Surgical Management of the Axilla

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Associate Member, Department of Oncology, McGill University
Vancouver, October 2014
Disclosures

• Institution received funding from the Quebec Breast Cancer foundation, Cancer Research Society, Week-end to End Women’s Cancers, Montreal Jewish General Segal Cancer Centre for the conduct of the SN FNAC trial.

• Speaking honoraria from Roche, Novartis, Amgen and Genomic Health.

• Travel support from Roche and GSK.

• Institution received research funding from Roche and Rna Diagnostics inc.
Objectives to be covered

• Is it considered appropriate to do an axillary node dissection in a clinically negative axilla?
  - Remote communities
  - Large tumors
  - Post neoadjuvant therapy

• What is the current management of a positive sentinel node?
  - Discuss Z0011
  - Discuss newer evidence since Z0011
  - After total mastectomy

• Current Indications for axillary node dissection.

• How does the multidisciplinary team work in Quebec?
Management of the Axilla

A short history
We’ve come a long way
William Halsted 1895

«There is definite more or less uninterrupted or quite uninterrupted connection between the original focus and the outlying deposits of cancer... »

Halstead Mastectomy

- “Extended radical” and “Super-radical” mastectomies were being considered to improve the treatment of breast cancer.

- The recommended surgery for breast cancer until the 1970’s.
The Revolution: Dr Bernard Fisher & the NSABP

• “Breast cancer is a systemic disease, and expansive loco-regional therapy is unlikely to improve survival”

• Brought clinical trials and statistical methodology to breast cancer research.

• NSABP B-01, B-04, B-06, etc.
Trials of less surgery
NSABP B-04 Schema

Operable Breast Cancer

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

- Radical Mast.
- Total Mast. + XRT
Survival; NSABP Protocol B-04

- Negative RM (RR=1.05, p-value=0.55)
- Negative TMR (RR=1.06, p-value=0.54)
- Negative TM (RR=1.01, p-value=0.75)
- Positive RM
- Positive TMR (RR=1.06, p-value=0.54)
**NSABP B-04 Events**

* Clinically significant axillary disease after total mastectomy alone = 18.6%
All patients with histology positive axillary nodes receive L-PAM + 5 FU. Total mastectomy performed in event of ipsilateral breast tumor recurrence.
Lessons Learned

• Less surgery is OK

• High rate of clinically significant axillary disease if no axillary treatment

• Patients with clinically positive nodes had similar outcome whether they had ALND or XRT
Why do an ALND?

- Improve regional control
- Improve survival
- Obtain information to guide systemic therapy
- Obtain information to guide radiotherapy
- Obtain information about prognosis
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Why do an ALND?

• Improve regional control  ✔
• Improve survival  ✔
• Obtain information to guide systemic therapy
• Obtain information to guide radiotherapy
• Obtain information about prognosis
Potential survival advantage of axillary node dissection

Overall 5.4% (95% CI = 2.7-8.0%, probability of survival benefit > 99.5%)

Orr, Annals Surg Oncol, 1999
Why do an ALND?

• Improve regional control ✔

• Improve survival ❓/ ✔

• Obtain information to guide systemic therapy ✔

• Obtain information to guide radiotherapy ✔

• Obtain information about prognosis ✔
Indications for ALND v.1

- All invasive breast cancers
The problem with ALND: associated morbidities

- Lymphedema
- Limited arm movement / frozen shoulder
- Numbness
- Pain
- Cording
- etc…

ALMANAC Trial
Sentinel node biopsy

A new gold standard for patients with clinically negative nodes
NSABP B-32

Operable Breast Cancer
Clinically Negative Nodes

Stratification
- Age
- Clinical Tumor Size
- Type of Surgery

Sentinel Node Biopsy

Axillary Node Dissection if Sentinel Node Positive

Sentinel Node Biopsy Followed by Axillary Node Dissection

*1.5% had tumors >4cm

*False Negative Rate: 9.8%
NSABP B-32
Why do a SNB?

