What is the clinical value of isolated tumor cells and micrometastases in the sentinel node?

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Maastricht University Medical Centre, NL
vcg.tjan.heijnen@mumc.nl
What is the clinical value of SN isolated tumor cells and micrometastases in breast cancer?

Size of treatment benefits

- loco-regional control
- distant metastasis
- survival

Size of treatment disadvantages

- Neurotoxicity, cognitive impairment
- menopausal complaints
- lymph edema, numbness, etc
1. Impact of isolated tumor cells and micrometastases on prognosis

→ relevant for adjuvant systemic treatment (AST) decisions
Micrometastases and Isolated tumor cells: Relevant and Robust Or Rubbish?

A cohort study from the Netherlands in 2707 early stage breast cancer patients who had undergone an SN procedure in 1997 – 2005

M. De Boer, NEJM, August 13, 2009
The Dutch MIRROR cohort study: DFS for pN0 vs. pN0(i+)/pN1mi

Impact of pN0(i+) and pN1mi corrected for age, tumor size, grade, ER/PR status:

HR 1.51 (95% CI 1.20-1.90)

M. De Boer, NEJM, 2009
MIRROR: disease-free survival AST* versus no AST

Impact of AST corrected for age, tumor size, grade, ER/PR:

HR for recurrence 0.57 (95%CI 0.44-0.74)

* Adjuvant systemic therapy

M. De Boer, NEJM, 2009

<table>
<thead>
<tr>
<th>Years since Diagnosis</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>856</td>
</tr>
<tr>
<td>1</td>
<td>823</td>
</tr>
<tr>
<td>2</td>
<td>753</td>
</tr>
<tr>
<td>3</td>
<td>588</td>
</tr>
<tr>
<td>4</td>
<td>423</td>
</tr>
<tr>
<td>5</td>
<td>275</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjuvant therapy</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
</tr>
</tbody>
</table>
The Dutch MIRROR study

Strong points:
- Large size, unselected
- Central pathology review, 6th version AJCC
- N-classification based on final nodal status
- Effect of AST taken into account

Weak points:
- Retrospective
- Disease-free not yet overall survival
- Relatively short 5-year follow up

M. De Boer, NEJM, 2009
Do all studies agree?

Impact of Micrometastases in the Sentinel Node of Patients With Invasive Breast Cancer

Nora M. Hansen, Baiba Grube, Xing Ye, Roderick R. Turner, R. James Brenner, Myung-Shin Sim, and Armando E. Giuliani

Conclusion
Patients with micrometastatic tumor deposits, pN0(i+) or pN1mi, do not seem to have a worse 8-year DFS or OS compared with SN-negative patients. As expected, there was a significant decrease in 8-year DFS and OS in patients with pN1 disease in the SN.

- Much smaller study: 84 pN0(i+) and 54 pN1mi patients
- SN status instead of final nodal status
- No central pathology revision
- 77% of patients received AST, not corrected for in MV analysis
Do all studies agree?

Breast Cancer Survival in Relation to the Metastatic Tumor Burden in Axillary Lymph Nodes

Yvette Andersson, Jan Frisell, Maria Sylvan, Jana de Boniface, and Leif Bergkvist

**Table 3.** Five-Year Event-Free Survival According to Nodal Involvement

<table>
<thead>
<tr>
<th>Lymph Node Status</th>
<th>Rate (%)</th>
<th>95% CI (%)</th>
<th>Hazard Ratio†</th>
<th>95% CI</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No metastases</td>
<td>87.1</td>
<td>85.4 to 88.8</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated tumor cells</td>
<td>88.9</td>
<td>82.3 to 95.4</td>
<td>0.96</td>
<td>0.53 to 1.84</td>
<td>.985</td>
</tr>
<tr>
<td>Micrometastases</td>
<td>79.6</td>
<td>71.0 to 88.2</td>
<td>1.71</td>
<td>1.05 to 2.80</td>
<td>.032</td>
</tr>
<tr>
<td>Macrometastases</td>
<td>80.1</td>
<td>76.8 to 83.5</td>
<td>1.24</td>
<td>1.24 to 2.43</td>
<td>.001</td>
</tr>
</tbody>
</table>

*Calculated from Kaplan-Meier estimates.
†Calculated from Cox regression model.
Do all studies agree?

