Modern Management of Axillary Lymph Nodes in Breast Cancer

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Disclosures

• none
Objectives

• Review historical trials evaluating sentinel node biopsy and axillary radiation
• Review ACOSOG Z0011
• Review AMAROS trial
• Discuss current indications for axillary node dissection
Axillary Surgery

- Sentinel Lymph Node Biopsy/Dissection (SLNB/SLND)
Axillary Surgery

- Axillary Lymph Node Dissection (ALND)
- Remove Level I-II nodes
NSABP B-04
25-year update

Comparison of chest wall radiation to ALND

Operable Breast Cancer

- Radical Mast.
- Total Mast.
- Total Mast. + XRT

- Radical Mast.
- Total Mast. + XRT

No difference in DFS, RFS, DDFS and OS

NSABP-B32

Comparison of ALND to SLND

5611 patients with clinically negative axillary nodes

Stratification
- Age (≤49 years, ≥50 years)
- Clinical tumour size (≤2.0 cm, 2.1-4.0 cm, ≥4.1 cm)
- Type of surgery (lumpectomy, mastectomy)

Random assignment

2807 in group 1
Sentinel node resection plus axillary dissection

2804 in group 2
Sentinel node resection

829 sentinel-node positive or unknown (not assessed)

1978 sentinel-node negative

793 sentinel-node positive or unknown (not assessed)

2011 sentinel-node negative

3 without follow-up (not assessed)

1975 with follow-up (assessed)

2011 with follow-up (assessed)

No difference in DFS, OS, and Regional Control
# Morbidity of Axillary Surgery

**NSABP-B32**

<table>
<thead>
<tr>
<th></th>
<th>ALND</th>
<th>SLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphedema</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Shoulder Abduction Deficit</td>
<td>75%</td>
<td>41%</td>
</tr>
<tr>
<td>Numbness</td>
<td>49%</td>
<td>15%</td>
</tr>
<tr>
<td>Tingling</td>
<td>23%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Ashikaga T et al, J Surg Onc 2010
ACOSOG Z0011

• To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer

Giuliano et al, JAMA 2011
Z0011 Selection Criteria
May 1999-Dec 2004

• Eligible
  – Clinical T1, T2 N0
  – H&E detected metastases in sentinel node
  – Lumpectomy with whole breast irradiation
  – Adjuvant systemic therapy

• Excluded
  – Metastases detected by IHC
  – Third field radiation
  – Matted nodes
  – 3 or more involved nodes
  – No gross extranodal disease

Giuliano et al, JAMA 2011
Z0011 Study Design

Clinical T1, T2 N0
n=891

Lumpectomy + SLND with positive SN

Randomization

ALND
n=420

Wholesale Breast Radiation Therapy + Adjuvant Systemic Therapy

Follow-up 6.3 years

No Further Surgery
n=436
Z0011

- Primary end point overall survival
- Secondary endpoint locoregional recurrence
- Goal accrual 1900
- Closed because of low event rate
  - Decision to close was based on the low observed mortality rate from the pooled data from both arms

Giuliano et al, JAMA 2011
## Z0011 Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SLNB</th>
<th>ALND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>54 years</td>
<td>56 years</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.6 cm</td>
<td>1.7 cm</td>
</tr>
<tr>
<td>Tumor grade 2</td>
<td>46.8%</td>
<td>48.9%</td>
</tr>
<tr>
<td>ER+/PR+</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>Adjuvant systemic therapy</td>
<td>97%</td>
<td>96%</td>
</tr>
<tr>
<td>Micrometastasis</td>
<td>44.8%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Macrometastasis</td>
<td>55.2%</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

Giuliano et al, JAMA 2011
Figure 2. Survival of the ALND Group Compared With SLND-Alone Group

No. at risk
ALND 420 408 398 391 378 313 223 141 74
SLND alone 436 421 411 403 387 326 226 142 74

ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Median follow-up 6.3 years
# Z0011 Locoregional Recurrences

<table>
<thead>
<tr>
<th></th>
<th>SLND</th>
<th>ALND</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Breast Tumor Recurrence</td>
<td>1.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Regional (Axilla or Supraclavicular)</td>
<td>0.9%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Total</td>
<td>2.8%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

median follow-up of 6.3 years

Giuliano et al, JAMA 2011
27.4% of patients treated by ALND had additional positive nodes beyond the SLN. The majority of patients had only 1 SLN with metastatic disease (ALND 58%, SLNB 71.1%).
Z0011 Criticisms

- Limited follow-up
- Older patients
- Mostly ER-positive patients
- Did not reach target accrual
- Concern over radiation fields
- Single study
# Time to Regional Recurrence

