What is the clinical value of isolated tumor cells and micrometastases in the sentinel node?
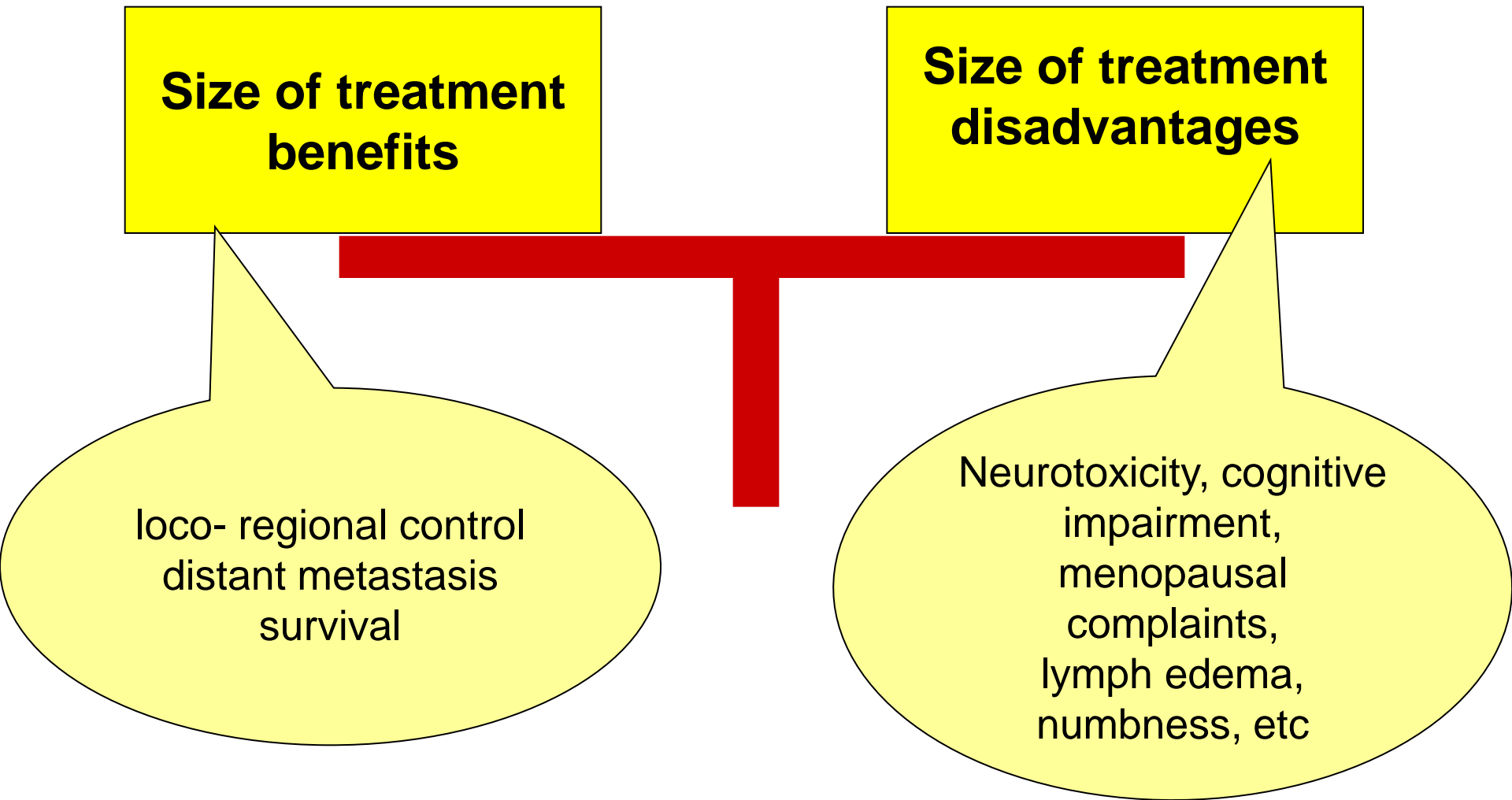
Prof.dr. Vivianne Tjan-Heijnen, MD, PhD

