AGGIORNAMENTI IN CHIRURGIA DELL’ASCELLA:
QUANDO LA DISSEZIONE ASCELLARE?

Maria Grazia Lazzaretti
VALUTAZIONE ASCELLA

- PROGNOSI
- RACCOMANDAZIONI PER LA TERAPIA ADIUVANTE

...NONOSTANTE MECCANISM NI MOLECOLARI...

...SE CI SONO METASTASI...

SOPRAVVIVENZA SOVRAPPONIBILE, MA:

✅ RISCHIO DI ULTERIORI METASTASI
✅ POSSIBILITA’ DI SVILUPPARE RECIDIVE ASCELLARI SINTOMATICHE
✅ RISCHIO DI SOTTOUTILIZZO DI TERAPIE ADIUVANTI PER MANCANZA DI CORRETTA STADIAZIONE
THE ACCURACY OF CLINICAL NODAL STAGING AND OF LIMITED AXILLARY DISSECTION AS A DETERMINANT OF HISTOLOGIC NODAL STATUS IN CARCINOMA OF THE BREAST

Fisher B et Al; Surg Gynecol Obstet 1981

BREAST CANCER: RISK OF AXILLARY RECURRENCE IN NODE-NEGATIVE PATIENTS FOLLOWING PARTIAL DISSECTION OF THE AXILLA

Graversen HP et Al; Eur J Surg Oncol 1988

DOES THE NUMBER OF LYMPH NODES EXAMINED IN PATIENTS WITH LYMPH NODE-NEGATIVE BREAST CARCINOMA HAVE PROGNOSTIC SIGNIFICANCE?

Salama JK et Al; Cancer 2005
“...only LNR was associated with prediction for outcome...

“...the prognostic property of LNR was consistent, unlike pN stage, irrespective of nodal yield.”
BRAUST CANCER SUBTYPE, AGE AND LYMPH NODE STATUS AS PREDICTORS OF LOCAL RECURRENCE FOLLOWING BREAST-CONSERVING THERAPY

Multi-institutional cohort 2233 pts

HR = 1.06/involved node

Braunstein LZ et Al; Breast Cancer Res Treat 2017
CHIRURGIA DELL’ASCELLEA = STADIAZIONE

RECIDIVE ASCELLARI < ATTESO

BIOPSIA DEL LINFONODO SENTINELLA

STANDARD NELLA STADIAZIONE DELL’ASCELLEA

...MA...:

- NON SERVE PER ALCUNE PAZIENTI
- SE POSITIVO, NON SEMPRE NECESSARIA UNA D.A.
- SE FNAC+ PRE-INTERVENTO: SEMPRE D.A.?
“Quando U. Veronesi iniziò, a distanza di quasi 20 anni, la sua nuova ricerca conservativa riguardante i linfonodi, l’edema nelle pubblicazioni riapparve alla grande, come esito talmente brutale da consigliare di lasciare i linfonodi in sede sacrificandone solo alcuni per studiarne lo stadio. Questo comportava comunque l’interruzione della catena.

Come per la conservazione della ghiandola, i senologi sono tornati ad essere appagati: il LS, dicono, evita il linfedema. E’ vero! Non si vedono più i linfedemi di un tempo: bracciarosse, indurite, pesanti, arrossate, ciondolanti. Ma l’interruzione sussiste!”
BREAST CANCER SUBTYPE, AGE AND LYMPH NODE STATUS AS PREDICTORS OF LOCAL RECURRENCE FOLLOWING BREAST-CONSERVING THERAPY

First 176 pts recruited
Quick D.A.S.H.
(Disability Arm, Shoulder and Hand Questionnaire)
94 SNB arm vs 82 observation arm

Gentilini O. et Al; EJSO 2016
KYOTO BREAST CANCER CONSENSUS CONFERENCE 1
DE-ESCALATION OF AXILLARY SURGERY IN EARLY
BREAST CANCER

35 MULTIDISCIPLINARY PANEL MEMBERS

TREND TO DE-ESCALATION

1. advent of sentinel node biopsy
2. improvements in adjuvant therapies
3. down-staging of disease with neo-adjuvant approaches
4. predictive biomarkers superseding nodal status as prime determinants of eligibility for adjuvant systemic therapy

Jatoi I et Al; Lancet Oncol 2016
KYOTO BREAST CANCER CONSENSUS CONFERENCE 1
DE-ESCALATION OF AXILLARY SURGERY IN EARLY
BREAST CANCER

35 MULTIDISCIPLINARY PANEL MEMBERS

74% No ALND in low volume +SNs
80% SNB after NACT
(60% >2 nodes removed
17% placed a marker)

“reduced morbidity and enhanced quality of life”

Jatoi I et Al; Lancet Oncol 2016
Surgery of the Axilla following Neo-Adjuvant Chemotherapy

20. In a patient who is clinically node-positive at diagnosis and who downstages after chemotherapy: Is SN biopsy appropriate with 1-2 LN detected?