Micrometastatic Node-Positive Breast Cancer: Long-Term Outcomes and Identification of High-Risk Subsets in a Large Population-Based Series

Pauline T. Truong, MDCM¹,²,³, Mary Lesperance, PhD⁴, Karen Hui Li, MSc⁴, Robyn MacFarlane, MD³,⁵, Caroline H. Speers, BA¹, and Stephen Chia, MD¹,³,⁵

The number of positive nodes should be considered in conjunction with tumor factors to estimate risk.

Multivariate correction for AST

- pN0 (n = 7,988)
- pNmic (n = 491)
- pNmac (n = 1,158)

The survival curves show different survival rates with varying numbers of positive nodes.
Do all studies agree?

Effect of Occult Metastases on Survival in Node-Negative Breast Cancer (NSABP-B32)

<table>
<thead>
<tr>
<th>Comparison</th>
<th>MV HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult vs no-occult met’s</td>
<td>1.40 (1.05 – 1.86)</td>
</tr>
<tr>
<td>pN0(i+) vs pN0</td>
<td>1.27 (1.04 – 1.54)</td>
</tr>
<tr>
<td>pN1mi vs pN0</td>
<td>1.60 (1.32 – 1.96)</td>
</tr>
<tr>
<td>Chemotherapy vs not</td>
<td>0.88 (0.68 – 1.13)</td>
</tr>
<tr>
<td>Endocrine therapy vs not</td>
<td>0.53 (0.42 – 0.66)</td>
</tr>
<tr>
<td>Other systemic R/ vs not</td>
<td>0.35 (0.09 – 1.39)</td>
</tr>
</tbody>
</table>
**Do all studies agree?**

Effect of Occult Metastases on Survival in Node-Negative Breast Cancer (NSABP-B32)

KM curves show unadjusted data.

I.e., the size of prognostic impact cannot be determined, unless shown separately for patients without AST.

<table>
<thead>
<tr>
<th></th>
<th>MV HR for death</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occult vs no-occult met’s</td>
<td>1.40</td>
<td>1.05 – 1.86</td>
</tr>
<tr>
<td>pN0(i+) vs pN0</td>
<td>1.27</td>
<td>1.04 – 1.54</td>
</tr>
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<td>1.60</td>
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<td>Endocrine therapy vs not</td>
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</tr>
<tr>
<td>Other systemic R/ vs not</td>
<td>0.35</td>
<td>0.09 – 1.39</td>
</tr>
</tbody>
</table>
The overall evidence from the pre-SN era

Breast Cancer Prognosis and Occult Lymph Node Metastases, Isolated Tumor Cells, and Micrometastases

M. de Boer, J. A. A. M. van Dijck, P. Bult, G. F. Borm, V. C. G. Tjan-Heijnen

*J Natl Cancer Inst 2010;102:410–425*

(total number of patients = 297,533)

Cohort studies:
HR: 1.44 (95%CI 1.29 - 1.62)

Occult metastases studies:
RR: 1.45 (95%CI 1.11 - 1.88)
Conclusions

- **Prognostic impact of pN0(i+) and pN1mi**

  The larger studies – if MV corrected for use of AST - show that low volume nodal disease is a **statistically significant** adverse prognostic risk factor in early breast cancer (adjusted HR ≈ 1.4 - 1.5).

