CURRENT CONTROVERSIES IN BREAST CANCER SURGERY
“Less or more !?”
Wolfgang Gatzemeier

Breast Unit
HUMANITAS CANCER CENTER
Milan, Italy

I have no Disclosures
De-escalating and escalating surgery in the management of early breast cancer

Monica Morrow

How to Achieve Optimal Care in Early Breast Cancer with ‘Less’ or ‘More’ Treatment

Giuseppe Curigliano

From the maximum tolerable to the minimum effective treatment: The Umberto Veronesi’s life commitment to breast cancer care
Optimal loco-regional Treatment without compromising outcome
Minimising morbidity of Loco-regional treatment without compromising outcomes

- Individualized axillary lymph node management of the node positive axilla in 2018 (upfront surgery)

  Avoiding axillary dissection (ALND)

- Surgery and Neoadjuvant Chemotherapy (NACT)
  - Breast
  - Axillary lymph nodes
Minimising morbidity of Loco-regional treatment without compromising outcomes

Management of the Axilla

Clinically Positive Axilla
- Primary Surgery
- Neoadjuvant Therapy
- ALND
- Possible SLN biopsy

Clinically Negative Axilla
- Primary Surgery
- Neoadjuvant Therapy

SLN biopsy

Final management dependent on:
- successful mapping
- disease burden
- type of breast surgery
- clinical trial options

ypN+ ALND
Axillary Management for the clinically Node-negative Patient in up-front surgery

cN0 SN-

Upfront staging of the axilla SLNB
high level of accuracy /identification rate (IR) 88-95% and low false negative rate (FNR) 7-10%

Consensus
SN- : ALND is not required
regional recurrence rate < 1%.
No difference in terms of DDFS and OAS

Clinically Negative Axilla
Positive Sentinel Lymph Node(s)

Primary Surgery

SLN

>=3 SLN+
ALND

1-2 SLN+

BCT
Z0011, AMAROS, IBCSG 23-01...

Mastectomy

IBCSG 23-01, AMAROS...
Clinical Trials, cT1-2N0 with 1-2+ SLN

<table>
<thead>
<tr>
<th>Trials</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>observation vs ALND</td>
</tr>
<tr>
<td>ACOSOG Z0011 (n=856)</td>
<td>macro or micromets</td>
</tr>
<tr>
<td>IBCSG 23-01 (n=933)</td>
<td>micromets</td>
</tr>
<tr>
<td>AATRM (n=233)</td>
<td>micromets</td>
</tr>
<tr>
<td>AMAROS (n=1425)</td>
<td>macro or micromets</td>
</tr>
<tr>
<td>OTOASAR (n=474)</td>
<td>macro or micromets</td>
</tr>
</tbody>
</table>

## Clinical Trials, cT1-2N0 with 1-2+ SLN

<table>
<thead>
<tr>
<th></th>
<th>Z0011 N=856</th>
<th>AMAROS N=1425</th>
<th>OTOASOR N=474*</th>
<th>IBCSG 23-01 N=933</th>
<th>AATRM N=233</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional positive nodes ALND</td>
<td>27.3%</td>
<td>32.8%</td>
<td>38.5%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Axillary recurrence: ALND</td>
<td>0.5%</td>
<td>0.4%</td>
<td>2%</td>
<td>0.2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Axillary recurrence: other tx</td>
<td>1.1%</td>
<td>1.2%</td>
<td>1.7%</td>
<td>1%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>9.25yrs</td>
<td>6.1yrs</td>
<td>8yrs (mean)</td>
<td>5yrs</td>
<td>5.1yrs</td>
</tr>
<tr>
<td>Breast Conservation</td>
<td>100%</td>
<td>83%</td>
<td>84%</td>
<td>91%</td>
<td>88%</td>
</tr>
</tbody>
</table>

No difference in axillary recurrence rates between ALND and "other" treatment (observation or AxRT)