medical oncologist

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

Size of treatment disadvantages

loco- regional control
distant metastasis
survival

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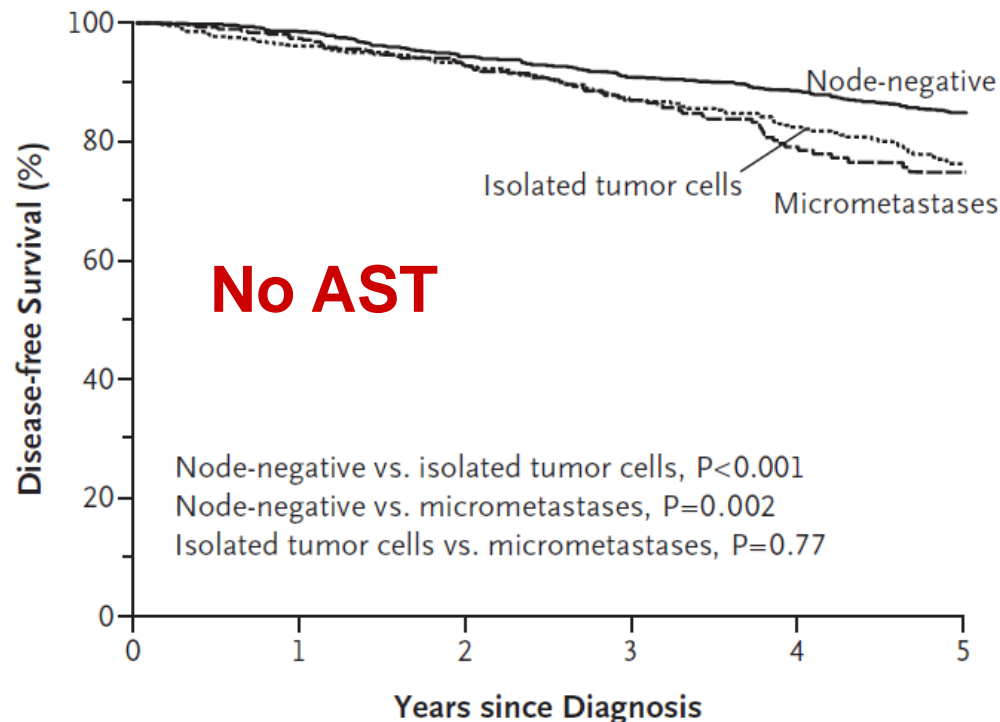
1. Impact of isolated tumor cells and micrometastases on prognosis

→ relevant for adjuvant systemic treatment (AST) decisions

The MIRROR study

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

# The Dutch MIRROR cohort study: DFS for pN0 vs. pN0(i+)/pN1mi

Disease-free Survival (%) vs. **Years since Diagnosis**

Node-negative

Isolated tumor cells

Micrometastases

No AST

Node-negative vs. isolated tumor cells, $P<0.001$
Node-negative vs. micrometastases, $P=0.002$
Isolated tumor cells vs. micrometastases, $P=0.77$

No. at Risk

Node-negative	856	838	800	761	722	628
Isolated tumor cells	513	493	453	367	282	199
Micrometastases	343	330	301	222	142	76

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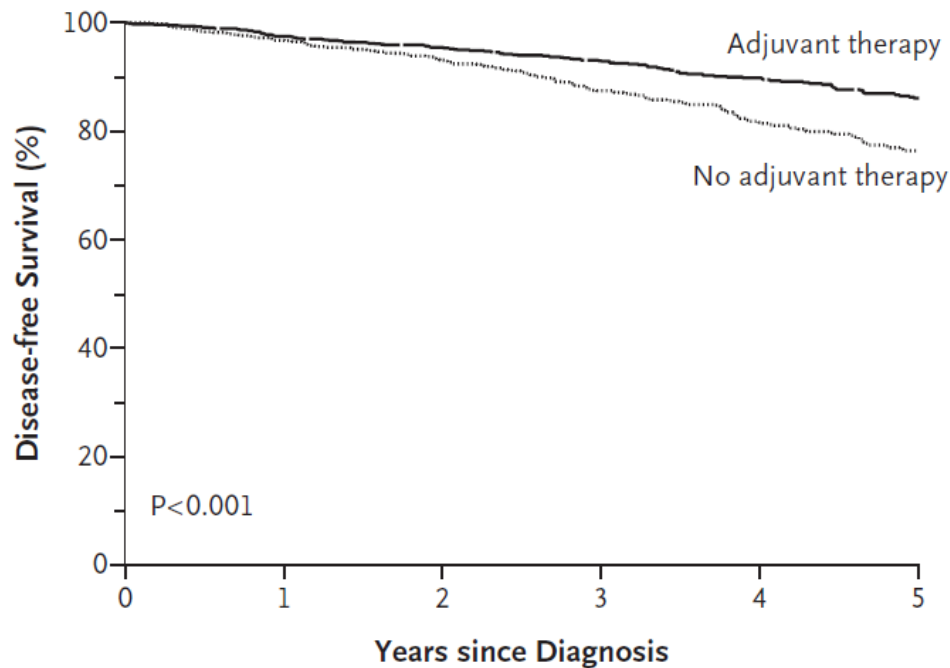
Impact of AST corrected for age, tumor size, grade, ER/PR:

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

Adjuvant systemic therapy

M. De Boer, NEJM, 2009

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. Giuliano

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

Lymph Node Status	5-Year Event-Free Survival*		Hazard Ratio†	95% CI	P†
	Rate (%)	95% CI (%)			
No metastases	87.1	85.4 to 88.8	1		
Isolated tumor cells	88.9	82.3 to 95.4	0.96	0.53 to 1.84	.985
Micrometastases	79.6	71.0 to 88.2	1.71	1.05 to 2.80	.032
Macrometastases	80.1	76.8 to 83.5	1.24	1.24 to 2.43	.001