- **Decision for AST**

  ✓ It depends on the **absolute size** of the prognostic impact
  ✓ **which also depends** on other risk factors, such as histological grade.
### Use of Adjuvant chemotherapy in the AMAROS study


<table>
<thead>
<tr>
<th></th>
<th>Odds ratio for receiving chemotherapy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per additional year</td>
<td>0.85</td>
<td>0.83-0.88</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1.73</td>
<td>0.99-3.01</td>
</tr>
<tr>
<td>III</td>
<td>7.05</td>
<td>3.56-13.96</td>
</tr>
<tr>
<td><strong>Size of SN metastasis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single ITC</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Clusters of ITC</td>
<td>1.85</td>
<td>0.27-12.49</td>
</tr>
<tr>
<td>Micro</td>
<td>4.90</td>
<td>0.80-29.98</td>
</tr>
<tr>
<td>Macro</td>
<td>9.83</td>
<td>1.65-58.79</td>
</tr>
<tr>
<td><strong>Multifocality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>4.91</td>
<td>2.02-11.90</td>
</tr>
</tbody>
</table>
2. Impact of SN isolated tumor cells and micro metastases on axillary recurrence (AR) rate if axillary treatment would be omitted

Size of treatment benefits

Size of treatment disadvantages
ITC and micrometastases: overall chance on second echelon node metastases

Non-Sentinel Lymph Node Metastases Associated With Isolated Breast Cancer Cells in the Sentinel Node

Carolien H. M. van Deurzen, Maaike de Boer, Evelyn M. Monninkhof, Peter Bult, Elsken van der Wall, Vivianne C. G. Tjan-Heijnen, Paul J. van Diest

12% chance on second echelon metastases, 64% = macromets!

Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer

G. Cserni¹, D. Gregori², F. Merletti³, A. Sapino³, M. P. Mano³, A. Ponti⁴, S. Sandrucci⁵, B. Baltás¹ and G. Bussolati³

20% chance on second echelon metastases

In contrast: SN macrometastases → 55% nonSN involvement (Chu, Ann Surg 1999)
Z0011: ALND vs no ALND in pts with SN metastasis
Giuliano A. et al. JAMA. 2011;305(6):569-575

Adjusted HR for OS (6.3 yrs FU)

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>ALND (n=420)</th>
<th>SN only (n=436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>3.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Regional</td>
<td>0.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Total</td>
<td>4.1%</td>
<td>2.8%</td>
</tr>
</tbody>
</table>
Z0011 trial
Giuliano A. et al. JAMA. 2011;305(6):569-575

Eligible
- Breast conserving therapy, mostly including 2D breast irradiation
- 1-2 H&E positive SN (which included pN0(i+))
- Most received AST (96%)

Patient characteristics → selection of favorable patients
- T1: 70%
- ER+: 83%
- Grade 1-2: 72%
- Micrometastases: 45% in SN – only arm
- ALND group: 27% positive non-SNs

Premature study closure,
which limits the power of the study to conclude that survival is non-inferior without axillary treatment in SN positive patients
## Do all studies agree?

Safety of avoiding routine use of axillary dissection in early stage breast cancer: a systematic review

Pepels M, Vestjens J, de Boer M, Smidt M, van Diest P, Borm G, Tjan-Heijnen V.
Breast Cancer Res Treat 2011: 301–313