NO difference in DFS or OS between ALND or observation in Z011, IBCSG, AATRM between ALND or nodal RT in AMAROS or OTOASOR
## Clinical Trials Axillary Management Z0011

### Breast Conservation

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>% Spared ALND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ngui et al</td>
<td>119</td>
<td>22%</td>
</tr>
<tr>
<td>Verhuevel et al</td>
<td>916</td>
<td>61%</td>
</tr>
<tr>
<td>Delpech et al</td>
<td>125</td>
<td>70%</td>
</tr>
<tr>
<td>Yi et al</td>
<td>488</td>
<td>75%</td>
</tr>
<tr>
<td>Morrow et al</td>
<td>793</td>
<td>84%</td>
</tr>
</tbody>
</table>

### ONGOING RCTs: Management of 1-2 positive SN (up-front surgery)

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Criteria</th>
<th>Randomization</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>POSNOC 1</td>
<td>uni- or multifocal cT$_{1-2}$ N0</td>
<td>1:1</td>
<td>1. AD or RT</td>
</tr>
<tr>
<td></td>
<td>1–2 macrometastatic SNs</td>
<td></td>
<td>2. No further local treatment</td>
</tr>
<tr>
<td></td>
<td>BCS or mastectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SINODAR ONE 2</td>
<td>40–75 year old women</td>
<td>1:1</td>
<td>1. AD</td>
</tr>
<tr>
<td></td>
<td>unifocal cT$_{1-2}$ N0</td>
<td></td>
<td>2. No further axillary surgery</td>
</tr>
<tr>
<td></td>
<td>1–2 macrometastatic SNs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BCS or mastectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SENOMAC 3</td>
<td>uni- or multifocal cT$_{1-3}$ N0</td>
<td>1:1</td>
<td>1. AD</td>
</tr>
<tr>
<td></td>
<td>1–2 macrometastatic SNs</td>
<td></td>
<td>2. No further axillary surgery</td>
</tr>
<tr>
<td></td>
<td>BCS or mastectomy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Axillary Management for the clinically Node-negative Patient in up-front surgery

1. Perform sentinel lymph node biopsy
   Prebiopsy axillary imaging is not necessary

2. Determine axillary management based on results of sentinel lymph node biopsy and planned breast surgical procedure

<table>
<thead>
<tr>
<th>Metastases in ≥3 sentinel lymph nodes or matted lymph nodes found intraoperatively</th>
<th>Axillary management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases in 1-2 sentinel lymph nodes</td>
<td>Axillary lymph node dissection</td>
</tr>
</tbody>
</table>

Supporting Evidence

- AMAROS
- ACOSOG Z0011
- IBCSG 23-01
- AATRM 48/13/2000
- MA.20
- EORTC 22922-10925

ALND vs

- SLN biopsy alone
- SLN biopsy plus nodal irradiation

Consider neoadjuvant therapy for patients with HER2-positive or TNBC and planned mastectomy if adjuvant chemotherapy is indicated based on patient and tumor features.

Monica Morrow, JAMA Oncology  February 2018  Volume 4, Number 2

High-risk patients include those with large tumors (≥3 cm), lymphovascular tumor invasion, or microscopic extracapsular extension of metastases in sentinel nodes.
NACT

RATIONAL AND FACTS

SELECTION CRITERIA FOR BEST CANDIDATES

INITIAL WORK-UP

RESPONSE MONITORING / ADJUSTMENT

SURGERY AFTER NACT: BREAST + AXILLARY MANAGEMENT

POST SURGERY STRATEGIES
NACT

Primary surgery resulted in high LRR and poor OAS. In the 80’s, NACT was used for LABC/ IBC (T4a-d)
- demonstrated improved DFS and OAS and
- major reduction of tumour burden.

- Prompt treatment of micromets to improve survival?
Downstaging: Allow more limited surgery

Breast: Decreases rates of mastectomies

  Reduced volume of resection in patients candidates for BCT

Axillary nodes: Potential for decreasing the extent of axillary surgery using SLNB

Decreasing morbidity of surgery without jeopardizing outcomes
No survival advantage or disadvantage

Addition of NACT to the treatment regimen failed to demonstrate an improvement in OAS compared with adjuvant therapy.