(1) Yes
   Yes 42.9%

(2) No
   No 53.6%

(3) Abstain
   Abstain 3.6%
### Axillary treatment for operable primary breast cancer (Review)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of Trials</th>
<th>Number of Participants</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Ax surgery vs ALND</td>
<td>10 trials</td>
<td>3849 pts</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ax sampling vs ALND</td>
<td>6 trials</td>
<td>1559 pts</td>
<td>Low</td>
</tr>
<tr>
<td>SLNB vs ALND</td>
<td>7 trials</td>
<td>9426 pts</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rt vs ALND</td>
<td>4 trials</td>
<td>2585 pts</td>
<td>High</td>
</tr>
</tbody>
</table>

**LESS SURGERY vs ALND:**
- **OS (HR=1.08)**
- **LR (HR 1.53)**

Low quality evidence suggests increased risk of lymphoedema with ALND.

"ALND of the clinically and radiologically uninvolved axilla is no longer acceptable practice in people with breast cancer."

Bromham N et Al; Cochrane Collaboration 2017
Axillary treatment for operable primary breast cancer

(Review)

Comparison 5 Less surgery versus ALND, Outcome 7 Lymphoedema. Increase in arm volume at 12 months postop.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Less surgery</th>
<th>More surgery</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No axillary surgery vs ALND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addenbrookes (1)</td>
<td>653</td>
<td>1245</td>
<td>4.2%</td>
<td>0.35</td>
<td>[0.12, 10.1]</td>
</tr>
<tr>
<td>Guy's (2)</td>
<td>0.01</td>
<td>6.01</td>
<td>2.2%</td>
<td>0.08</td>
<td>[0.00, 1.49]</td>
</tr>
<tr>
<td>Institut Bergonie (3)</td>
<td>3/258</td>
<td>41/274</td>
<td>1.44%</td>
<td>0.07</td>
<td>[0.02, 0.32]</td>
</tr>
<tr>
<td>NSABP B-04 (4)</td>
<td>48/312</td>
<td>177/577</td>
<td>38.4%</td>
<td>0.51</td>
<td>[0.29, 0.79]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>714</strong></td>
<td><strong>1000</strong></td>
<td>59.4%</td>
<td>0.31</td>
<td>[0.23, 0.43]</td>
</tr>
<tr>
<td>Total events: 57 (Less surgery), 226 (More surgery)</td>
<td></td>
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</tr>
</tbody>
</table>

Comparison 5 Less surgery versus ALND, Outcome 4 Local recurrence

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Less surgery</th>
<th>More surgery</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio 95% CI</th>
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<tbody>
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<td>No axillary surgery vs ALND</td>
<td></td>
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</tr>
<tr>
<td>Milan (3)</td>
<td>4/259</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>259</strong></td>
<td></td>
<td>59.4%</td>
<td>0.31</td>
<td>[0.23, 0.43]</td>
</tr>
<tr>
<td>Total events: 11 (Less surgery), 20 (More surgery)</td>
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</tbody>
</table>

Comparison 5 Less surgery versus ALND, Outcome 10 All-cause mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Less surgery</th>
<th>More surgery</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio 95% CI</th>
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<td></td>
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</tbody>
</table>

p < 0.00001
POSSIBILITÀ' DI RIDURRE GLI EFFETTI NEGATIVI A LIVELLO DI QUELLI DA RADIOTERAPIA?

Axillary Reverse Mapping
IS AXILLARY REVERSE MAPPING FEASIBLE IN BREAST CANCER PATIENTS?
Noguchi M et Al; EJSO 2015

IS THERE A ROLE FOR AXILLARY REVERSE MAPPING IN THE CURRENT MANAGEMENT OF BREAST CANCER TREATMENT?
Rutgers EJTh et Al; EJSO 2016

SYSTEMATIC REVIEW OF AXILLARY REVERSE MAPPING IN BREAST CANCER
Ahmed M et Al; BJS 2016

THE FEASIBILITY AND ONCOLOGICAL SAFETY OF AXILLARY REVERSE MAPPING IN PATIENTS WITH BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE STUDIES
Han C et Al; PLOSone 2016

AXILLARY REVERSE MAPPING IN N0 PATIENTS REQUIRING SENTINEL NODE BIOPSY – A SYSTEMATIC REVIEW OF THE LITERATURE AND NECESSITY OF A RANDOMIZED STUDY
Parks RM et Al; The Breast 2017

“…preservation of these nodes in patients with proven axillary node metastasis warrants further research as does the role of lymphatic and lymphovenous anastomosis.”

