4th ESO-ESMO Latin-American Masterclass in Clinical Oncology

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Mexico City, Mexico

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Under the auspices of

CMO
SMeO

LATIN-AMERICA PROGRAMME
Optimal loco-regional management of breast cancer

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Professor of Surgery
Memorial Sloan-Kettering Cancer Center
Universita’ Statale - Milan

Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, NY 10065
### Invasive cancer
**Milan at 20 years**

<table>
<thead>
<tr>
<th>Operation</th>
<th># pts</th>
<th>LR</th>
<th>Breast CA-specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRM</td>
<td>349</td>
<td>2.3%</td>
<td>76%</td>
</tr>
<tr>
<td>Quad/ALND plus RT</td>
<td>352</td>
<td>8.8%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Veronesi U et.al. NEJM 2002;347:1227
Extended Radical Mastectomy Vs Conservation
ONCOPLASTIC SURGERY
Oncoplastic: More Conservative Surgery in Larger Cancers
Nationwide Trends in Mastectomy for Early-Stage Breast Cancer

Kummerow K et Al: JAMA Surg. 2015
Mastectomy Trend in National Comprehensive Cancer Network centers (10249 stage 1)

Ines Vaz-Luis et Al, Breast res and Treat. 2016
ISSUES OF LOCAL RELAPSES

• Psychologically devastating for the Patient (Andersen, Cancer 2009)
• Need of systemic therapy after invasive local relapse (NCI guidelines 2004)
• More difficult reconstruction after mastectomy in Irradiated breasts (McCarthy, Plast. Rec. Surg. 2008)
• Additional health costs (Thomas, Br J Cancer. 2009)
• Local relapses may influence the prognosis (EBCTCG Lancet 2011)
**Hereditary Breast and Ovarian Cancer (HBOC) syndrome**

Breast Cancer

- 7%

- Genes with high/low penetrance
  - Unknown
  - SNPs, high/low risk
  - FGFR2
  - TNRC9
  - MAP3K1
  - LSP1
  - CASP8 (poligenic model)

Ovarian Cancer

- 10%

- BRCA1/BRCA2 25%

- TP53 1%

- PTEN 1%

- CHEK2 (1100delC)
- ATM
- BRIP1
- PALB2 1%

Do not duplicate or distribute without permission from the author and ESO.
Risk for ipsilateral breast recurrence: BRCA mutation carriers versus non-carriers

Valachis A, et Al, BCRT, 2014
BENEFIT OF CONTRALATERAL PROPHYLACTIC MASTECTOMY

Metcalfe K et Al: BMJ 2014
• No Survival Advantage

• Increase in costs
  • The mean cost of UM with surveillance was $14,141 and CPM was $20,319.
  
  Treatment with CPM resulted in $6178 more in costs

• Quality of Life
  • Equivalent QALYs (17.93) compared with UM over 30 years of follow-up
PASTIC SURGERY IMPROVEMENT

Do not duplicate or distribute without permission from the author and ESO.
Quality of life following total mastectomy with and without reconstruction versus breast-conserving surgery for breast cancer

Howes BHL et Al, J P Rec Aest Surgery, 2016
Cumulative incidence of loco-regional recurrence by genomic risk in patient treated with BCS

<table>
<thead>
<tr>
<th>Genomic Risk</th>
<th>Patient at risk at beginning of Year 5</th>
<th>Cumulative numbers of LRR</th>
<th>Cumulative Incidence (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>1887</td>
<td>43</td>
<td>1.39 (0.97; 1.80)</td>
</tr>
<tr>
<td>High risk</td>
<td>860</td>
<td>60</td>
<td>3.56 (2.66; 4.46)</td>
</tr>
</tbody>
</table>

Number of patients at risk:

- **G-risk**
  - Low risk: 54, 3578, 3465, 3400, 3307, 3033, 1903, 888, 273, 39
  - High risk: 66, 1891, 1817, 1751, 1684, 1521, 867, 425, 126, 12

Courtesy of Emiel Rutgers
Univariate analysis in BCS patient (n=5280)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Events/Patients</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had chemotherapy received</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her2 (local lab)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm, log transformed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant metastasis resistant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her2 (local lab)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Courtesy of Emiel Rutgers*
Multivariate analysis in BCS patients (n=5280)