NACT vs Adjuvant (OA/DF/RF) survival

NSABP-B18  1500 pts. (AC) FU 16 yrs.

NSABP-B 27  2300 pts. (AC/T) FU 8.5 yrs.

Effectiveness of NACT varies by molecular subtypes:

Degree of pathologic response correlates with both DFS and OA.

pCR powerful prognostic factor

Pathologic complete response (pCR): heterogeneous definitions

**ypT0/is ypN0**: Absence of any residual invasive cancer of the tumour and lymph nodes

*The data show comparable EFS or OS regardless of the presence or absence of DCIS.*

**ypT0 ypN0**: Strict pCR (spCR) is defined as an absence of invasive and non-invasive residuals in the breast and invasive disease in the axillary nodes

Definitions **not considering nodal involvement** or even **including focal invasive residuals** should no longer be used
Generally, any patients considered for adjuvant chemotherapy

Patients less than optimal for BCT (tumour/ breast ratio)

Both anatomical and biological factors are useful in selecting best candidates for NACT
Effectiveness of NACT varies by molecular subtypes:

NACT is most likely to result in tumour downstaging in:

- unicentric
- high-grade
- ER-negative and/or HER2-positive


Oncotype DX© is predictive of the probability of pCR to NACT

Clinical examination

Imaging: mammography
ultrasound

*MRI 9% additional +
  3% contral. +

Staging

(Pre-treatment photo documentation of extent of skin involvement)

* Has not been demonstrated to improve outcome (mortality / RR)

- Define baseline extent of disease
- Evaluate for multifocality /centricity
- Pathologic microcalcification
- Contralateral lesions
- Initial assessment of candidate for BCT
- Dist. mets


17th ESO-ESMO Masterclass in Clinical Oncology
Core needle biopsy: histological type, G  
- All suspicious lesion
- Clip in case of complete clinical / radiological response

ER, PgR, HER, Ki-67  
(define type/ schedule of pre-treatment)

Ultrasound of axillary nodes:
- US + FNA: Specificity 97-100%
- US: Sensitivity 49-87%  
  ➔ N- us/ c need SNB

u/c N-: SNL suspicious: FNA / CNB  
Clip biopsied nodes  
(NCCN 2016 GL)  
„Targeted Axillary Dissection“ TAD
SURGICAL CHALLENGES

• Need a standard method for monitoring response

• Need accurate imaging tools for quantifying response

• Take into consideration the differences in response by subtype
RESPONSE MONITORING / ADJUSTMENT OF THERAPY

Modality comparison for residual tumor size compared to pathologic tumor size

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBE</td>
<td>49–50</td>
<td>49–50</td>
<td>54</td>
</tr>
<tr>
<td>Mammography</td>
<td>79–81</td>
<td>79–81</td>
<td>32</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>89–90</td>
<td>30–33</td>
<td>60</td>
</tr>
<tr>
<td>MRI</td>
<td>86–92</td>
<td>60–86</td>
<td>90</td>
</tr>
</tbody>
</table>

CBE clinical breast examination, MRI magnetic resonance imaging.


Need for improved diagnostic tools to more accurately quantify disease response! (Dynamic contrast enhanced MRI, MRI spectroscopy, PET etc.)
NACT and Breast conserving surgery (BCS)

Meta-analysis: 14 prospective randomized trials of neoadjuvant versus adjuvant chemotherapy in a total of 5,500 patients with breast cancer demonstrated that NACT was associated with an absolute decrease in the mastectomy rate of 16.6%

Paradoxically, although rates of pCR to NACT have increased markedly with the use of newer therapeutic agents and targeted therapies, rates of BCS have not risen.

**Possible explanations:**

- Evaluation of the extent of residual disease?
- Volume to be resected (former/new tumour bed)?
- Residual ductal carcinoma *in situ* (DCIS)?
- Patients upfront candidates for BCS
- Patient preference for mastectomy?
- Surgeon (advice/decision making process?)

