Recent Update in Surgery for the Management of Breast Cancer

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De-escalation in breast cancer surgery

• Because of the improvement in multimodality treatment and improved clinical outcome, now focus has moved to enhancing QOL of the patients.

• We now know that adjuvant systemic therapy has positively impact on the outcome of local treatment.

• We have also learned that bigger surgery cannot cure bad biology.
Contents of my talk

- Active surveillance for low risk DCIS
- Axilla lymph node surgery
- Omitting surgery for primary breast lesion after neoadjuvant chemotherapy
Background: Low rates of death from breast cancer and concerns for overdiagnosis during screening programs

ACTIVE SURVEILLANCE FOR LOW RISK DCIS
Active Surveillance for Low-Risk Cancers

- Appropriate imaging and other monitoring method.
- Appropriate duration of monitoring
- What is the benefit of the patient?
- Which patients are appropriate candidates?
- Effect on patients’ emotional health

Survival Benefit of Breast Surgery for Low-Grade Ductal Carcinoma In Situ
A Population-Based Cohort Study

Sagara et al. JAMA Surg 2015

57,222 cases of DCIS,
1,169 cases (2.0%) without surgery
56,053 cases (98.0%) with surgery
LORIS
A Phase III Trial of Surgery versus Active Monitoring for Low Risk Ductal Carcinoma in Situ (DCIS)

To assess whether Active Monitoring is non-inferior to Surgery, in terms of ipsilateral invasive breast cancer free survival time

932 women with confirmed low risk DCIS

University of Birmingham, United Kingdom
Phase III, non-inferiority trial to assess the safety of active surveillance for low risk DCIS – The LORD study

1240 women aged > 45 years with asymptomatic screen-detected pure low-grade DCIS diagnosed with VAB of microcalcifications

The primary outcome is the proportion of patients free of ipsilateral invasive breast cancer at 10 yrs; secondary objectives include patient-reported outcome measures and cost-effectiveness analyses.
COMET study: Comparison of Operative to Monitoring and Endocrine Therapy for low-risk DCIS

- Gr I/II DCIS, ER+, absence of comedo necrosis
- 1200 patients
- Guideline Concordant Care: Surgery +/- radiation choice for endocrine therapy (MMG q 12 months x 5 years usual care for recurrent disease)
- **Active Surveillance**: Choice for endocrine therapy (MMG q 6 months x 5 years)
- Primary outcome: Proportion of new diagnoses of ipsilateral invasive cancer at 2 years of follow up
AXILLARY LYMPH NODE SURGERY
Summary of locoregional recurrence rates from key surgical trials

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of locoregional recurrence rates from key surgical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial (mean/median follow-up duration)</strong></td>
<td><strong>Locoregional recurrence rates</strong></td>
</tr>
<tr>
<td></td>
<td>SNB (%)</td>
</tr>
<tr>
<td>NSABP B04;23 patients with palpable nodes (25 years)</td>
<td>NA</td>
</tr>
<tr>
<td>NSABP B322 (8 years)</td>
<td>0.7</td>
</tr>
<tr>
<td>ACOSOG Z0011.18 (6 years)</td>
<td>0.9</td>
</tr>
<tr>
<td>IBCSG 23-01;7 patients with micrometastases (5 years)</td>
<td>1</td>
</tr>
<tr>
<td>AMAROS;34 patients with axillary recurrence (5 years)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; AMAROS, After Mapping of the Axilla: Radiotherapy or Surgery; IBCSG, International Breast Cancer Study Group; NA, not applicable; NS, not significant; NSABP, National Surgical Adjuvant Breast and Bowel Project; SNB, sentinel node biopsy.

ACOSOG Z0011

Clinically Negative Patients 1-2 Positive SNs by H & E

Lumpectomy + Breast XRT

Randomization

Completion ALND (n=445)

No Further Surgery (n=446)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SLNB Alone</th>
<th>SLNB + ALND</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 or More Positive Nodes</td>
<td>3.6%</td>
<td>21%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional Positive Nodes on ALND</td>
<td>N/A ??</td>
<td>27.3%</td>
<td>97 pts</td>
</tr>
<tr>
<td>5-Year Local Recurrence</td>
<td>1.6%</td>
<td>3.1%</td>
<td>0.11</td>
</tr>
<tr>
<td>5-Year Axillary Nodal Recurrence</td>
<td>0.9%</td>
<td>0.5%</td>
<td>NS</td>
</tr>
<tr>
<td>5-Year Overall Survival</td>
<td>92.5%</td>
<td>91.8%</td>
<td>HR: 0.87</td>
</tr>
<tr>
<td>5-Year DFS</td>
<td>83.9%</td>
<td>82.2%</td>
<td>HR: 0.88</td>
</tr>
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Early closure of the study
Earlier stage and ER+ disease than usual practice
Radiation field
Need long term follow up