The 70-gene is no longer independently associated with LRR

LRR and distant disease has distinct different biology
Lymphedema, 7-20% risk (W/O RT)
Z0011 CHANGING THE SURGICAL PRACTICE OF BREAST CANCER

Fillion MM at Al The Breast Journal 2016
## Overall Costs Based On Year of Procedure for Z0011 Eligible Patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Average overall cost per patient, mean (SD)</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>$55,148 ($16,149)</td>
<td>r = 0.991</td>
</tr>
<tr>
<td>2011</td>
<td>$46,113 ($12,831)</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>$42,439 ($13,289)</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>$42,248 ($17,110)</td>
<td></td>
</tr>
</tbody>
</table>

- **Rate of ALND**
  - 2010: 75%
  - 2011: 26%
  - 2012: 16%
  - 2013: 16%

- **Reduction in overall cost from 2010**
  - 2010: −16%
  - 2011: −23%
  - 2012: −22%

*Fillion MM at Al The Breast Journal 2016*
Z0011 used **clinical** N status, not axillary imaging.  
Do we need axillary imaging?  
Are the axillary images part of the clinical staging?  
How to deal with abnormal axillary images?
Axillary imaging abnormal and needle biopsy+

CT1-2N0 breast cancer patients
MSKCC 2006-2013

Abnormal axillary imaging and preoperative needle biopsy+
141 patients

1-2 total positive LNs:
66 (47%)

>2 total positive LNs:
75 (53%)

Axillary imaging needle biopsy+
Are we ready for Z11 in Mastectomy?

Do we need to dissect the axilla in case of positive sentinel node in mastectomy (no RT)?

Is the adjuvant systemic therapy able to destroy the residual lymph-node disease?
• Comparing axillary dissection Vs observation in micrometastatic SN
• 934 Randomized Patients
• 9% mastectomy
• No difference in local control and OS

IBCSG – Galimberti, Lancet Oncol, 2013
Randomised Trial for Patients with Sentinel Node Macrometastases “POSNOC”

Patients with T1-2 invasive breast cancer undergoing lumpectomy or mastectomy and sentinel node biopsy

1 or 2 Sentinel Node Macrometastases

Randomise (n=1900)

Adjuvant therapy alone

Breast or Chest wall RT, Systemic Therapy, Follow-up 5 years

Adjuvant therapy plus axillary treatment (axillary node clearance or axillary RT)

Axillary recurrence, Arm morbidity, QoL, Survival
**AMAROS: Mastectomy Vs Conservative Surgery**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Patients</th>
<th>N(A) 6 Con.</th>
<th>HS 6 Con.</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery to the primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>21/12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast conserving</td>
<td>0/1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Duration of DFS

Mila Donker et Al Lancet Oncol 2014
Lymphedema: clinical observation AMAROS/Z11

1 Years after randomization

![Graph showing lymphedema outcomes](image)
Sentinel Node and Neoadjuvant Chemotherapy

**No** sentinel node biopsy before neoadjuvant (low detection rate at second mapping (60%) High false negative results (51%)

Sentinel node after neoadjuvant in N1 (+FNA):
- 14% false negative (Sentina Trial)
- 12% False negative (ACOSOG Z1071 (Alliance)
  Dual mapping, blue and radioactive and 3 SN removed)
False negative rate by clip location

<table>
<thead>
<tr>
<th>Clip Location</th>
<th>N</th>
<th>Residual disease identified in SLNs or ALND</th>
<th>FNR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clip in SLN</td>
<td>107</td>
<td>59 (55.1%)</td>
<td>6.8</td>
<td>1.9 to 16.5</td>
</tr>
<tr>
<td>Clip not placed</td>
<td>355</td>
<td>209 (59.0%)</td>
<td>13.4</td>
<td>9.1 to 18.8</td>
</tr>
</tbody>
</table>