### Table

<table>
<thead>
<tr>
<th>Trial and treatment</th>
<th>pCR (%)</th>
<th>BCS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSABP B-27</strong>&lt;sup&gt;44&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin and cyclophosphamide (4 cycles)</td>
<td>13.7</td>
<td>62</td>
</tr>
<tr>
<td>Doxorubicin and cyclophosphamide plus docetaxel (4 cycles)</td>
<td>26.1</td>
<td>64</td>
</tr>
<tr>
<td><strong>GeparQuinto GBG 44</strong>&lt;sup&gt;17&lt;/sup&gt; (<strong>HER2-positive disease</strong>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epirubicin, cyclophosphamide and docetaxel (4 cycles) plus trastuzumab</td>
<td>44.6</td>
<td>64</td>
</tr>
<tr>
<td>Epirubicin, cyclophosphamide and docetaxel (4 cycles) plus lapatinib</td>
<td>30.2</td>
<td>59</td>
</tr>
<tr>
<td><strong>CHER-LOB</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (12 cycles) plus trastuzumab, and FEC (4 cycles)</td>
<td>25</td>
<td>67</td>
</tr>
<tr>
<td>Paclitaxel (12 cycles) plus lapatinib, and FEC (4 cycles)</td>
<td>26</td>
<td>58</td>
</tr>
<tr>
<td>Paclitaxel (12 cycles) plus trastuzumab and lapatinib, and FEC (4 cycles)</td>
<td>47</td>
<td>69</td>
</tr>
<tr>
<td><strong>NeoALTO</strong>&lt;sup&gt;46&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib plus paclitaxel (12 cycles)</td>
<td>24.7</td>
<td>43</td>
</tr>
<tr>
<td>Trastuzumab plus paclitaxel (12 cycles)</td>
<td>29.5</td>
<td>35</td>
</tr>
<tr>
<td>Lapatinib and trastuzumab plus paclitaxel (12 cycles)</td>
<td>51.3</td>
<td>41</td>
</tr>
</tbody>
</table>

**Abbreviations:** BCS, breast-conserving surgery; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; NACT, neoadjuvant chemotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project; pCR, pathological complete response.

King, T. A. Nat. Rev. Clin. Oncol. 12, 335–343 (2015);
Surgical intervention is necessary for every patient (microscopic residual disease in complete clinical/radiological response) (Define extent of residual disease).

Experienced and dedicated breast surgeon, radiologist, pathologist.

If possible BCT (optimal selection criteria still matter of debate: Volume, Margins)

**Multidisciplinary approach is key!**
Loco-regional therapy decision is based on:
• extend of the disease pre- and after treatment

Success of BCT depends on:
• careful patients selection
• achievement of negative margins (invasive + DCIS)
• removal of any suspicious clinical or radiological finding
• generous sample of “normal” breast tissue
• specimen radiography useful to assess margins
• Malignant appearing microcalcifications should be completely excised!


• IT IS NOT NECESSARY TO REMOVE THE ENTIRE VOLUME OF TISSUE
  INITIALLY OCCUPIED BY THE TUMOUR

RT is mandatory after BCT
Scattered microscopic foci of residual viable tumour, has been shown to predict an increased risk of local recurrence.

Specimen radiography might be useful.

Resection and detailed pathology review are often the only way to determine suitability for BCT.