At a median follow-up of **9.25 years**

<table>
<thead>
<tr>
<th></th>
<th>ALND arm</th>
<th>SLND arm</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 yr LN recurrence</td>
<td>0.5%</td>
<td>1.5%</td>
<td>0.28</td>
</tr>
<tr>
<td>10 yr locoregional recurrence</td>
<td>6.2%</td>
<td>5.3%</td>
<td>0.36</td>
</tr>
</tbody>
</table>

ALND and Nodal Irradiation Can Be Avoided for Most Node-positive Z0011-eligible Breast Cancers: A Prospective Validation Study

- 793 patients (84% no ALND)
- 5-year event-free survival after SLN alone was 93% with no isolated axillary recurrences
- Cumulative 5-year rates of breast+nodal and nodal+distant recurrence were each 0.7%
- Nodal recurrence was very low and did not differ significantly by RT fields (prone, supine tangent, breast+nodes)
- Even without preoperative axillary imaging or routine use of nodal RT, ALND can be avoided in a large majority of Z0011-eligible patients with excellent regional control.

Z0011-eligible cohort, n=1,750 in 5 centers of Korea

- SLNB alone (N=707) vs ALND (N=990)
- Propensity score matching
- DFS analysis

Jung JW, et al. unpublished data
AMAROS Trial:
Axillary Dissection vs. Axillary XRT After (+) SLN

Donker M. Et al: Lancet Oncol, 2014

HR: 1.17;    P = 0.18
HR: 1.17;    P = 0.34

Overall Survival

Disease-Free Survival

5-year Axillary Recurrence Rate
ALND 0.43%
AxRT 1.19%
Design Assumption:
2% for ALND
Planned Comparison is Underpowered

Lymphedema

Years after Randomization

ALND
AxRT

21.7%  16.7%  13.6%
Trends on Axillary Surgery in Breast Cancer Patients Treated Between 2011 and 2015
A Dutch Population-based Study in the Z0011 and AMAROS Era

However, only 10.3% Korean surgeons follow Z0011 trial result in the survey done early 2016
Omission of sentinel node biopsy: Rising doubts on the role of SLNB itself

Now we make adjuvant treatment decision based more and more on molecular subtype and genomic tests not based on nodal status.

Is there any therapeutic effect of SLNB at all?

Consideration points
Any subtype?  BCS patients only?  Radiation field?

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

Restricted Axillary Staging in Clinically and Sonographically Node-Negative Early Breast Cancer in the Context of Breast Conserving Therapy: Intergroup-Sentinel-Mamma (INSEMA) Trial


* According to protocol amendment #4 changed to ≤ 3 macrometastases. Direct inclusion of patients in the randon2 is then possible for all trial centres.
SLNB AFTER NEOADJUVANT CHEMOTHERAPY IN PATIENTS WITH DOCUMENTED (+) AXILLARY NODES
Three prospective trials were recently published (ACOSOC Z1071, SENTINA, SN FNAC)

- IRs were lower with SLNB after NC (80-93%) compared to upfront SLNB (>95%)
- FNRs ranged between 9.6%-14% and were mainly affected by number of removed SNs
Optimizing SLNB After NCT in Patients with Documented (+) Axillary Nodes Before NCT

- Appropriate candidate selection for SLNB \((T_{1-3}, N_1)\)
- **Dual agent** lymphatic mapping (isotope + dye)
- Identification and removal of \(>2\) SNs
- **Clip placement** in the positive node with radiologic clip localization and retrieval
- **Consideration** of performing **IHC staining** in the SLN and consider completion ALND even with N0i+ disease
Radioactive Iodine Seeds

Prior to NST, proven tumor-positive axillary lymph nodes were marked with a $^{125}$I seed (MARI-node.)

<table>
<thead>
<tr>
<th></th>
<th>Additional LN+</th>
<th>Additional LN-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARI node+</td>
<td>46</td>
<td>19</td>
<td>65</td>
</tr>
<tr>
<td>MARI node-</td>
<td>5</td>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

Overall accuracy: 95%
FNR: 7%

Survival outcome of sentinel lymph node biopsy-guided decision in breast cancer patients with negative axillary conversion after neoadjuvant chemotherapy

Clinically axilla node-positive
: Fine needle aspiration biopsy/Core needle biopsy (+) or Imaging study (+)

Neoadjuvant Chemotherapy

Clinically lymph node positive

Clinically lymph node negative
: Non-palpable and all images shows no suspicious node

Group A
SLNB-guided decision

Pathologic node negative and no ALND
Pathologic node positive with ALND

Group B
ALND without SLNB

Kang and Han, et al. BCRT 2017
Survival outcome of sentinel lymph node biopsy-guided decision in breast cancer patients with negative axillary conversion after neoadjuvant chemotherapy