<table>
<thead>
<tr>
<th>Source</th>
<th>No pts</th>
<th>% T1</th>
<th>AST % chemo / endocr.</th>
<th>Ax RT %</th>
<th>SN status</th>
<th>Median FU (mo)</th>
<th>Axillary recurrence %</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009 Bulte</td>
<td>20</td>
<td>71*</td>
<td>21 / 23*</td>
<td>NR</td>
<td>20&quot;micro&quot;</td>
<td>46 (11-64)</td>
<td>0</td>
</tr>
<tr>
<td>2009 Bilimoria</td>
<td>1,988</td>
<td>63</td>
<td>71/ 41</td>
<td>NR</td>
<td>530&quot;micro&quot;; 1,458macro</td>
<td>64 (60-72)</td>
<td>0.6 / 1.2</td>
</tr>
<tr>
<td>2007 Takei</td>
<td>120</td>
<td>30</td>
<td>92</td>
<td>54</td>
<td>Not specified</td>
<td>34 (2-83)*</td>
<td>0</td>
</tr>
<tr>
<td>2007 Hwang</td>
<td>196</td>
<td>72</td>
<td>56 / 27</td>
<td>64</td>
<td>67itc; 90micro; 39macro</td>
<td>30 (1-62)</td>
<td>0</td>
</tr>
<tr>
<td>2007 Park</td>
<td>287</td>
<td>78</td>
<td>NR</td>
<td>15</td>
<td>Not specified</td>
<td>23 (6-87)</td>
<td>2.1 (5.0)^</td>
</tr>
<tr>
<td>2006 Schulze</td>
<td>6</td>
<td>100*</td>
<td>3 / 68*</td>
<td>-</td>
<td>1itc; 4micro; 1macro</td>
<td>49 +/- 17*</td>
<td>0</td>
</tr>
<tr>
<td>2006 Pejavar</td>
<td>16</td>
<td>80*</td>
<td>30/34*</td>
<td>100</td>
<td>Not specified</td>
<td>24-60*</td>
<td>0</td>
</tr>
<tr>
<td>2006 Haid</td>
<td>10</td>
<td>77*</td>
<td>32 / 93*</td>
<td>-</td>
<td>2itc; 6micro; 2macro</td>
<td>47 (7-90)</td>
<td>0</td>
</tr>
<tr>
<td>2005 Fan</td>
<td>38</td>
<td>71</td>
<td>NR</td>
<td>63</td>
<td>27micro; 11macro</td>
<td>29 (6-76)</td>
<td>2.6</td>
</tr>
<tr>
<td>2005 Jeruss</td>
<td>73</td>
<td>57*</td>
<td>85 / 70*</td>
<td>-</td>
<td>73 “micro”</td>
<td>27 (1-98)</td>
<td>0</td>
</tr>
<tr>
<td>2005 Langer</td>
<td>27</td>
<td>72*</td>
<td>20 / 76@</td>
<td>-</td>
<td>27 “micro”</td>
<td>42 (12-64)</td>
<td>0</td>
</tr>
<tr>
<td>2005 Swenson</td>
<td>67</td>
<td>82*</td>
<td>42/58*</td>
<td>-</td>
<td>32 itc; 31micro; 4 macro</td>
<td>33 (2-73)</td>
<td>1.5</td>
</tr>
<tr>
<td>2005 Chagpar</td>
<td>15</td>
<td>89*</td>
<td>33</td>
<td>-</td>
<td>2itc; 12micro; 1macro</td>
<td>40 (1-54)</td>
<td>0</td>
</tr>
<tr>
<td>2004 Vegt</td>
<td>10</td>
<td>85*</td>
<td>NR</td>
<td>100</td>
<td>4micro; 6macro</td>
<td>35 (17-59)</td>
<td>0</td>
</tr>
<tr>
<td>2003 Fant</td>
<td>31</td>
<td>81</td>
<td>100</td>
<td>3</td>
<td>27&quot;micro&quot;; 4macro</td>
<td>28 (21-48)</td>
<td>0</td>
</tr>
<tr>
<td>2003 Guenther</td>
<td>46</td>
<td>67</td>
<td>100</td>
<td>2</td>
<td>23itc; 16&quot;micro&quot;; 7macro</td>
<td>32 (4-61)</td>
<td>0</td>
</tr>
</tbody>
</table>
Do all studies agree? → No

Comparison of Sentinel Lymph Node Biopsy Alone and Completion Axillary Lymph Node Dissection for Node-Positive Breast Cancer

Karl Y. Bilimoria, David J. Bentrem, Nora M. Hansen, Kevin P. Bethke, Alfred W. Rademaker, Clifford Y. Ko, David P. Winchester, and David J. Winchester


N=97,314

Conclusion
Compared with SLNB alone, completion ALND does not appear to improve outcomes for breast cancer patients with microscopic nodal metastases; however, there was a nonsignificant trend toward better outcomes with completion ALND for those with macroscopic disease.
Do all studies agree? → No


