Results of the ACOSOG Z0011 Trial

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Axillary Node Dissection

Staging, Regional control, Survival
Meta-Analysis: ALND versus None

- 6 trials
- 3000 pts


**FIG. 2.** Bayesian analysis of survival benefit. Black line: results of meta-analysis. Numbers 1-6, individual studies. 1, Copenhagen; 2, B-04; 3, Curie; 4, Guy’s I; 5, SouthEast Scotland; 6, Guy’s 2.
Complications of ALND

- Lymphedema
- Shoulder dysfunction
- Paresthesias
- Pain
- Persistent seroma
Is Axillary Treatment Important?

Can persistent disease in the axilla be a source of distant metastasis and cause of death?
Case Example #1

64 year old s/p lumpectomy and SLND

- 1.5 cm tumor, negative margins, ER+, HER2-, 1/1 +SLN, 3 mm, no LVSI, ECE
- Planned for endocrine therapy

You recommend

1. Completion ALND, breast radiation
2. No axillary treatment, breast radiation
3. Tangents to treat breast and axilla
4. Breast + SCF/ full axillary radiation
Case Example #2

64 year old s/p mastectomy and SLND

- 1.5 cm tumor, negative margins, ER+, HER2-, 1/1 +SLN, 3 mm, no LVSI, ECE
- Planned for endocrine therapy

You recommend

1. No further treatment
2. Completion ALND
3. Radiation of axilla and SCF
4. Chest wall and lymphatic radiation
Importance of Local and Regional Therapy

Benefits of Local-regional Therapy

- Persistent local-regional disease recurs
- Persistent LR disease leads to DM and death
- Timing of events
  - LRR develops within 5 yrs
  - OS differences happen between year 5-15

Early Breast Cancer Trialists’ Collaborative Group, Lancet 2011
Era of SLN Surgery

Injection of dye and/or radiolabelled colloid

Identification of SLN
Lymph Node Processing

Bivalve axillary lymph nodes along the long axis

Section SLNs along the short axis of the nodes
Sentinel Lymph Node
Immunohistochemistry for Cytokeratin
A prognostic study of sentinel node and bone marrow micrometastases in women with clinical T1 or T2 N0 M0 breast cancer

Primary objectives:
• To estimate the prevalence and to evaluate the prognostic significance of sentinel node micrometastases detected by IHC.
• To estimate the prevalence and to evaluate the prognostic significance of bone marrow micrometastases by ICC.
Z0010 Overall SLN and BM Results

5210 Eligible and Evaluable Patients

SLN H&E Negative
N=3995 (76%)

SLN H&E Positive
N=1215 (24%)

IHC Negative
N=2977 (90%)

IHC Positive
N=349 (10%)

3413 Bone Marrow Specimens

IHC Positive
N=104 (3%)

Lymph node data – n=5,210
- H&E 24% positive
- IHC 10.3% positive

Survival by SLN Status

P=0.0009

Bone marrow data – n= 3,502
- 3% occult metastases

Bone marrow micromets identifies a subset of clinical T1/T2N0M0 pt with poor prognosis

P=0.01

Alive (%)

Years

ACOSOG Z0010: Conclusions

• Micromets in SLN detected by H&E associated with significantly shorter OS, DFS
  – Overall very good survival outcome (> 90%) in patients with histologically positive SLN

• Micromets detected in SLN by IHC do not appear to impact OS
  – Routine examination of SLN by IHC not supported in this patient population
Role of Completion ALND After A Positive SLN?

- Total number of involved nodes:
  - Has prognostic information
  - May guide adjuvant therapy decisions

- Regional control is important
Additional Axillary Disease after a Positive SLN

- Meta-analysis of 69 trials
  - 8059 patients undergoing SLN surgery and ALND
  - average percentage of LNs considered positive = 42%
  - 53% of patients with +SLN had additional positive axillary nodes

Primary Objective: To assess whether OS after SLND alone was not inferior to that for patients who underwent completion ALND for a positive SLN
Z0011: A randomized trial of axillary node dissection in women with clinical T1 or T2, N0, M0 breast cancer who have a positive sentinel node

**Rationale**
- NSABP B04 results
- Clinical equipoise regarding management of axillary LN in early stage breast cancer
- Adjuvant treatment of patients with nodal disease

**Primary & secondary objectives**
- Overall survival
- Surgical morbidity

**Accrual:**
- Activation: 4/1999
- Completed: 12/2004
- Total accrual: 891 patients
All analyses performed on both intent-to-treat and actual treatment received.

No meaningful differences in findings.

Intent-to-treat analysis reported.