“…ARM is contraindicated for patients with clinically positive breast cancer.”

“…this literature review does not show enough evidence to mandate the introduction of ARM into current cancer guidelines.”
DISSEZIONE ASCELLARE

INDICAZIONI RESIDUE:

1. CLINICAMENTE N+ (palpazione, US, FNAC?)
2. CARCINOMA INFIAMMATORIO
3. MALATTIA RESIDUA ASCELLARE DOPO CTNA
4. LINFONODO SENTINELLA NON IDENTIFICATO
5. MASTECTOMIA CON MACROMETASTASI NEL SENTINELLA
6. PAZIENTI PER LE QUALI SONO NECESSARIE ULTERIORI INFORMAZIONI SUL NUMERO DI LINFONODI METASTATICI
D.A. & ASCELLA cN+  

TUMOUR BURDEN
PREDICTING THE EXTENT OF NODAL DISEASE IN EARLY-STAGE BREAST CANCER

“...having metastases identified by US was the strongest predictor of having more than three positive lymph nodes (OR = 4.01).”

“...lobular histology was also predictive of having more than three positive lymph nodes (OR = 1.77).”

Caudle AS et Al; Ann Surg Oncol 2014
META-ANALYSIS OF ULTRASOUND-GUIDED BIOPSY OF SUSPICIOUS AXILLARY LYMPH NODES IN THE SELECTION OF PATIENTS WITH EXTENSIVE AXILLARY TUMOUR BURDEN IN BREAST CANCER

“Patients with no suspicious nodes on ultrasound imaging and those with a negative ultrasound-guided biopsy could possibly be spared the sentinel lymph node procedure.”
**SNB & TUMOUR LOAD**

TOTAL TUMOUR LOAD ASSESSED BY ONE-STEP NUCLEIC ACID AMPLIFICATION ASSAY AS AN INTRAOPERATIVE PREDICTOR FOR NON-SENTINEL LYMPH NODE METASTASIS IN BREAST CANCER

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI) Univariate</th>
<th>P Univariate</th>
<th>OR (95% CI) Multivariate</th>
<th>P Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.99 (0.94−1.05)</td>
<td>0.711</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size (mm)</td>
<td>1.08 (1.00−1.16)</td>
<td>0.047</td>
<td>1.06 (0.98−1.15)</td>
<td>0.168</td>
</tr>
<tr>
<td>Log TTL (copies/μL)</td>
<td>3.56 (1.57−8.09)</td>
<td>0.002</td>
<td>2.67 (1.06−6.70)</td>
<td>0.036</td>
</tr>
<tr>
<td>SLN macrometastases</td>
<td>4.64 (1.55−13.92)</td>
<td>0.006</td>
<td>2.83 (0.94−7.36)</td>
<td>0.066</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>1</td>
<td>0.974</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive + ductal carcinoma in situ</td>
<td>0.97 (0.09−10.26)</td>
<td>0.974</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>0.58 (0.06−5.51)</td>
<td>0.669</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive papillary carcinoma</td>
<td>1</td>
<td>0.974</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histological tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>0.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0.15 (0.02−1.05)</td>
<td>0.069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1.14 (0.18−7.28)</td>
<td>0.471</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion (yes vs no)</td>
<td>1.60 (0.45−5.74)</td>
<td>0.451</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER (positive vs negative)</td>
<td>2.33 (0.26−21.17)</td>
<td>0.091</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR (positive vs negative)</td>
<td>6.28 (0.75−52.90)</td>
<td>0.091</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 (positive vs negative)</td>
<td>0.71 (0.13−3.94)</td>
<td>0.699</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocality (yes vs no)</td>
<td>2.78 (0.53−14.48)</td>
<td>0.226</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TTL only independent predictor of non SN metastases (OR = 2.67)

Nabais C et Al; The Breast 2016
SENTINEL NODE BIOPSY PERFORMANCE AFTER NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

72 eligible studies
7451 pts
IR 89.6%
FNR 14.2%

...BUT...

