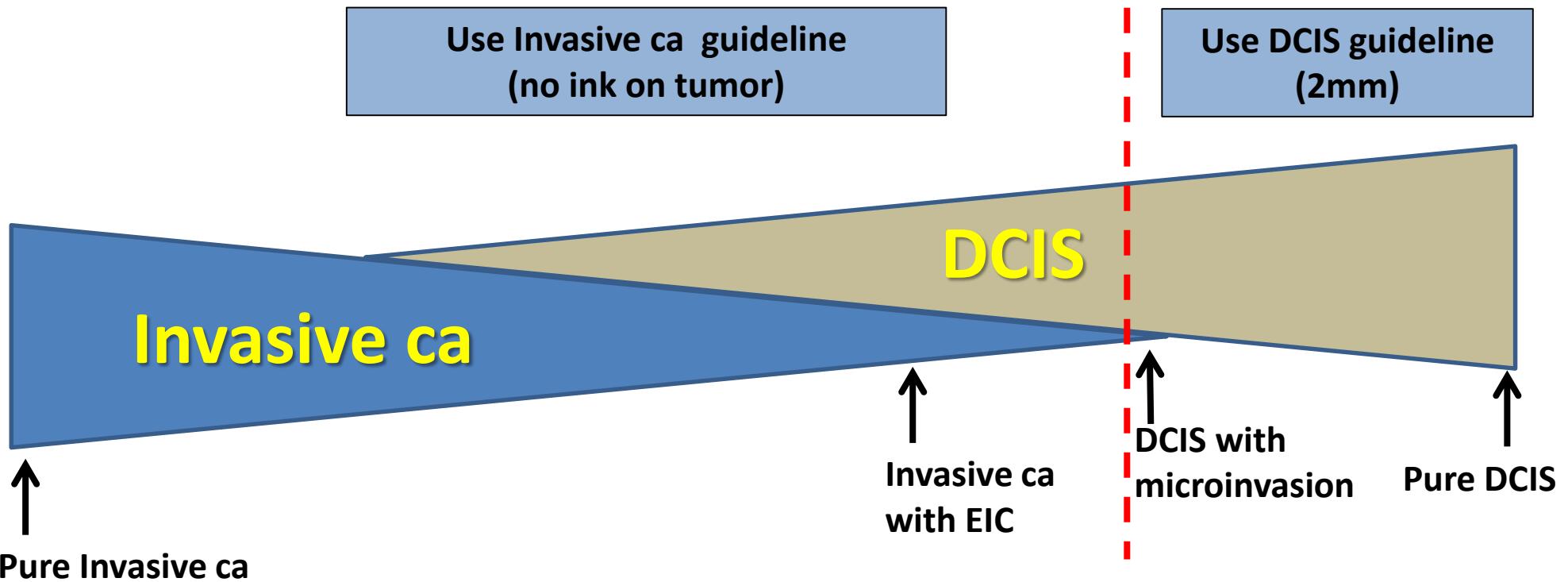
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# Which Margins Guideline to Use?



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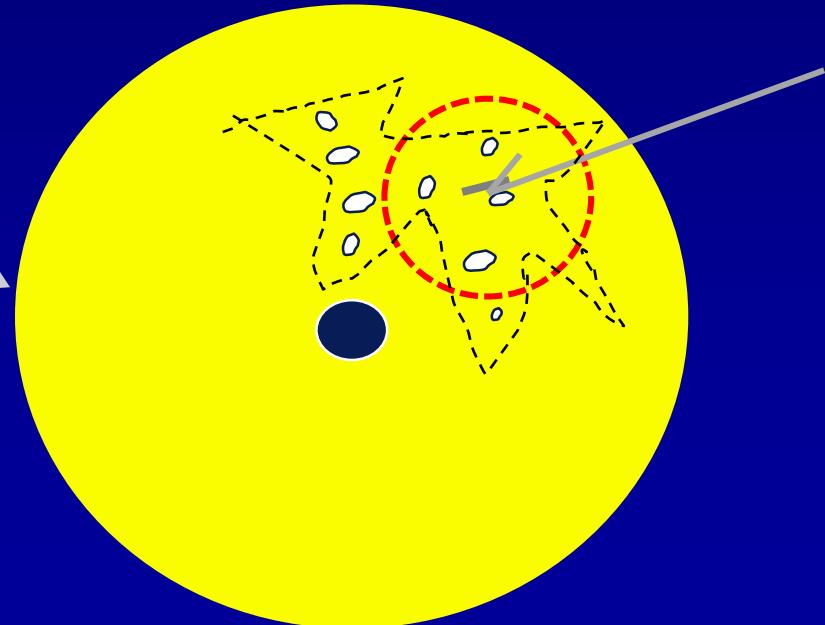
# Topics