Patients without cALND:
- older, more favorable tumors, more likely to have BCT
- lower predicted risk of non-SN metastases: 9% vs. 37%, \( P \ 0.001 \)
- higher AR after 23-30 mo FU: 2% vs. 0.4%, \( P \ 0.004 \)
- AR of 5% in H&E positive SN
Do all studies agree? → No

Dutch MIRROR Study
pN1mi(sn) without axillary treatment

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log T size</td>
<td>8.62 (1.4–54)</td>
<td>0.021</td>
</tr>
<tr>
<td>Hist Grade 3</td>
<td>25.05 (1.3–497)</td>
<td>0.035</td>
</tr>
<tr>
<td>Neg ER / PR</td>
<td>4.96 (1.5–17)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

SN only: HR 4.39 (95% CI 1.46 –13.24)

5-yr AR (# pts)
5% (141)
1% (793)
0% (94)

Possible explanations for different findings in literature

- Selection of favorable patients with an intrinsic low risk of non-SN involvement.
- Relative short FU information.
- Incomplete FU data in cancer registries.
- Mixing up different groups: classifying isolated tumor cells in the ‘micrometastases’ group in some studies.
- Different rate of AST delivery in SN only patients (e.g. 13% in the MIRROR study versus 96% in the Z0011 study).
- Different loco-regional treatments related to BCT.
What is the clinical value of SN isolated tumor cells and micrometastases in breast cancer?

Can we decide on the size of benefits minimally needed to accept the treatment-related side effects?
Case with limited macrometastases

Vivianne Tjan-Heijnen
A 46-year old woman underwent breast conserving surgery

Histology:
- Tumor size of 33 mm
- Histological grade II
- Lymph vessel invasion: yes
- Multifocal: no
- Triple negative
- 2 SNs macrometastasis (largest: 3 mm)

She will undergo AST and breast RT (3D)

Would you offer cALND?
Would you use a nomogram or other scoring systems to guide treatment decision-making?
### TABLE 4. Observed and predicted proportion of positive non-SNs in relation to primary tumor and SN characteristics

<table>
<thead>
<tr>
<th>pN(sn)</th>
<th>Lymph and/or blood vessel invasion</th>
<th>Tumor size (cm)</th>
<th>Patients (n)</th>
<th>Positive non-SNs (n)</th>
<th>Observed proportion of positive non-SNs (%)</th>
<th>95% CI</th>
<th>Predicted proportion of positive non-SNs (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0(i+)</td>
<td>No</td>
<td>&lt;1.0</td>
<td>24</td>
<td>0</td>
<td>0.0</td>
<td>0–14</td>
<td>9.7</td>
<td>4–23</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.1–3.0</td>
<td>14</td>
<td>1</td>
<td>7.1</td>
<td></td>
<td>24.9</td>
<td>9–53</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3.1–5.0</td>
<td>4</td>
<td>0</td>
<td>0.0</td>
<td></td>
<td>17.6</td>
<td>7–37</td>
</tr>
<tr>
<td>pN1mi</td>
<td>No</td>
<td>1.1–3.0</td>
<td>27</td>
<td>8</td>
<td>29.6</td>
<td></td>
<td>39.8</td>
<td>17–68</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3.1–5.0</td>
<td>4</td>
<td>1</td>
<td>25.0</td>
<td></td>
<td>50.8</td>
<td>27–75</td>
</tr>
<tr>
<td>pN1+</td>
<td>No</td>
<td>1.1–3.0</td>
<td>50</td>
<td>15</td>
<td>30.0</td>
<td></td>
<td>67.3</td>
<td>40–87</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3.1–5.0</td>
<td>5</td>
<td>4</td>
<td>80.0</td>
<td></td>
<td>30.0</td>
<td>20–42</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.1–3.0</td>
<td>20</td>
<td>9</td>
<td>45.0</td>
<td></td>
<td>46.1</td>
<td>30–63</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3.1–5.0</td>
<td>4</td>
<td>2</td>
<td>50.0</td>
<td></td>
<td>72.6</td>
<td>47–89</td>
</tr>
</tbody>
</table>

