Highlights of Imaging and Management of Local and Regional Disease

SABCS Dec 5-9, 2017

Aislinn Vaughan, MD, FACS
SSM Breast care, Breast surgeon
Financial Disclosure(s)

I currently have or have had the following relevant financial relations to disclose:

Consultant: Genomic Health
Off Label Use Disclosure

I do not intend to discuss an off-label use of a product during this activity.
GS5-01: Appropriate margins for breast conserving surgery in patients with early stage breast cancer: A meta analysis.

GS5-02: Axillary dissection vs. no axillary dissection in patients with cT1-T2cN0M0 breast cancer and only micrometastases in the sentinel node(s): Ten-year results of the IBCSG 23-01 trial.

GS5-05: Primary endocrine therapy for ER-positive ductal carcinoma in situ (DCIS) CALGB 40903 (Alliance)
Appropriate margins for breast-conserving surgery in patients with early stage breast cancer: A meta-analysis

Frank Vicini, Vivek Verma, Harlan Sayles, Abram Recht, Chirag Shah

This study made me cringe.
Background

Wider margins for breast-conserving surgery in patients with early stage BC may reduce local recurrence, but also could result in:

- Increased morbidity
- Worse cosmetic outcomes
- Higher cost (due to re-excision) in patients undergoing BCT

Previous meta-analysis\(^1\) concluded that wider margins are unlikely to have substantial local control benefit

Accordingly, current SSO-ASTRO guidelines\(^2\) for invasive cancers with lumpectomy: no ink on tumor

To reconfirm the new narrower margins guidelines, an updated meta-analysis was conducted, which included additional studies, and, applied different margin definition models

Inclusion Criteria and Study Selection

- Systematic literature review (1995-2016)
- Inclusion criteria:
  - Minimum follow-up: 50 months
  - Explicit pathologic definition of margin status
  - Local recurrence reported in relation to margin status

- 38 studies with 55,302 patients identified, including 31 of the 33 studies from the previous meta-analysis (>20,000 additional patients)
  - 1 updated study
  - 1 follow-up <50 months (eliminated)
- Median follow up 7.2 years
Margin definition: Similar to previous analysis
"Positive" = invasive cancer or DCIS at the surgical margin
"Negative" = no tumor within specified distance from margin
"Close" = no tumor on ink but there was tumor less than specified distance from the margin

Previous Analysis: 2 Models
Model 1: all studies included
  Negative margins compared with close/positive margins
Model 2: included studies where available
  Comparison of negative, close, and positive margins
Present Analysis: 3 Models (instead of 2)

Model 1: similar to previous analysis (Model 1) of negative vs. close/positive

Model 2: performed to assess impact of margin width range rather than a set margin width
   0-2 mm, 2-5 mm, >5 mm
   *Was not included in previous analysis*

Model 3: similar to previous meta-analysis (Model 2) of negative/close/positive margins
**Results of Current Analysis**

### Model 1: Local Recurrence for negative vs. close/positive margins
- >0 mm: p<0.001
- >1 mm: p<0.001
- >2 mm: p<0.001
- >5 mm: p<0.001

### Model 2: Local Recurrence for negative/close vs. positive margins
- >0-2 mm: 7.2% • p<0.001
- >2-5 mm: 3.6% • p<0.001
- >5 mm: 3.2% • p<0.001

### Model 3: Local Recurrence for negative/close/positive margins
- Close vs Negative: >2 mm
- Positive vs Negative: >5 mm

- 1 mm: 8.0%/13.0%/14.0%
- 2 mm: 3.6%/5.5%/9.5%
- 5 mm: 2.9%/4.1%/12.8%

- **Best odds ratio for 1 mm margin, as compared to close/positive margin**
- **Similar results to previous meta-analysis**
- **Odds ratios are very similar: unable to say what’s the optimal margin**

- **Looking at range of margins, a wider margin further reduced local recurrence and was validated on MVA**
- **Multivariate Analysis: margin width only significant variable (larger margin, lower recurrence)**

- **When modeling as negative, close, or positive margins, reduced rates seen with negative margins with lowest rates seen at 2 and 5 mm**
- **MVA confirmed margin status and width as factors associated with local recurrence**

---

*Vicini et al. Appropriate margins for breast-conserving surgery in patients with early stage breast cancer: A meta-analysis. Abs. GS5-01*
Conclusions:

- Limitations of meta-analysis preclude definitive conclusion regarding appropriate margins.
- Study authors suggested a margin width beyond 'no ink on tumor' may further reduce rates of local recurrence.
- Suggested that prospective studies are required to validate appropriate margin width.
- Clinical question: should we aim for a 1-2 mm margin as compared to tumor on ink?
Ongoing debate for many years, which is why a consensus guideline was so welcome.

Will be interested to see how SSO-ASTRO respond to this, if they do.

Will need to see the manuscript to know which additional studies were included in this meta-analysis compared to the prior one.

For now, I’m continuing to use “no tumor on ink” for early invasive breast cancers.
Axillary dissection vs. no axillary dissection in patients with cT1-T2 N0 breast cancer and micrometastases only in the sentinel node: ten-year results of the IBCSG 23-01 trial


Activated 4/2001 and accrued pts through 2/2010; nodal assessment H&E only.
Only 86 (out of 931) pts with mastectomy, accounting for 9% in each arm
Background

- For patients with a metastatic sentinel node (SN), axillary dissection (AD) had been the standard approach to the axilla.
  - 5-year results of 23-01 and 10-year results of Z0011 showed that, for patients with moderate axillary involvement, AD provided no advantage in terms of overall or disease-free survival while axillary failure rates were low.
  - Updated follow-up of 23-01 was successful for 83% of patients who had not withdrawn.