• Same regional control ✓
• Same survival ✓
• Obtain information to guide systemic therapy ✓
• Obtain information to guide radiotherapy ✓
• Obtain information about prognosis ✓
## SLNB after Neoadjuvant Chemotherapy in Node Negative Patients

<table>
<thead>
<tr>
<th>Who</th>
<th>Where</th>
<th>What</th>
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<th>Identification Rate</th>
<th>False Negative Rate</th>
</tr>
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<tbody>
<tr>
<td>Mamounas, E.P.</td>
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<td>Unplanned NSABP B-27 Subgroup</td>
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<td>FN (0/29) = 0%</td>
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<tr>
<td>Kinoshita, T.</td>
<td>Breast Cancer 2007</td>
<td>Series, node negative NAC</td>
<td>104</td>
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<td>Classe, J.M.</td>
<td>J Clin Oncol 2005</td>
<td>Series</td>
<td>130</td>
<td>IR (123/130) = 94.6%</td>
<td>FN (3/40) = 7.5%</td>
</tr>
</tbody>
</table>
Indications for ALND v.2

• Patients that are not eligible for SNB:
  - T4/Inflammatory breast cancer
  - Clinically/biopsy proven node positive disease

• Patients with positive SNs
Objectives

• Is it considered appropriate to do an axillary node dissection in a **clinically negative** axilla? **SENTINEL NODE BIOPSY IS THE GOLD STANDARD.**

  - Remote community: **PATIENT NEEDS TO BE INFORMED OF THE ALTERNATIVES AND DECIDE: REFERRAL/TRAVEL VS INCREASED MORBIDITY.**

  - Large tumors: **ACCEPTABLE UNLESS INFLAMMATORY.**

  - Post neoadjuvant therapy: **ACCEPTABLE AND RECOMMENDED.**
Positive sentinel node biopsy

Should we always do an ALND?
ACOSOG Z0011

Non-inferiority:
If 5 yr survival for SNB is not less than 75% of that seen with ALND ...

Excluded:
- Mastectomy
- Neoadjuvant therapy
- Extracapsular invasion (>2mm)

T1-2
1-2 SLN+
Lumpectomy

ALND
No ALND

Rads Tangential
Overall Survival

Planned N=1900
Non-inferiority:
Accept as non-inferior a reduction of mortality from 80% to 60% ...
ACOSOOG Z011

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group

ALND 91.8% (89.1-94.5)
SLND 92.5% (90.0-95.1)

ALND 82.2% (78.3-86.3)
SLND 83.9% (80.2-87.9)

N=856/1900
ACOSOG Z0011: Perfect guide on how to do a bad non-inferiority trial

- Compliance/adherence
- Withdrawals
- Inclusion/exclusion criteria
- Losses to follow-up
- Missing data
- Any deviation from protocol
- ITT analysis adds bias

Study must be even more closely examined if assessments of any of the above reveal inconsistencies
... But ...

• Many patients with positive sentinel node biopsy do have a good prognosis and can benefit from what we learned from Z0011.

• It is likely that if the trial was better designed and executed, the results would be identical.

• When we do lumpectomy, we know that we leave disease behind that is treated with radiation -- why would leaving clinically undetected disease in the axilla be any different?
## IBCSG 23-01

**SLN micromet/no ALND**

<table>
<thead>
<tr>
<th>Event</th>
<th>ALND n=464</th>
<th>No ALND n=467</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Regional</td>
<td>0.2%</td>
<td>1%</td>
</tr>
<tr>
<td>Distant</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Death</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Indications for ALND v.3

• Patients that are not eligible for SNB:
  - T4/Inflammatory breast cancer
  - Clinically/biopsy proven node positive disease

• Patients with positive SNs that do not fit the Z0011 criteria:
  - T3
  - Mastectomy
  - 3+ positive SNs
  - SNs with extracapsular invasion > 2mm
  - Patients who have positive SNs after neoadjuvant therapy
SNB, ALND and RNI
Intertwined options for best local control
NCIC-CTG MA.20
An Intergroup Trial of Regional Nodal Irradiation (RNI) in Early Breast Cancer


On behalf of the NCIC-CTG, TROG, RTOG, SWOG, NCCTG, and NSABP Cooperative Groups
Study Design

Node positive or high risk node negative post-BCS

Stratification

- Axillary nodes removed (<10, ≥10)
- Positive axillary nodes (0, 1-3, >3)
- Chemotherapy (anthracycline, other, none)
- Endocrine therapy (yes, no)
Disease Free Survival

HR = 0.67 (95% CI 0.52 to 0.87)
P = 0.003 (Stratified)