GUIDELINES FOR RE-EXCISION / MASTECTOMY AFTER NACT

RE-EXCISION

In the setting of downstaging for BCT after NACT, if “viable tumour is present throughout the specimen even if it does not extent to the margins a further re-excision should be considered”


MASTECTOMY

Persistent positive margins
multicentric lesions
widespread DCIS or microcalcifications
planned contralateral mastectomy
APPROACH TO BCT AFTER NACT

LRR after Neoadjuvant therapy

- LRR not different in patients downstaged to BCT
- No differences in LRR after NAC by surgery type

<table>
<thead>
<tr>
<th>Surgery</th>
<th>10-yr incidence of LRR</th>
<th>Local LRR</th>
<th>Regional LRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>12.3 %</td>
<td>8.9 %</td>
<td>3.4 %</td>
</tr>
<tr>
<td>BCT</td>
<td>10.3 %</td>
<td>8.1 %</td>
<td>2.2 %</td>
</tr>
</tbody>
</table>

Factors associated with LRR: N2/N3, LVI, multifocal pattern after NACT, residual disease >2 cm after NACT

Minimising morbidity of Loco-regional treatment without compromising outcomes

Management of the Axilla

- Clinically Positive Axilla
  - Primary Surgery
  - Neoadjuvant Therapy
  - Possible SLN biopsy

- Clinically Negative Axilla
  - Primary Surgery
  - Neoadjuvant Therapy
  - SLN biopsy

Final management dependent on: successful mapping, disease burden, type of breast surgery, clinical trial options

ypN+ ALND
AXILLARY MANAGEMENT AND NACT

- NACT downstages the axilla in about 20-40% (varies by subtype; > 50% in HER+ disease with CHT + Anti Her+ therapy)
- Potential to consider SLNB after NACT to avoid ALND
AXILLA: SLNB and NACT

TIMING: pre/ post NACT

FEASIBILITY (IR)

ACCURACY (FNR)

SAFETY (LRR)
AXILLA: SLNB and NACT

TIMING: post NACT!

(disadvantage pre: - two surgical procedures
- does not take advantage of the potential downstaging
- commits all patients with +SN pre NACT to ALND
- uncertain prognostic value of negative nodes if the SN was the only positive node and was removed.)

FEASIBILITY (IR)
ACCURACY (FNR)
SAFETY (LRR)
## SLNB and NACT

Rates of Nodal Positivity Among Women Undergoing Axillary Staging Prior to Systemic Therapy vs Following Neoadjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Source</th>
<th>% Upfront Surgery</th>
<th>NAC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-18,2 1997</td>
<td>48</td>
<td>33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NSABP B-27,1 2003</td>
<td>49</td>
<td>40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hunt et al,13 2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>19</td>
<td>13</td>
<td>.04</td>
</tr>
<tr>
<td>T2</td>
<td>37</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>51</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NAC, neoadjuvant chemotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project.
EVIDENCE for SLNB after NAC
(Multicenter studies: NSABP B-27)

428 pts SLNB + ALND after NAC

IR 85%
FNR 11% (no significant differences in pts who presented with cN- / cN+)

Mamounas EP et al. JCO 2005;23:2694-702
Axillary recurrence rates with SLNB after NACT N-
Axillary recurrence rates with SLNB after NACT N-
Axillary recurrence rates with SLNB after NACT cN0

### Events

418 Patients SLN alone without ALND  
Median Follow-up = 36 months

<table>
<thead>
<tr>
<th>Relapse</th>
<th>N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis</td>
<td>3</td>
</tr>
<tr>
<td>Breast relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 homo L</td>
</tr>
<tr>
<td>Axillary relapse</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3 years survival</th>
<th>N= 418 (SLN alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>97.8% [94.9-99.1]</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>94.8% [91.0-97.1%]</td>
</tr>
</tbody>
</table>
SLNB after NACT

Intraoperative frozen section examination of SLN

ALND:

- for failed mapping
- for any positive SLN including micrometastasis / ITC

RT decisions made with combination of pre-treatment factors and final pathohistological status of nodes and breast
SLNB and NACT  N+

Rates of Nodal Pathologic Complete Response Following Neoadjuvant Chemotherapy in Patients With Biopsy-Proven Node-Positive Disease