- IBCSG 23-01 trial was undertaken to compare axillary dissection vs. no axillary dissection for patients clinically node negative and micrometastases in the sentinel node.
If tumor/nodal eligibility criteria met, randomized:
Tumor size $\leq$ 5 cm;
unicentric or multicentric;
one or more micrometastatic ($\leq$2 mm) sentinel nodes

Primary endpoint: invasive disease-free survival (DFS)
Secondary endpoint: overall survival, incidence of reappearance of tumor in un-dissected axilla
Galimberti et al. Axillary dissection vs. no axillary dissection in patients with cT1-T2 N0 breast cancer and micrometastases only in the sentinel node: ten-year results of the IBCSG 23-01 trial. Abs. GS5-02

Results

Disease-Free Survival  Overall Survival

Cumulative Incidence of Breast Cancer Events

5-year % 10-year % 5-year % 10-year %
No AD 88% 91% No AD 88% 91%
AD 97% 88% AD 97% 88%

HR (no AD/AD)=0.77 (95% CI 0.56–1.07); log-rank p=0.20

Number at risk

Years from randomization

Cumulative incidence of breast cancer events (%)

Years from randomization

at risk

AD
Results & Conclusions

After a median follow-up of 9.8 years in comparing AD and no AD:

- No difference between the groups for main endpoint (DFS) or secondary endpoint overall survival

- Rate of axillary failure in no AD arm was low at 1.7% (0.8% in BCS)

- Results are consistent with those of the Z0011 trial
Bottom Line:

- Don’t need to do ALND for micromets

- This trial had small number of patients treated by mastectomy without radiation.

  - 352 pts with T1-T2 tumors having mastectomy. 60% ITC pos, and 40% micromets.
  - 95% systemic therapy. 9% had postmastectomy radiation.
  - At median followup 6 years, 2.8% local recurrence risk (9 pts) with NO AXILLARY RECURRENCES
Phase II Single Arm Study of Preoperative letrozole for ER(+) Postmenopausal DCIS Alliance/CALGB 40903

E. Shelley Hwang, Terry Hyslop, Stephanie Duong, Isabelle Bedrosian, Dorota Wisner, Elissa Price, Abigail Caudle, Tina Hieken, Joseph Guenther, Cliff Hudis, Eric Winer, Alan P. Lyss, Diane Dickson-Witmer, Richard Hoefer, David W. Ollila, Maura Dickler, Timothy Hardman, Jeff Marks, Yunn-Yi Chen, Gregor Krings, Laura Esserman, Nola Hylton
Background

- Ductal carcinoma in situ (DCIS) is a non-obligate precursor for invasive breast cancer
- DCIS comprises approximately 20% of all newly diagnosed BC in the US
- Standard treatment for ductal carcinoma in situ (DCIS):
  - Surgery
  - Adjuvant radiation therapy
  - Endocrine therapy
Study Design and Endpoints

Primary Objective
- Estimate the mean change in MRI tumor volume from baseline to completion of preoperative letrozole in ER(+) DCIS

Secondary Objectives
- Assess radiographic and pathologic outcomes of patients with DCIS treated with preoperative letrozole
- To determine whether ER, PR, and Ki67 are altered with treatment
Change in MRI Volume From Baseline

Wang et al. Phase II Single Arm Study of Preoperative letrozole for ER(+) Postmenopausal DCIS Alliance/CALGB 40903 Abs. GS5-05

3 months

Waterfall plot for changes in DCIS volume at 3 months

Average **33%** reduction
95% CI (0.39, 0.95)
\( p < 0.0001 \)

6 months

Waterfall plot for changes in DCIS volume at 6 months

Average **37%** reduction
95% CI (0.36, 0.89)
\( p < 0.0001 \)
Complete Response

Baseline

3 months

6 months

Wang et al. Phase II Single Arm Study of Preoperative letrozole for ER(+) Postmenopausal DCIS Alliance/CALGB 40903 Abs. GS5-05
Conclusions:

- Imaging response to preoperative letrozole was evaluable with serial MRI
- Significant reduction in MRI enhancement (33%) was seen by 3 months; mammography was less clear
- High rate of successful lumpectomy was seen even among patients with extensive calcifications
- Both invasive cancer and pathological CR were seen at excision
- Letrozole treatment was associated with reduction in ER, PR and Ki67
Conclusions:

The study authors further conclude:

- Preoperative AI is safely and effectively for low risk, ER+ postmenopausal DCIS
- Preoperative AI may make breast conservation an option
- This approach may help identify patients who are most likely to respond to adjuvant endocrine therapy
- Future studies will help determine whether early radiologic response correlates with long-term disease-free survival in ER+ DCIS
- To have a clearer understanding of de-escalating treatment in DCIS, expert opinion is to wait for ongoing Phase 3 trials
Bottom line

- Serial MRI are expensive and may have trouble with insurance coverage.
- Might be reasonable to do neoadjuvant antihormonal therapy in patients with more extensive radiographic disease who are HIGHLY motivated for breast conservation.
  - If doing, may want to consider repeat MRI after neoadjuvant antihormonal therapy to make sure response occurred, since mammogram extent not as helpful.
- I am unlikely to use neoadjuvant antihormonal therapy on DCIS at this point.