**Axilla recurrence**

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cT</strong> T3/4 vs T1/2</td>
<td>1.35 (1.02-1.78)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>cN</strong> N2/3 vs N1</td>
<td>1.39 (1.05-1.86)</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>pCR</strong> Yes, No</td>
<td>0.24 (0.12-0.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ER</strong> (+), (-)</td>
<td>0.47 (0.35-0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Group</strong> A vs B</td>
<td><strong>1.10 (0.81-1.50)</strong></td>
<td>0.529</td>
</tr>
</tbody>
</table>

**4-year axilla recurrence free survival**

97.8% vs 99.0%; p=0.148

Kang and Han, et al. BCRT 2017
My strategy for LN management

Axilla LN

Clinically LN-

BCS

SLN 0-2+
No ALND, no AxRT

SLN 3 or more+
ALND or AxRT

SLN 0
No ALND, no AxRT

CLINICALLY LN+

TM

SLN+
ALND or AxRT

Converted to LN-
SLNB and ALND if +

NAC

Still LN+
ALND
Currently Accruing US Clinical Trials of Loco-Regional Therapy After NC
NO SURGERY FOR PRIMARY LESION IN PREDICTED PCR PATIENTS AFTER NEOADJ TX
The purpose of this study was to evaluate how accurately pCR can be predicted using MRI and image-guided biopsy.
Previous studies

- 164 patients, CNB or VABB
- NPV 71.3%, FNR 49.3%
- Existence of a clip marker tended to improve the NPV
- None of the mammo-guided VABs was false-negative

Heil et al., Br J Cancer 2015. PMID: 26554654

- 40 patients with T1-3N0-3 TNBC or HER2+
- Combined FNA/VACB demonstrated an accuracy of 98%
- FNR 5%
- NPV 95%

Kuerer, et al., Ann Surg 2017
Prediction of pCR by multiple-CNB or VABB before surgery in breast cancer with clinical CR after neoadjuvant chemotherapy: a Pilot Study (NCT03273426) in SNUH.

Neoadjuvant Chemotherapy → Clinical and Radiologic CR

Clip insertion for responsive tumor

cCR on MRI

Core needle biopsy (14G x ≥5)

VABB (Mammotome ELITE)

Wide Local Excision

20 cases

20 cases

Pathological evaluation

Pathological evaluation

Correlation of pCR (ypTis(-))
Negative predictive value (NPV)
False-negative rate (FNA)
### NPV & pCR rates according to Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>N</th>
<th>No tumor</th>
<th>Residual tumor</th>
<th>Biopsy</th>
<th>Surgical Excision</th>
<th>NPV</th>
<th>pCR (ypT0)</th>
<th>pCR (ypT0/Tis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR(-)/HER2(-)</td>
<td>19</td>
<td>16</td>
<td>3</td>
<td>14</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>73.7%</td>
</tr>
<tr>
<td>HR(-)/HER2(+)</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>75.0%</td>
</tr>
<tr>
<td>HR(+)/HER2(+/-)</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td>40</td>
<td>31</td>
<td>9</td>
<td>27</td>
<td>13</td>
<td>2</td>
<td>11</td>
<td>72.50%</td>
</tr>
</tbody>
</table>

For MRI $\leq 0.5$cm, **Accuracy 97.1%**

For 5 or more Bx core, **Accuracy 93.9%**
OPTIMIST trial (Omission of surgery for Predicted pCR patients with MRI and core biopsy in breast cancer after neoadjuvant chemotherapy)

- Neoadjuvant Chemotherapy
  - TNBC & HER2(+) cT1-2 N0-1
    - Residual Lesion
  - Vacuole CR on MRI

- Vacuum-assisted breast biopsy
  - 8~12 G ≥ 5 cores
  - No tumor nor atypia

- Intervention
  - Negative (pCR)
    - No Breast Surgery & Sentinel Lymph Node Biopsy
  - Positive (non-pCR)
    - No Breast Surgery & Sentinel Lymph Node Biopsy

- Radiotherapy

- Event-free survival
  - IBTR
  - distant metastasis
- Overall survival
- QoL, Cost

* 10% drop-out

Korean Breast Cancer Study Group (KBCSG)
Conclusions

• Changes in the surgery of the axillary and breast over the past 10 years highlight the potential to de-escalate in the era of multimodality therapy

• No surgery for low grade DCIS
• Less use of ALND and even skipping SLNB
• No surgery for primary breast lesion after NCT

• On-going and future clinical trials will answer the oncological safety and benefit in patients’ QOL of the de-escalation strategy in breast surgery
Thank You very much