- no survival benefit
- no therapeutic role of AD
- role of minimal residual disease?

SENTINEL NODE BIOPSY AFTER NEOADJUVANT TREATMENT IN BREAST CANCER: FIVE YEAR FOLLOW-UP OF PATIENTS WITH CLINICALLY NODE-NEGATIVE OR NODE-POSITIVE AXILLARY DISEASE BEFORE TREATMENT

- FNR irrelevant
- AD has no effect on outcomes

Mocellin S et Al; Int J Cancer 2016
Galimberti V et Al; EJSO 2016
HOW TO AVOID AXILLARY LYMPH NODE DISSECTION?

1. cN0, ER+, Her2neu- (suggested BCS)
   Initial surgery is the path most likely to avoid ALND

2. cN0, TN or Her2neu+
   ???

3. cN+ or mastectomy pts
   NAC reduces the likelihood of ALND

Pilewskie M et Al; Jama Oncol 2017
OUTCOMES OF SENTINEL LYMPH NODE-POSITIVE BREAST CANCER PATIENTS TREATED WITH MASTECTOMY WITHOUT AXILLARY THERAPY

REGIONAL RECURRENCES

525 SN+ pts

RELAPSE-FREE SURVIVAL

OVERALL SURVIVAL

p=0.11
IR = 99.72%
Corretta indicazione EOL ascella = 90%
Corretta indicazione = 56.60%

DA d'embleè
SLNB
DA per +SN

4.9%
**INDICAZIONI**
- cN0 (EOL, US, FNAC)
- T < 3cm
- unicentrico

**CONTROINDICAZIONI**
- reine dopo SNB
- T > 3cm
- cN+
- infiammatorio
- DA anche per micromets
- DA solo per macromets

**SNB+**
- cN0 (EOL, US, FNAC)
- CTNA
- multicentrico
- recidiva dopo SNB
### CASISTICA DISSEZIONE ASCELLARE
(264 pazienti operate dal 2010 al 2016)

<table>
<thead>
<tr>
<th></th>
<th>n°</th>
<th>n° medio linfonodi asportati (range)</th>
<th>n° medio linfonodi metastatici (range)</th>
<th>casi con =&gt; 3 linfonodi + (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US/FNAC+</td>
<td>108</td>
<td>22.9 (8-65)</td>
<td>8.7 (0-51)</td>
<td>84 (77.8)</td>
</tr>
<tr>
<td>SNB+</td>
<td>91</td>
<td>20.4 (9-41)</td>
<td>2.0 (0-19)</td>
<td>21 (23.1)</td>
</tr>
<tr>
<td>DA dopo NACT in cN+ negativizzati</td>
<td>35</td>
<td>22.2 (9-56)</td>
<td>1.5 (0-14)</td>
<td>5 (14.3)</td>
</tr>
</tbody>
</table>

**controind. o volontà pazienti**

<table>
<thead>
<tr>
<th></th>
<th>n° (%)</th>
<th>casi con =&gt; 3 linfonodi + (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCELLEA POSITIVA ALLA PALPAZIONE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US/FNAC+</td>
<td>51 (47.2)</td>
<td>43 (84.3)</td>
</tr>
<tr>
<td>SNB+</td>
<td>4 (4.4)</td>
<td>4 (100)</td>
</tr>
</tbody>
</table>
CONSIDERAZIONI CONCLUSIVE

SNB REDUNDANT?

AXILLARY ULTRASOUND AND FINE-NEEDLE ASPIRATION CYTOLOGY IN THE PREOPERATIVE STAGING OF AXILLARY NODE METASTASES IN BREAST CANCER PATIENTS

Gipponi M et Al; The Breast 2016

PREOPERATIVE ULTRASOUND STAGING OF THE AXILLA MAKES PEROPERATIVE EXAMINATION OF THE SENTINEL NODE REDUNDANT IN BREAST CANCER: SAVING TISSUE, TIME AND MONEY

1. T => 5 cm
2. > 3 linfonodi metastatici
3. importante EEC
4. linfonodi metastatici alla palpazione
“With decreasing use of ALND, opportunities for junior staff, fellows, and residents to practice this procedure will continue to decline. In parallel, the technical complexity of performing ALND will continue to increase in the more advanced, chemotherapy-resistant, or recurrent disease. Therefore, breast surgeons will not retire from lymph node surgery; instead, they will be challenged by performing more difficult procedures with less experience.”
“...tailor more than to omit lymph node treatment....”

Poortmans 2016