SN, sentinel lymph node; 95% CI, 95% confidence interval; pN1+, pN1a and higher pN positive stages.
Examples of existing nomograms and calculators for prediction of non-SN involvement
For low predicted probability cut-off values of no more than 5, 10 and 15 per cent:

- False-negative rates: 20%, 14% and 19%, resp.
- Specificities: 4%, 27% and 32%, resp.
- The low-risk category (5% or less) consisted of only 3% of the study population.
High Intersystem Variability for the Prediction of Additional Axillary Non-Sentinel Lymph Node Involvement in Individual Patients with Sentinel Node-Positive Breast Cancer

Ingrid van den Hoven, MD¹, Gerrit P. Kuijt, MD¹, Adri C. Voogd, PhD², and Rudi M. H. Roumen, MD, PhD¹
Moreover, prediction of axillary recurrence

- ≠ prediction of non-SN involvement
- AR rate is lower, because of AST and axRT
Patient selection: based on the MIRROR study AR rates in pts with pN0(i+) and pN1mi, offset against predicted risk of non-SN involvement

<table>
<thead>
<tr>
<th>Model</th>
<th>Low predicted non-SN risk ≤10%</th>
<th>5 year regional recurrence rate (%)</th>
<th>High predicted non-SN risk &gt; 10%</th>
<th>5 year regional recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC</td>
<td>300</td>
<td>2.8</td>
<td>166</td>
<td>3.4</td>
</tr>
<tr>
<td>Stanford</td>
<td>465</td>
<td>3.2</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Tenon</td>
<td>438</td>
<td>2.3</td>
<td>48</td>
<td>10.1</td>
</tr>
<tr>
<td>Bolster</td>
<td>384</td>
<td>2.2</td>
<td>102</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Pepels et al. SABCS 2011: PD 02-07
What to do?
Case with micrometastasis

Gabor Cserni
50-year-old woman: mastectomy & SNB

- Preoperative: 2 cm + 3x4 cm microcalcification (DCIS on core biopsy) & AXUS negative

- Histology:
  - Ductal carcinoma with extensive intraductal component; extent 5 cm; 13.7 mm and 1.5 mm sized invasive foci: pT1c(2)
  - Histological grade II
  - LVI+
  - ER+, PR+, HER2-
  - 1/1 SLN with micrometastasis 0.9 mm in greatest dimension identified on HE (pN1mi)

- Would you recommend completion ALND? (ASCO 2005)
- Would you use a nomogram?
- Would you recommend against ALND? (e.g. St Gallen 2011)
Despite differences in methods, the results of several studies point to the factors below as the most likely to be associated with NSN positivity in SN+ patients:

- SN metastasis >2mm (macrometastasis)
- EC extension of SN metastasis (not present)
- Tumor size > 2cm
- >1 SN+
- LVI in the primary tumor

Factors associated with a NSN+ status in SN+ patients

- **Tumor**
  - Size
  - LVI

- **SN metastasis**
  - Size
  - Method of detection (HE vs IHC)
  - Extracapsular extension
  - Number of positive SNs
  - Number of negative SNs
  - SN ratio (SNs+/all SNs)

*Based on 34 studies (≥100 patients)
** Based on 56 candidate studies

Nomograms: role of institutional validation

• **Significant inter-institutional differences in:**
  – Median T size
  – % with LVI
  – % of ER+ cases
  – % with low histological grade (%)
  – % of histological types
  – mean number of SNs
  – % of cases with MIC/ITC
  – % with extracapsular invasion
  – % of cases allocated to the low risk category
  – and outcome measure: % of cases with non-SN metastasis

• Each predictive tool used in clinical practice for patient and physician decision on further axillary treatment of SN-positive patients may require individual institutional validation; such validation may reveal different predictive tools to be the best in different institutions.