<table>
<thead>
<tr>
<th>Source</th>
<th>Biopsy proven pN+ No Pts</th>
<th>Converted to ypN0 after NACT No Pts</th>
<th>pCR rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boughey</td>
<td>525</td>
<td>215</td>
<td>41</td>
</tr>
<tr>
<td>Mamtami</td>
<td>195</td>
<td>96</td>
<td>49</td>
</tr>
<tr>
<td>Boileau</td>
<td>145</td>
<td>50</td>
<td>35</td>
</tr>
<tr>
<td>Kim</td>
<td>415</td>
<td>159</td>
<td>38</td>
</tr>
</tbody>
</table>

## SLNB and NACT cN+

<table>
<thead>
<tr>
<th>Study</th>
<th>Population cN1-2</th>
<th>Biopsy mandatory</th>
<th>cN0 after NACT</th>
<th>IR</th>
<th>FNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENTINA</td>
<td>592</td>
<td>no</td>
<td>100 US</td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td>ACOSOG Z1071</td>
<td>689</td>
<td>yes</td>
<td>93</td>
<td>93</td>
<td>13</td>
</tr>
<tr>
<td>SN FNAC</td>
<td>153</td>
<td>yes</td>
<td>88</td>
<td>88</td>
<td>13</td>
</tr>
</tbody>
</table>

Kuehn T. GBG: SENTINA. Lancet Oncol 2013 May;14:609-18  
Pre- vs post-treatment nodal status impact on LRR

NSABP B-18 (AC)/B-27 (AC-T)

- cN(+), ypN(+) / No breast pCR
- cN(+), ypN(+) / Breast pCR
- cN(+), ypN(-) / No breast pCR
- cN(+), ypN(-) /
- cN(-), ypN(+) / No breast pCR
- cN(-), ypN(+)
- cN(-), ypN(-) / Breast pCR
- cN(-), ypN(-) / Breast pCR

Mastectomy

cN+ ypN+  LLR >25%
cN+ ypN-  no breast pCR
cN+ ypN-  breast pCR

Mamounas E et al JCO 2012
SLNB and NAC

Results from the prospective trials in SLN after NAT in clinically positive patients.

<table>
<thead>
<tr>
<th></th>
<th>ACOSOG Z0171</th>
<th>SN FNAC</th>
<th>SENTINA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>756</td>
<td>153</td>
<td>592</td>
<td>1501</td>
</tr>
<tr>
<td>FNR ≥ 2 SLNS</td>
<td>12.6%</td>
<td>4.9%</td>
<td>9.6%</td>
<td>10.8%</td>
</tr>
<tr>
<td>FNR dual tracer</td>
<td>10.8%</td>
<td>5.2%</td>
<td>8.6%</td>
<td>9.5%</td>
</tr>
<tr>
<td>FNR inclusion of N0(i+)</td>
<td>8.7%</td>
<td>8.4%</td>
<td>N/A</td>
<td>8.6%</td>
</tr>
<tr>
<td>FNR clip nodes</td>
<td>7.4%</td>
<td>N/A</td>
<td>N/A</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

FNR — False negative rate.
N0(i+) — Isolated tumor cells in the sentinel node.
SLN After Neoadjuvant Therapy, cN1 -> cNO

• Consistent unacceptable FNR unless ≥ 3 SN removed
  – Concern that residual disease resistant to therapy
  – Efforts to minimize FNR: dual tracer, IHC, MARI procedure, TAD + SLN
    RISAS study (Netherlands: MARI and SLN)

• Limited data on LRR when ALND not performed in this setting
  – Galimberti et al. 70 pts cN1/2 and neg SLN after NAC
    Median f/u 60 months, no axillary recurrences

• Importance of path node status in predicting LRR
  – NSABP-B18/27 mastectomy no PMRT, cN1 → ypN1 after NAC
    10yr LRR rates 20-25%

j.m.simons@umcu.nl; Galimberti V et al Eur J Surg Oncol 2016; Mamounas E et al JCO 2012
Axillary recurrence rates with SLNB after NACT N-/N+

Sentinel node biopsy after neoadjuvant treatment in breast cancer: Five-year follow-up of patients with clinically node-negative or node-positive disease before treatment