Boughev JC et Al, Ann Surg, 2017
### Surgical outcomes after NAC

**NODAL pCR**

N = 133

<table>
<thead>
<tr>
<th>Tumor Subtype</th>
<th>N</th>
<th>% Nodal pCR</th>
<th>% Breast pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>65  (133)</td>
<td>49</td>
<td>30</td>
</tr>
<tr>
<td>ER+/HER2-</td>
<td>12  (52)</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>ER+/HER2+</td>
<td>20  (27)</td>
<td>74</td>
<td>50</td>
</tr>
<tr>
<td>ER-/HER2+</td>
<td>16  (18)</td>
<td>89</td>
<td>63</td>
</tr>
<tr>
<td>ER-/HER2-</td>
<td>17  (36)</td>
<td>47</td>
<td>24</td>
</tr>
</tbody>
</table>

Barrio A: SSO 2016
ARE WE READY TO OMIT SURGERY IN BREAST CANCER PATIENTS??

CONCEPT OF INTEGRATE TREATMENTS
(Surgery, Chemotherapy, Target systemic therapy, Radiation Therapy, Immunotherapy)

CAN WE OMIT SOME THERAPIES??
Exceptional response in some cancer to only one therapy.
Sentinel node vs Observation after axillary Ultra-sound

(N=1454)

T1 N0
Any Age
Axillary positive US with FNA+ proceed to axillary dissection
Axillary Negative Ultra Sound or Negative FNA on the most suspicious node

(N=721)
Sentinel node biopsy.
If > nodes+ /frozen section axillary dissection

(N=733)
Observation

IEO – Milan (NOT TO BE REPRODUCED)
## SOUND Follow up

Available for 1015 pts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>SLN biopsy</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>516</td>
<td>498</td>
</tr>
<tr>
<td>Median fup (months)</td>
<td>25.7 (0.8-62.8)</td>
<td>25.4 (1.2-62.3)</td>
<td>25.9 (0.8-62.7)</td>
</tr>
<tr>
<td>Event Local recurrence</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Axillary metastases</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Contralateral carcinoma</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other primary cancer</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Death as first event</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Deaths Other cancer</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other-non cancer cause</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unknown cause</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

IEO – Milan (NOT TO BE REPRODUCED)
SLN 2017
SOUND trial

cT1N0 breast cancer negative axillary US
n=1454

SLNB
n=721

Observation
n=733

no difference in local, regional or distant events at 2 yr f/u

SLN-
no ALND
n=640

SLN+
ALND
n=81

ALND negative
40%
micromets only
43%
1 node+
14%
2 nodes+
1%
>2 nodes+
2%

minimal residual nodal tumor burden in SLN+ patients
Omitting Breast Surgery after Neoadjuvant Treatment

At First Visit For Potential Study Candidates in Surgery Clinic Post NAC and MRI
- Post-treatment MRI results are reviewed
- Non-study lumpectomy or mastectomy date is scheduled
- Informed consent is provided

Percutaneous Biopsy Eligibility
- Potential study candidate evaluated for eligibility
- If eligible then:
  - Informed consent signed
  - MRI core biopsy date set for 0-30 days before surgery

Percutaneous MRI Biopsy
- MRI examination will be performed (depending upon schedule, availability) on either a 1.5T or 3T MRI unit (GE Medical Systems, Waukesha, WI), equipped with either a 16- or 18-channel surface breast coil.

Standard of Care Surgery

Compare MRI Biopsy With Final Surgery Pathology
Eliminating Breast Cancer Surgery in Exceptional Responders with Neoadjuvant Therapy

T1/T2* HER2+/TN

Neoadjuvant Systemic Therapy

rCR/rPR

Image Guided Biopsy

12 9G VACB

No Residual Disease (Inv and In Situ)

Radiotherapy Alone

Follow Q 6 mo

Primary Endpoint
Local Regional Recurrence

Standard Surgery
Radiotherapy

Secondary Endpoints
Need for bx on F/u
Cosmetic Outcome
Quality of Life
Correlate CTC and cDNA
Cost
SUMMARY - MESSAGE

Conservation Surgery Corner Stone of Breast Surgery
Introduction of the concept of Precision Surgery
  Genomic Susceptibility
  Local Recurrence Prediction
  Cosmesis Prediction
  Patient Choice Decision with empowerment of Women

Axillary dissection less and less necessary

Possible avoiding surgery in the future in selected cancers