<table>
<thead>
<tr>
<th>Institutional value</th>
<th>Low risk (obs. NSN+)</th>
<th>Non low risk obs. NSN+</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOOD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stanford</td>
<td>22% (9%)</td>
<td>33%</td>
</tr>
<tr>
<td>F micrometastasis</td>
<td>66% mic (5%)</td>
<td>30%</td>
</tr>
<tr>
<td>SUITABLE (&lt;20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSKCC</td>
<td>27% (16%)</td>
<td>33%</td>
</tr>
<tr>
<td>Masaryk</td>
<td>33% (16%)</td>
<td>32%</td>
</tr>
<tr>
<td>Tenon score</td>
<td>52% (18%)</td>
<td>39%</td>
</tr>
<tr>
<td>UNSUITABLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louisville CPR</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Mayo nomogram</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>MDA score</td>
<td>(&gt;20%)</td>
<td></td>
</tr>
</tbody>
</table>
Results of the institutional validation (tumours ≤ 15 mm)
The observed rate of NSN metastases in the predicted low risk group was really low in only two models:

- **STANFORD:**
  - 22/138 (22%) allocated to low risk, and 2/22 had NSN+ (9%)
  - for patients outside the low risk category, NSN+ rate was 37/116 (32%)!

- **French MICROMETASTASIS:**
  - 38/138 (28%) of all, and 38/58 (66%) of micrometastatic cases allocated to low risk; 2/36 (5%) had NSN+
  - for patients outside the low risk category, NSN+ rate was 6/20 (30%) NSN+!

STANFORD NOMOGRAM

https://www3-hrpdcc.stanford.edu/nsln-calculator/

Tumor size / ITC vs MIC vs MAC / LVI

French micrometastasis nomogram

Pure vs mixed type / Method of metastasis detection / Tumor size / LVI

Our case

- French MICROMETASTASIS nomogram:
  19% risk of non-SN metastases
- Discussion with the patient *
- ALND: 7/17 macrometastases – pT1c(2) pN2a
- Adjuvant treatment:
  CT (6 FEC) + RT + HT (LHRH + TAM)

10-15% NSN involvement associated with micrometastasis may be influenced by other factors (multivariable models).

Nomograms have different performances at different institutions: e.g. area under ROC curves for micrometastasis nomograms:
- Helsinki nomogram (ASO 2012): 0.848 in Center B 0.501 in Center A
- French nomogram (EJSO 2009): 0.598 in Center B 0.599 in Center A
- Revised French n. (Breast 2012): 0.600 in Center B 0.562 in Center A

Current nomograms perform not good enough in predicting high risk patients.

Case with micrometastasis and modern breast RT

Vivianne Tjan-Heijnen
A 54-year old woman underwent breast conserving surgery + SNB

Histology:
- tumor size of 15 mm
- histological grade III
- lymph vessel invasion: no
- ER positive, HER2 negative
- 1 SNs positive, with micrometastasis (1.3 mm)

She receives breast RT (3D) and AST

Is use of modern breast irradiation technique important for your preference regarding axillary treatment?
TAKE HOME MESSAGES
Gabor Cserni and Vivianne Tjan-Heijnen

- Not only SN metastasis size and number is important!
- Take also primary tumor risk factors into account...
- .. in addition to type of breast surgery, breast irradiation technique and use of AST.
- But, prediction models need to be improved.
Proposed algorithm for axillary therapy: Who still needs cALND if pN1+(sn) ?

- Patients treated with mastectomy, except low risk* pN1mi(sn) treated with AST
- Patients not receiving AST
- Patients with \( \geq 3 \) macrometastases
- Patients with clinically positive nodes

* High risk: \( T > 3\text{cm or } G \text{ III or LVI} \)
Proposed algorithm for axillary therapy
if SN+ and BCS + 3D breast RT + AST

- Low risk → no axillary treatment
  - micrometastases without risk factors*
- Intermediate risk → level 1 axRT (≈ Z0011)
  - micrometastases with \( \geq 1 \) risk factor
  - 1-2 macrometastases without risk factors
- High risk → cALND
  - macrometastases with \( \geq 1 \) risk factor

* \( T > 3\text{cm}, \ G \text{ III}, \ LVI \)
Thank you!