<table>
<thead>
<tr>
<th>Local Treatment</th>
<th>Median Time to Regional Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-B04</td>
<td>Mastectomy +/- XRT</td>
</tr>
<tr>
<td>Milan</td>
<td>Lumpectomy + WBI</td>
</tr>
</tbody>
</table>

Most regional recurrences occur before Z0011 median follow-up time of 76 months

Greco et al, Ann Surg 2000
Z-0011 Locoregional Recurrences in Young Patients

<table>
<thead>
<tr>
<th></th>
<th>SLND</th>
<th>ALND</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Breast Tumor Recurrence</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Regional Recurrence</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Younger (< 50 y/o) women do not have a higher rate of regional recurrence

Giuliano et al, JAMA 2011
ER-negative Tumors

• Higher likelihood of systemic recurrence than axillary
• Earlier recurrences
  – Before 5 years
• Less likely to have axillary metastases
High-Risk Tumors Defined as

- Triple Negative
- Her-2 Positive
- Young Age <50 years old
High-risk patients
n=125

ALND
n=105

SLNB
n=20

No difference in OS or LR

Chung A et al Ann Surg Onc 2015
Z0011 Radiation Fields

SLND arm (n = 124)
- SC field (n = 21; 16.9%)
  - Also had PAB (n = 12; 57.1%)
  - Sufficient records to determine field height (n = 76; 73.8%)
    - With high tangents (n = 40; 52.6%)
    - Mean distance to humeral head, 0.56 cm

ALND arm (n = 104)
- SC field (n = 22; 21.2%)
  - Also had PAB (n = 82; 78.8%)
  - Sufficient records to determine field height (n = 66; 80.5%)
    - With high tangents (n = 33; 50.0%)
    - Mean distance to humeral head, 0.69 cm
Z-0011 Radiation Fields

- ACOSOG review of Z0011 radiation fields showed the majority of patients received standard tangents without definitive radiation to the axilla.
- 200 patients from both SLNB and ALND had no difference in radiation fields and showed no benefit to ALND.

Jagsi et al, J Clin Onc 2014
• Which patients are at highest risk for non-sentinel lymph node metastases and could be considered for exclusion from Z0011 criteria?
Risk of Additional Positive Nodes is higher with >2mm ECE

<table>
<thead>
<tr>
<th>No. of additional positive ALNs</th>
<th>No ECE (n = 513)</th>
<th>≤2 mm (n = 128)</th>
<th>&gt;2 mm (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 positive SLN (n = 396)</td>
<td>2 positive SLNs (n = 117)</td>
<td>1 positive SLN (n = 91)</td>
</tr>
<tr>
<td>0</td>
<td>311 (78.5%)</td>
<td>90 (76.9%)</td>
<td>56 (61.5%)</td>
</tr>
<tr>
<td>1–3</td>
<td>76 (19.2%)</td>
<td>23 (19.7%)</td>
<td>28 (30.8%)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>9 (2.3%)</td>
<td>4 (3.4%)</td>
<td>7 (7.7%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.7140</td>
<td>0.2390</td>
<td>0.0936</td>
</tr>
</tbody>
</table>
After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS Trial)

- Objective to determine if axillary radiotherapy provides equivalent local control to axillary dissection with fewer side effects in patients with a positive sentinel node

Donker M et al, Lancet Oncol 2014
AMAROS Selection Criteria
February 2001-April 2010

• Eligible
  – Clinical T1, T2 N0
  – Lumpectomy or mastectomy
  – Adjuvant systemic therapy
AMAROS Study Design

Clinical T1, T2 N0
n=4806

Randomization

Lumpectomy (82%)
or
Mastectomy (17%)
+ SLND → ALND
n=2402

SLN Positive
n=744

Adjuvant Systemic Therapy

Follow-up 6.1 years
Lymphedema and QoL Assessment

Lumpectomy (82%)
or
Mastectomy (18%)
+ SLND → Radiation
n=2404

SLN Positive
n=681

AMAROS Study Design

Donker M et al, Lancet Oncol 2014
AMAROS

• Primary end point 5-year regional recurrence rate
  – Recurrence in axillary, infraclavicular fossa, or interpectoral nodes
  – This analysis was underpowered due to low event rate

• Secondary endpoints
  – recurrence-free survival
  – disease-free survival
  – overall survival
  – shoulder mobility
  – lymphedema
  – QoL