<table>
<thead>
<tr>
<th>Patient and Tumor Characteristics</th>
<th>ALND (420 pts)</th>
<th>SLND (436 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median range)</td>
<td>56 (24-92)</td>
<td>54 (25-90)</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>67.9%</td>
<td>70.6%</td>
</tr>
<tr>
<td>T2</td>
<td>32.1%</td>
<td>29.4%</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>83.0%</td>
<td>83.0%</td>
</tr>
<tr>
<td>(-)</td>
<td>17.0%</td>
<td>17.0%</td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>67.7%</td>
<td>69.9%</td>
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<tr>
<td>(-)</td>
<td>32.3%</td>
<td>30.1%</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40.6%</td>
<td>35.2%</td>
</tr>
<tr>
<td>No</td>
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</tr>
</tbody>
</table>

Median Number of Lymph Nodes Removed

Size of SLN Metastasis

- **P=0.05**
- **62.5%**
- **55.2%**
- **N=228**
- **N=202**

### Size of Metastasis

- **Micrometastasis (≤ 2.0mm)**
  - ALND: 37.5%
  - SLND: 44.8%
  - N=137
  - N=164

- **Macrometastasis**
  - ALND: N=228
  - SLND: N=202
Number of Positive Lymph Nodes

- ALND: 420
- SLND: 436
- p < 0.001

<table>
<thead>
<tr>
<th>Number of Positive Lymph Nodes</th>
<th>ALND</th>
<th>SLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58.0%</td>
<td>71.1%</td>
</tr>
<tr>
<td>2</td>
<td>19.8%</td>
<td>18.3%</td>
</tr>
<tr>
<td>3 or more</td>
<td>21.0%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>
106 (27.4%) patients treated with ALND had additional positive nodes removed beyond SLND

ACOSOG Z0011
ACOSOG Z0011: Total Locoregional Recurrences Higher in ALND Group

• No differences in local or regional recurrences
• Routine use of ALND does not improve outcomes in early stage breast cancer

ALND

No ALND

Median follow-up: 6.3 yr
P=0.25

### ACOSOG Z0011: DFS and OS by ER/PgR Status

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>ALND (n = 420)</th>
<th>SLND (n = 436)</th>
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<tbody>
<tr>
<td>5-yr DFS</td>
<td>82.2</td>
<td>83.9</td>
</tr>
<tr>
<td>ER+/PgR+</td>
<td>90.0</td>
<td>86.7</td>
</tr>
<tr>
<td>ER-/PgR-</td>
<td>71.0</td>
<td>80.9</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>91.8</td>
<td>92.5</td>
</tr>
<tr>
<td>ER+/PgR+</td>
<td>95.4</td>
<td>92.2</td>
</tr>
<tr>
<td>ER-/PgR-</td>
<td>82.1</td>
<td>85.5</td>
</tr>
</tbody>
</table>

Giuliano AE, et al. JAMA 2011
ACOSOG Z0011

It is highly improbable that the 0.9% regional or 2.8% local-regional recurrence with SLND would significantly impact survival.
ACOSOG Z0011: Conclusions

- ALND provided no survival or recurrence benefit vs SLND in node-positive breast cancer
- Factors impacting survival and locoregional recurrence by multivariate analysis not related to operation or lymph nodes
  - Locoregional recurrence: older than 50 yrs of age, modified Bloom-Richardson grade
  - DFS: ER status, adjuvant systemic therapy
  - OS: older than 50 yrs of age, ER status, adjuvant systemic therapy
- Study does not support routine use of ALND in patients with early nodal metastatic breast cancer

Giuliano AE, et al. JAMA 2011
Reasons for Low LRR?

Difference between rate of +ALND and LRR?
• ER+ disease still being treated with hormones
• LN disease eradicated by systemic therapy
• LN disease eradicated by “breast” radiation
• LN disease is “biologically irrelevant”
International Breast Cancer Study Group Trial 23-01

- Axillary dissection versus no axillary dissection in patients with clinically node negative breast cancer and micrometastases in the sentinel nodes
- Target accrual 1960 pts, 934 randomized
- No difference in DFS or OS between study arms
- Better than anticipated DFS

Galimberti V, et al. SABCS 2011
Tangential Fields – Impact on Regional Nodes

High tangent fields includes most areas at risk

- nondivergent beam just below humeral head
- nondivergent beam 2 cm within the lung
- includes:
  - over 95% of SLN
  - over 80% of level I and II axilla

Those not included in Z0011:

- Clinically positive axillary nodes
- Neoadjuvant chemotherapy patients
- Other considerations
  - Younger age
  - Triple negative disease
- Pts who wouldn’t otherwise need XRT
  - MRM w/ low-risk stage II disease

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You recommend

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2. completion ALND
3. radiation of axilla and SCF
4. chest wall and lymphatic radiation
Conclusions

• Treatment of patients with early stage breast cancer in the SLN era
  • SLN dissection replaces ALND
  • Immunohistochemistry is not warranted for evaluation of H&E negative SLNs
  • Patients with 1-2 positive SLNs can avoid ALND when planned for BCT with whole breast irradiation
Thank you!