Percentage

Years

WBI

WBI + RNI
## Adverse Events*

**Grade ≥ 2**

<table>
<thead>
<tr>
<th></th>
<th><strong>WBI</strong> n=927</th>
<th></th>
<th><strong>WBI + RNI</strong> n=893</th>
<th></th>
<th><strong>P Value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Grade</strong></td>
<td><strong>2</strong></td>
<td><strong>3</strong></td>
<td><strong>4/5</strong></td>
<td><strong>Any</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation Dermatitis</td>
<td>349</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>40%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>Delayed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphedema</td>
<td>34</td>
<td>3</td>
<td>1</td>
<td>-</td>
<td>4%</td>
</tr>
</tbody>
</table>

*NCI Common Toxicity Criteria v.2 1998
Implications

- Women with node +ve breast cancer are treated WBI following BCS
- Women with large primary tumours or >3 +ve nodes are also offered RNI

Results from MA.20 suggest that all women with node +ve disease be offered RNI provided they are made aware of the associated toxicities
Implementation of MA.20 and use of RNI will decrease the use of ALND

- Patients with node positive sentinel nodes are likely to receive RNI regardless of the axillary operation.

- We know that ALND + RNI increases the risk of lymphedema.

- In the presence of RNI, surgeons will limit the use of ALND.

- In post-mastectomy patients that are treated with RNI, can we omit ALND?
The final blow...
Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial

By the EORTC Breast Cancer Group and Radiation Oncology Group
In collaboration with the Dutch BOOG Group and ALMANAC Trialists’ Group

Emiel J.T. Rutgers
The Netherlands Cancer Institute, Amsterdam

Clinical trial information: NCT00014612
AMAROS Trial

Trial design

cT1-2 N0 → R → ALND → SNB → AxSN+ → AxSN- → AxRT

Stratification: institution
Adjuvant systemic therapy by choice

EORTC
Eligibility Criteria

**Inclusion**
- Invasive breast cancer 0.5-5 cm
- Clinically N0
- BCT or mastectomy
- Any age
- Informed consent

**Exclusion**
- Multicentric disease
- Neoadjuvant systemic treatment
- Previous axillary treatment
- Prior malignancy

EORTC
## Baseline treatment

<table>
<thead>
<tr>
<th></th>
<th>ALND (744 pts)</th>
<th>ART (681 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>81.9 %</td>
<td>81.8 %</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>17.1 %</td>
<td>17.8 %</td>
</tr>
<tr>
<td><strong>Systemic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemotherapy</td>
<td>60.9 %</td>
<td>61.3 %</td>
</tr>
<tr>
<td>hormonal therapy</td>
<td>78.6 %</td>
<td>77.1 %</td>
</tr>
<tr>
<td>immunotherapy</td>
<td>6.0 %</td>
<td>6.4 %</td>
</tr>
<tr>
<td>no systemic treatment</td>
<td>9.0 %</td>
<td>9.4 %</td>
</tr>
<tr>
<td>RT breast/chest wall</td>
<td>84.8 %</td>
<td>87.7 %</td>
</tr>
</tbody>
</table>
Endpoints and statistical design

**Primary:** 5-years axillary recurrence free rate

**Non inferiority hypothesis (design):**
- assumption: ALND 98%; ART >96%
- one-sided log-rank; alpha = 0.05; power = 80%
- 52 events needed

**Secondary:**
- **Efficacy:** OS and DFS
- **Safety:** shoulder function, lymphedema, QoL
5-years axillary recurrence rate:
ALND 0.43% (4 / 744 events (0.54%))
AxRT 1.19% (7 / 681 events (1.03%))
<< hypothesis (2%)
Consequence: planned comparison is underpowered
AMAROS Trial

Disease-free survival

HR: 1.17; 95% CI: 0.93-1.51
P = 0.18

Number of patients at risk:

<table>
<thead>
<tr>
<th>Year</th>
<th>ALND</th>
<th>AxRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>124744</td>
<td>134681</td>
</tr>
<tr>
<td>2</td>
<td>686</td>
<td>633</td>
</tr>
<tr>
<td>4</td>
<td>511</td>
<td>468</td>
</tr>
<tr>
<td>6</td>
<td>322</td>
<td>284</td>
</tr>
<tr>
<td>8</td>
<td>140</td>
<td>131</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>24</td>
</tr>
</tbody>
</table>

EORTC
AMAROS Trial

Overall survival

Breast cancer specific deaths:
ALND: 53 (7.1 %)
AxRT: 54 (7.9 %)