Donker M et al, Lancet Oncol 2014
Axillary Radiotherapy

- 25 fractions of 2Gy
- Levels I-III and medial part of supraclavicular fossa

Donker M et al, Lancet Oncol 2014
## AMAROS Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ALND</th>
<th>Axillary Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>56 y/o</td>
<td>57 y/o</td>
</tr>
<tr>
<td>Tumor size</td>
<td>1.7 cm</td>
<td>1.8 cm</td>
</tr>
<tr>
<td>Tumor grade 2</td>
<td>48.0%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Adjuvant systemic therapy</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Micrometastasis</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>Macrometastasis</td>
<td>59%</td>
<td>62%</td>
</tr>
<tr>
<td>Adjuvant breast/chest wall radiotherapy</td>
<td>85%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Donker M et al, Lancet Oncol 2014
AMAROS Overall Survival

Number at risk
- Axillary lymph node dissection: 744, 708, 552, 352, 157, 38, 0
- Axillary radiotherapy: 681, 661, 505, 316, 151, 29, 0

Overall survival
- HR 1.17 (95% CI 0.85-1.62); p=0.34
AMAROS Disease Free Survival

![Graph showing disease-free survival rates with two lines: one for axillary lymph node dissection and another for axillary radiotherapy. The graph includes a hazard ratio (HR) of 1.18 (95% CI 0.93-1.51), p=0.18, and a table showing the number at risk at different time points for both interventions.](image-url)
AMAROS 5-Year Regional Recurrences

<table>
<thead>
<tr>
<th></th>
<th>ALND</th>
<th>Axillary Radiotherapy</th>
<th>Negative SLND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary Recurrences</td>
<td>0.43%</td>
<td>1.19%</td>
<td>0.72%</td>
</tr>
</tbody>
</table>

Donker M et al, Lancet Oncol 2014
Lymphedema

<table>
<thead>
<tr>
<th>Clinical sign of lymphoedema in the ipsilateral arm</th>
<th>Axillary lymph node dissection</th>
<th>Axillary radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3/655 (&lt;1%)</td>
<td>0/586 (0%)</td>
<td>0.25</td>
</tr>
<tr>
<td>1 year</td>
<td>114/410 (28%)</td>
<td>62/410 (15%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 years</td>
<td>84/373 (23%)</td>
<td>47/341 (14%)</td>
<td>0.003</td>
</tr>
<tr>
<td>5 years</td>
<td>76/328 (23%)</td>
<td>31/286 (11%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm circumference increase &gt;10% of the ipsilateral upper or lower arm, or both</th>
<th>Axillary lymph node dissection</th>
<th>Axillary radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>33/655 (5%)</td>
<td>24/586 (4%)</td>
<td>0.497</td>
</tr>
<tr>
<td>1 year</td>
<td>32/410 (8%)</td>
<td>24/410 (6%)</td>
<td>0.332</td>
</tr>
<tr>
<td>3 years</td>
<td>38/373 (10%)</td>
<td>22/341 (6%)</td>
<td>0.080</td>
</tr>
<tr>
<td>5 years</td>
<td>43/328 (13%)</td>
<td>16/286 (5%)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Lymphedema was significantly more frequent in the ALND group but this did not impact QoL between groups
AMAROS

• 33% of patients treated by ALND had additional positive nodes beyond the SLN

• The majority of patients had only 1 SLN with metastatic disease (ALND 78%, Axillary Radiotherapy 75%)

Donker M et al, Lancet Oncol 2014
Surgeon Uptake of Limited Axillary Surgery

- 57% ASBS never or rarely perform ALND after Z0011
- MDACC performance of ALND before and after Z0011 85% → 24%
Indications for ALND

• Clinically positive axilla
  – Neoadjuvant and adjuvant therapy
• Clinically negative axilla
  – Three or more positive sentinel nodes
  – Contraindication to radiation
• What is the future of axillary surgery?
**Trial SOUND**

Sentinel node vs Observation after axillary **Ultrasound**

- Patients with breast cancer \(< 2.0\) cm
  - Any age
- Candidates to Breast Conserving Surgery
- Negative preoperative axillary assessment
  (negative ultra-sound of the axilla or negative FNAC
  of a single doubtful axillary lymph node)

**Randomization**

SNB policy  No axillary surgery

Accruing January 2012-January 2017
Summary

• Axillary recurrences are rare and occur early
• Z0011 and AMAROS support that ALND does not improve survival or regional recurrence rates in patients with positive SLND
• Which patients require 3rd field radiation versus high tangents remains uncertain
• In the future, surgical staging of the axilla may be unnecessary in a subset of patients
Thank you!
• Determine if women with high-risk node positive early breast cancer receive benefit from regional nodal irradiation compared to whole-breast radiation alone after lumpectomy