Patients scheduled for neoadjuvant treatment

Initially cN0

- cN0
  - post-neoadjuvant (n=249)
    - SN- (n=157)
    - SN+ (n=92)

- Axillary recurrences
  - 1 (0.6%)
    - Ipsilateral breast recurrences
      - 10 (6.4%)
    - Distant metastases
      - 12 (7.6%)

Initially cN1/2

- cN0
  - post-neoadjuvant (n=147)
    - SN- (n=70)
    - SN+ (n=77)

- Axillary recurrences 0
  - Ipsilateral breast recurrences
    - 0
  - Distant metastases
    - 9 (12.8%)

V. Galimberti et al. / EJSO 42 (2016) 361–368
Nodal pCR After Neoadjuvant Therapy

- Why include ITCs?
  - Lowest FNR in prospective studies with IHC detected disease
    - SN-FNAC (mandated IHC): FNR 4.9% w/ 2 SLN removed
      - No relationship between size of SLN met and likelihood of additional nodal disease
        » 57% of patients with ypN0(i+) had positive non-SLN
    - Z1071 subset with IHC: FNR 8.7% when mets <0.2mm on IHC or HE included and 2 SLN removed

Significance of disease <0.2mm (ypN0i+) after NAC unclear

Ongoing clinical trials of loco-regional Treatment after NACT

ALLIANCE A11202 Schema

- Clinical T1–T3 N1 MO breast cancer
- NACT
- Breast-conserving surgery or mastectomy and sentinel lymph-node surgery
- SLN negative
- SLN positive
- Randomization
- ALND plus breast/chest wall and nodal XRT (without XRT to dissected axilla)
- No further axillary surgery, but breast/chest wall and nodal XRT

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

- Clinical T1–T3 N1 MO breast cancer
- Axillary nodal involvement (FNA or core-needle biopsy)
- NACT (plus anti-HER2 therapy for HER2+ patients)
- Definitive surgery with histological documentation of negative axillary nodes (either by axillary dissection or by SLNB ± axillary dissection)
- Stratification
  - By type of surgery (mastectomy vs lumpectomy), ER status (+ vs −), HER2 status (+ vs −), pCR in breast (yes vs no)
- Randomization
- No regional nodal XRT
  - Breast XRT if breast-conserving surgery, but no chest-wall XRT if mastectomy
- Regional nodal XRT
  - With breast XRT if breast-conserving surgery, or chest-wall XRT if mastectomy
TAKE HOME: 1

Four RCTs (AMAROS, ACOSOG Z0011, IBCSG 23-01 and AATRM 48/13/2000) have shown evidence that SLNB either alone or followed by nodal irradiation is effective for the management of the clinically negative axilla and low axillary tumour burden in early breast cancer to avoid axillary lymph node dissection (ALND).

NACT does not prolong survival compared with adjuvant chemotherapy, but reduces the need for mastectomy and axillary lymph-node dissection, and thus surgical morbidity, without increasing the risk of locoregional recurrence.

Increasing rates of pCR have not translated into increasing rates of BCT (likely multifactorial).

High-grade oestrogen receptor (ER)-negative and/or HER2-positive breast cancers are more likely to experience pathological complete response to NACT than low-grade, ER-positive tumours.
Evaluating the extent of residual disease remains a problem.

Tumour resection, following NACT, does not need to remove the entire volume of breast tissue initially occupied by the tumour. Persistent finding of scattered, viable tumour in resection specimens should prompt consideration of re-resection.

Sentinel lymph-node biopsy (SLNB) after NACT accurately stages the axilla and is associated with a low rate of nodal recurrence in patients presenting with clinically negative axillary lymph nodes.

In patients who convert to clinically node-negative disease, SLNB after NACT has a false-negative rate of <10% only when ≥3 sentinel nodes are identified; nodal recurrence rates after SLNB alone in this population are (still) unknown.

The relative contribution of pre-NACT and post-NACT stage (degree of pathological response) to local control is uncertain; tailoring local therapy based on response to NACT is being evaluated in ongoing trials.