HR: 1.17; 95% CI: 0.85-1.62
P = 0.34
AMAROS Trial

Lymphedema: clinical observation and/or treatment

![Graph showing percentage of lymphedema occurrence over years after randomization.](image)

- 1 year after randomization: 40.0% (ALND), 21.7% (AxRT), P < 0.0001
- 3 years after randomization: 29.8% (ALND), 16.7% (AxRT), P < 0.0001
- 5 years after randomization: 28.0% (ALND), 13.6% (AxRT), P < 0.0001
Lymphoedema: clinical observation

![Bar chart showing years since randomisation and lymphoedema rates for ALND, ART, and ALND+ART]
Lymphoedema: arm circumference ≥ 10%

years since randomisation

ALND
ART
ALND+ART
AMAROS Trial

Conclusion

Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients

Significantly less lymphedema after AxRT

AxRT can be considered standard
Objectives

• What is the current management of a positive sentinel node?

  - Discuss Z0011: IMPERFECT TRIAL THAT HAS BEEN PRACTICE CHANGING

  - Discuss newer evidence since Z0011: AMAROS

  - After total mastectomy: ACCEPTABLE TO CONSIDER NO ALND IF T1-T2 AND RNI.
Node positive breast cancer after neoadjuvant therapy

Can sentinel node biopsy be used to avoid node dissection?

...stay tuned for Dr Wright’s presentation in 30 minutes!!
Objectives

- Current Indications for axillary node dissection.
Indications for ALND v.2014

• Patients that are not eligible for SNB:
  - T4/Inflammatory breast cancer
  - Clinically/biopsy proven node positive disease (unless they receive neoadjuvant therapy and SNB is negative?)

• Patients with positive SNs that do not fit Z0011 or AMAROS:
  - T3
  - Mastectomy if PMRT/RNI is not given
  - 3+ positive SNs or extracapsular invasion >2mm (if RNI is not given?) - Currently favour ALND - Always discussed at multidisciplinary rounds.
  - Patients who have positive SNs after neoadjuvant therapy (TBD by the ALLIANCE A11202 Trial…)
Objectives

• How does the multidisciplinary team work in Quebec? MANY DIFFERENT SETTINGS...
Conclusions

• Since the 1970’s, we have been constantly pushing the barriers of the established surgical management of breast cancer - it is unlikely to stop now.

• We are currently witnessing the gradual extinction of surgical axillary node dissection, while there is a marked increase in the loco-regional use of radiotherapy.

• As personalized treatments and targeted therapies become more effective in the future, the need for loco-regional therapies will likely decrease for certain subtypes of breast cancer.

• Surgeons need to stay vigilant and recognize the situations where axillary node dissection might still be of benefit.
Appendix
Node positive breast cancer after neoadjuvant therapy

Can sentinel node biopsy be used to avoid node dissection?
## SLNB after Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Who</th>
<th>Where</th>
<th>What</th>
<th>N</th>
<th>Identification Rate False Negative Rate</th>
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<td>Gimbergues, P.</td>
<td>Ann Surg Oncol 2008</td>
<td>Series</td>
<td>129</td>
<td>IR (121/129) = 93.8% FN (8/56) = 14.3%</td>
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<tr>
<td>Xing, Y.</td>
<td>Breast J Surg 2006</td>
<td>Meta-analysis</td>
<td>1273</td>
<td>IR (1142/1273) = 88%; FN (65/540) = 12%</td>
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<tr>
<td>Classe, J.M.</td>
<td>J Clin Oncol 2005</td>
<td>Series</td>
<td>195</td>
<td>IR (176/195) = 90%; FN (6/52) = 11.5%</td>
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## SLNB after Neoadjuvant Chemotherapy in Node Negative Patients

<table>
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</table>
SLNB after Neoadjuvant Chemotherapy in Node Positive Patients