- Current recommendations for lumpectomy margins for patients with *invasive breast cancer* treated with breast conserving surgery and whole breast irradiation
- Current recommendations for lumpectomy margins for patients with *DCIS* treated with breast conserving surgery and whole breast irradiation
- Evaluation of lumpectomy margins ***post-NAST***

# Pre-Treatment

# Post-Treatment

How best to assess adequacy of excision in  
post-treatment lumpectomy specimens?



# **Recommendations for standardized pathological characterization of residual disease for neoadjuvant clinical trials of breast cancer by the BIG-NABCG collaboration**

V. Bossuyt<sup>1\*</sup>, E. Provenzano<sup>2</sup>, W. F. Symmans<sup>3</sup>, J. C. Boughey<sup>4</sup>, C. Coles<sup>5</sup>, G. Curigliano<sup>6</sup>, J. M. Dixon<sup>7</sup>, L. J. Esserman<sup>8</sup>, G. Fastner<sup>9</sup>, T. Kuehn<sup>10</sup>, F. Peintinger<sup>11,12</sup>, G. von Minckwitz<sup>13</sup>, J. White<sup>14</sup>, W. Yang<sup>15</sup>, S. Badve<sup>16</sup>, C. Denkert<sup>17</sup>, G. MacGrogan<sup>18</sup>, F. Penault-Llorca<sup>19</sup>, G. Viale<sup>20</sup> & D. Cameron<sup>21</sup> of the Breast International Group-North American Breast Cancer Group (BIG-NABCG) collaboration

*Ann Oncol* 2015;26:1280-1291

*margins.* Assessment of margins may be less reliable post-NAST in cases with scattered response. Tumor bed extending to the margins should be documented.



**Not clear how this information should be used to guide management in the absence of tumor cells at margin**

# **Lumpectomy Margins after NAST**

- At the present time, definition of an adequate negative margin in the post –neoadjuvant treatment setting is an unresolved issue
- Other factors may also influence risk of local recurrence
  - »Residual tumor size, LVI, extent of residual DCIS, nodal status, use of RT, additional systemic therapy, tumor biology

# De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

G. Curigliano<sup>1\*†</sup>, H. J. Burstein<sup>2†</sup>, E. P. Winer<sup>2</sup>, M. Gnant<sup>3</sup>, P. Dubsky<sup>34</sup>, S. Loibl<sup>5</sup>, M. Colleoni<sup>1</sup>, M. M. Regan<sup>6</sup>, M. Piccart-Gebhart<sup>7</sup>, H.-J. Senn<sup>8</sup> & B. Thürlimann<sup>9</sup>, on behalf of the Panel Members of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017 *Annals Oncol* 2017

- **Extent of residual tumor should guide the extent of breast surgery; full resection of initial tumor bed not necessary**
- **Panel favored the “no ink on tumor” standard for surgical margins**
- **However, in cases of multifocal residual disease and/or scattered residual disease, many panelists favored “more generous margins”**

# Where Do We Go From Here?

- Additional studies assessing impact of 2014 SSO-ASTRO invasive cancer margin guideline on reducing re-excision/re-operation rates
- Studies assessing impact of 2016 DCIS SSO-ASTRO-ASCO margin guideline on reducing re-excision/re-operation rates

# **Where Do We Go From Here?**

- Evidence based consensus on definition of adequate negative margin in patients treated with NAST
  - However, evidence-based consensus requires evidence!