<table>
<thead>
<tr>
<th>Who</th>
<th>Where</th>
<th>How (were positive nodes determined)</th>
<th>N</th>
<th>Identification Rate False Negative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mamounas, E.P.</td>
<td>J Clin Oncol 2005</td>
<td>Clinical</td>
<td>102</td>
<td>IR (88/102) = 86.3% FN (3/43) = 7.0%</td>
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<tr>
<td>Gimbergues, P.</td>
<td>Ann Surg Oncol 2008</td>
<td>Clinical</td>
<td>47</td>
<td>IR (44/47) = 93.7% FN (8/27) = 29.6%</td>
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<tr>
<td>Lee, S.</td>
<td>Breast Cancer Res Treat 2007</td>
<td>Clinical and Radiological</td>
<td>219</td>
<td>IR (170/219) = 77.6% FN (7/124) = 5.6%</td>
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<tr>
<td>Classe, J.M.</td>
<td>J Clin Oncol 2005</td>
<td>Clinical</td>
<td>65</td>
<td>IR (53/65) = 81.5%; FN (3/25) = 12%</td>
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<tr>
<td>Newman, E.A.</td>
<td>Ann Surg Oncol 2007</td>
<td>Biopsy Proven</td>
<td>40</td>
<td>IR (40/40) = 100%; FN (3/28) = 11%</td>
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<td>Shen, J.</td>
<td>Cancer 2007</td>
<td>Biopsy Proven</td>
<td>69</td>
<td>IR (64/69) = 92.8% FN (10/40) = 25%</td>
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Sentinel Node biopsy Following NeoAdjuvant Chemotherapy in biopsy proven node positive breast cancer: The SN FNAC study.


A study funded by the Quebec Breast Cancer Foundation, the Cancer Research Society, the Week-end to End Women’s Cancer and the Montreal Jewish General Segal Cancer Centre.
SN FNAC Trial

• 1/3 of patients will have a pathologic complete axillary response to neoadjuvant therapy.

• Can we identify which patients have residual disease after neoadjuvant therapy using sentinel node biopsy?
SN FNAC – Study design

T0-T3 breast cancer N1-2 biopsy proven (FNA or core biopsy)
- Clinical examination 1
- Ultrasound evaluation 1

Neoadjuvant chemotherapy (NAC)
- Clinical examination 2
- Ultrasound evaluation 2

SNB + completion node dissection (CND)
- SNB surgical form
- Pathology form (SNB, CND, Breast)

N=153
Methods

• **SNB surgery**:
  - Radiocolloid marked with Tc99 mandatory.
  - Blue dye optional.

• **SNB pathology**:
  - Nodes sliced $\leq 2\text{mm}$.
  - IHC used if H&E was negative.
  - Pathology (SNB + CND slides) reviewed centrally.

* Sentinel nodes (SNs) with metastases of any size (ypN0(i+), ypN1mi and ypN1) were considered as positive.*

IHC: Immunohistochemistry
H&E: Hematoxylin and eosin stain
## Results

### Table 3. Size of SN metastasis

<table>
<thead>
<tr>
<th>SNs with metastases &lt; 0.2mm: positive vs. negative</th>
<th>FNR</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ypN0(i+) SN = node positive</td>
<td>8.4% (7/83)</td>
<td>86.3% (44/51)</td>
<td>94.5% (120/127)</td>
</tr>
<tr>
<td>ypN0(i+) SN = node negative</td>
<td>13.3% (11/83)</td>
<td>80.0% (44/55)</td>
<td>91.3% (116/127)</td>
</tr>
</tbody>
</table>

**FNR** = False negative rate  
**NPV** = Negative predictive value
The rate of positive non-SNs is independent of the size of SN metastases after NAT.

<table>
<thead>
<tr>
<th>Size of largest SN metastasis</th>
<th>ypN0(i+) ≤ 0.2 mm</th>
<th>ypN1mi &gt; 0.2 – 2 mm</th>
<th>ypN1 &gt; 2 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of positive non-SNs at CND</td>
<td>57% (4/7)</td>
<td>38% (3/8)</td>
<td>56% (34/61)</td>
</tr>
</tbody>
</table>

P=NS
## Results

Table 2. False negative SNB: Number of positive axillary nodes

<table>
<thead>
<tr>
<th>False negative patient #</th>
<th>Positive SNs/ Total SNs</th>
<th>Positive nodes CND/ Total nodes CND</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>0/2</td>
<td>1/13</td>
</tr>
<tr>
<td>#2</td>
<td>0/3</td>
<td>1/3</td>
</tr>
<tr>
<td>#3</td>
<td>0/1</td>
<td>1/9</td>
</tr>
<tr>
<td>#4</td>
<td>0/1</td>
<td>1/15</td>
</tr>
<tr>
<td>#5</td>
<td>0/1</td>
<td>1/19</td>
</tr>
<tr>
<td>#6</td>
<td>0/2</td>
<td>1/7</td>
</tr>
<tr>
<td>#7</td>
<td>0/1</td>
<td>3/8</td>
</tr>
</tbody>
</table>
## Results

### Table 4. Number of SNs removed

<table>
<thead>
<tr>
<th>Number of SNs removed</th>
<th>FNR</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.2%</td>
<td>71.4%</td>
<td>87.5%</td>
</tr>
<tr>
<td>1 SN removed</td>
<td>(4/22)</td>
<td>(10/14)</td>
<td>(28/32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ SNs removed</td>
<td>4.9%</td>
<td>91.9%</td>
<td>96.8%</td>
</tr>
<tr>
<td></td>
<td>(3/61)</td>
<td>(34/37)</td>
<td>(92/95)</td>
</tr>
</tbody>
</table>

FNR = False negative rate  
NPV = Negative predictive value
## Results

Table 5. Accuracy clinical examination vs. US vs. SNB

<table>
<thead>
<tr>
<th>Modality</th>
<th>FNR</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination</td>
<td>82%</td>
<td>38%</td>
<td>45%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>47%</td>
<td>48%</td>
<td>62%</td>
</tr>
<tr>
<td>Sentinel node biopsy</td>
<td>8%</td>
<td>86%</td>
<td>94%</td>
</tr>
</tbody>
</table>

FNR = False negative rate
NPV = Negative predictive value
Conclusions

• The accuracy (94.5%) and FNR (<10%) of SNB after NAC in biopsy proven node positive breast cancer is acceptable and similar to that seen for patients that present with clinically negative nodes in the absence of neoadjuvant therapy.

• The technical success rate of SNB in this setting (87.6%) is slightly inferior to 90%. In the presence of a technical failure, axillary node dissection is warranted.

• SNB is more accurate than both clinical examination and ultrasound evaluation of the axilla.
Conclusions

• Following NAC, SNs with metastases of any size should be considered as positive.

• The accuracy of SNB is increased when more than one node is removed.

• Axillary node dissection could potentially be avoided in 1/3 of patients that present with node positive breast cancer by using SNB after NAC.

• In an era where regional nodal radiation is increasingly used, the relevance of leaving residual disease in the undissected axilla of patients after NAC is unknown and remains to be investigated.
The role of sentinel lymph node surgery in patients presenting with node positive breast cancer (T0-T4, N1-2) who receive neoadjuvant chemotherapy – results from the ACOSOG Z1071 trial

Judy Boughey, Vera Suman, Elizabeth Mittendorf, Gretchen Ahrendt, Lee Wilke, Bret Taback, Marilyn Leitch, Teresa Flippo-Morton, David Byrd, David Ollila, Tom Julian, Sarah McLaughlin, Linda McCall, Fraser Symmans, Carisa Le-Petross, Bruce Haffty, Tom Buchholz, Kelly Hunt
Z1071 schema

T0-4, N1-2, M0 invasive breast cancer
(pretreatment axillary ultrasound with FNA or core biopsy documenting axillary metastases)

REGISTER*

Neoadjuvant chemotherapy

REGISTER*

SLN and ALND
Hypothesis: SLN surgery is an accurate method of axillary staging after NAC in node positive patients

Primary Endpoint: False negative rate of SLN surgery in patients with node positive disease at presentation with at least 2 SLNs examined after NAC

ClinicalTrials.gov Identifier: NCT00881361
level I and II nodes, which would have been detected by palpation if ALND was performed prior to preoperative chemotherapy, but may no longer be palpable after completion of preoperative chemotherapy.

1.4 Objectives

Primary and secondary objectives will be carried out in patients with clinical N1 disease independently of patients with clinical N2 disease.

1.4.1 Primary Objective

To determine the false negative rate for SLN surgery. Among the patients who have at least one sentinel lymph node identified and removed, false negative rate is defined as the number of patients declared to have no evidence of cancer in the SLN and are found to have at least one positive lymph node in the ALND divided by the total number of patients with at least one positive axillary lymph node by ALND.

1.4.2 Secondary Objectives

1. To determine how the axillary ultrasound status of the patient upon completion of preoperative chemotherapy (evidence of residual lymphadenopathy on the ultrasound examination versus no evidence of lymphadenopathy in the ultrasound examination) affects the false negative rate of SLN and how sonographic findings correlate with residual disease on final pathology.

2. To determine the node status of patients after preoperative chemotherapy. Patients will be classified as node positive if they were determined to have at least one positive lymph node by SLN or ALND. Patients will be classified as node negative if all nodes examined by SLN and ALND were negative.

3. To determine whether the false-negative rate for SLN surgery after preoperative chemotherapy is related to the extent of residual cancer burden (RCB) overall, or separately in the breast or regional nodal basin.

4. To evaluate pathological complete response (pCR) rates (defined as no invasive disease in breast or lymph nodes) and disease-free survival (DFS) rates in node positive patients receiving preoperative chemotherapy.
Methods

Recommended surgical standards

- Resection of minimum of 2 SLNs
- Use of dual tracer (radiocolloid and blue dye)

Pathologic assessment

- Standard processing with H&E staining
- Node positive defined as tumor >0.2mm on H&E
Node positive disease
637 pts

Chemotherapy

Technical success rate 92.7%

FN rate 56/382 = 14.7%

Node negative
255 pts (40%)

Residual nodal disease
382 pts (60%)

SLN positive
326 pts

SLN negative / ALND positive
56 pts

SLN correctly identified nodal status in 91.2%
False negative rate among pts with cN1 disease and at least 2 SLNs examined

\[
FNR = \frac{\# \text{ pts SLN} - / \text{ALND} +}{\# \text{ pts SLN} + \text{ or ALND} +}
\]

310 patients had residual nodal disease
39 of these patients had negative SLNs

\[
FNR = 12.6\%
\]

95% probability that the FNR lies in the range of 9.4 to 16.7%.
Only 1 SLN identified

78 patients with cN1 had only 1 SLN examined

24 pts had no residual nodal disease

17 of the 54 pts with residual nodal disease had false negative SLN findings

FNR = 31.5%
ACOSOG Z1071

CONCLUSIONS AND RELEVANCE Among women with cN1 breast cancer receiving neoadjuvant chemotherapy who had 2 or more SLNs examined, the FNR was not found to be 10% or less. Given this FNR threshold, changes in approach and patient selection that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND.
Can sentinel node biopsy accurately stage the axilla after NAT in patients with biopsy proven node positive axilla?

<table>
<thead>
<tr>
<th>Who</th>
<th>Where</th>
<th>How (were positive nodes determined)</th>
<th>N</th>
<th>N0(i+) SN’s considered as positive</th>
<th>Identification Rate</th>
<th>False Negative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boughey, J.</td>
<td>SABCS 2012</td>
<td>Biopsy Proven</td>
<td>756</td>
<td>no</td>
<td>IR (639/689) = 92.7%</td>
<td>FN (56/382) = 14.7%</td>
</tr>
<tr>
<td>Boileau, JF.</td>
<td>ASCO 2013</td>
<td>Biopsy Proven</td>
<td>153</td>
<td>yes</td>
<td>IR (127/145) = 87.6%</td>
<td>FN (7/83) = 8.4%</td>
</tr>
</tbody>
</table>
Beyond 2014…
Future Studies

**ALLIANCE A11202 Schema**

- Clinical T1-3 N1 M0 BC
  - Neoadjuvant Chemotherapy
  - BCT or Mastectomy
    - Sentinel Lymph Node Surgery
      - SLN Negative
      - SLN Positive
        - Randomization
          - ALND \(\oplus\)
            - Breast/chest wall and nodal XRT
          - No further axillary surgery. Breast/chest wall and nodal XRT

**NSABP B-51/RTOG 1304 (NRG 9353) Schema**

- Clinical T1-3 N1 M0 BC
  - Axillary nodal involvement (FNA or core needle biopsy)
    - Neoadjuvant chemo (+ Anti-HER-2 therapy for HER-2 neu \(\oplus\) pts)
  - Definitive surgery with histologic documentation of negative axillary nodes (either by axillary dissection or by SLNB ± axillary dissection)
    - Stratification
      - Type of surgery (mastectomy vs lumpectomy)
      - ER status (+ vs -), HER-2 status (+ vs -)
      - pCR in breast (yes vs no)
        - Randomization
          - No Regional Nodal XRT with breast XRT if BCS & No chest wall XRT if mastectomy
          - Regional Nodal XRT with breast XRT if BCS and chest wall XRT if mastectomy