*Calculated from Kaplan-Meier estimates.
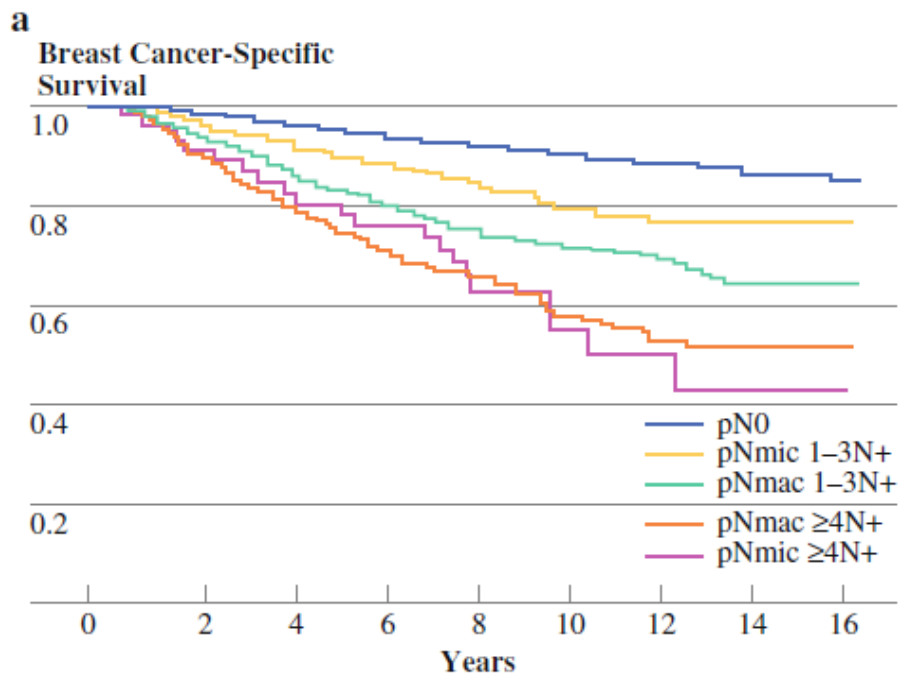†Calculated from Cox regression model.

N=2383
N=107
N=123
N=756

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, MDCM[1,2,3], Mary Lesperance, PhD[4], Karen Hui Li, MSc[4], Robyn MacFarlane, MD[3,5], Caroline H. Speers, BA[1], and Stephen Chia, MD[1,3,5]

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

Multivariate correction for AST

pNmic$_{1-3}$ versus pN0	1.74 (1.33, 2.60)
pNmic$_{\geq 4}$ versus pN0	4.26 (2.56, 7.10)
pNmac$_{1-3}$ versus pN0	2.22 (1.82, 2.70)
pNmac$_{\geq 4}$ versus pN0	3.04 (2.47, 3.75)
	<0.001

a
Breast Cancer-Specific Survival

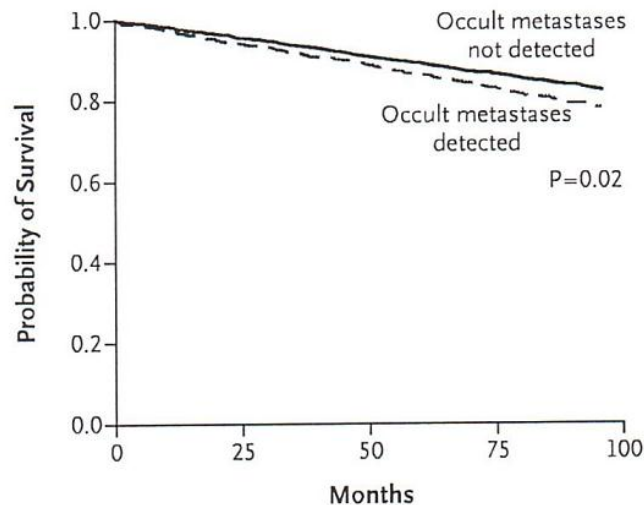Legend: pN0, pNmic 1–3N+, pNmac 1–3N+, pNmac ≥4N+, pNmic ≥4N+

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

Do all studies agree?

Effect of Occult Metastases on Survival in Node-Negative Breast Cancer (NSABP-B32)
Donald L. Weaver, *et al.* NEJM 2011: 412-421.

B Disease-free Survival

	MV HR for death	95% CI
Occult vs no-occult met's	1.40	1.05 – 1.86
pN0(i+) vs pN0	1.27	1.04 – 1.54
pN1mi vs pN0	1.60	1.32 – 1.96
Chemotherapy vs not	0.88	0.68 – 1.13
Endocrine therapy vs not	0.53	0.42 – 0.66
Other systemic R/ vs not	0.35	0.09 – 1.39

Probability of Survival

No. at Risk
Occult metastases not detected   3092   2897   2115   520
Occult metastases detected   574   539   375   92

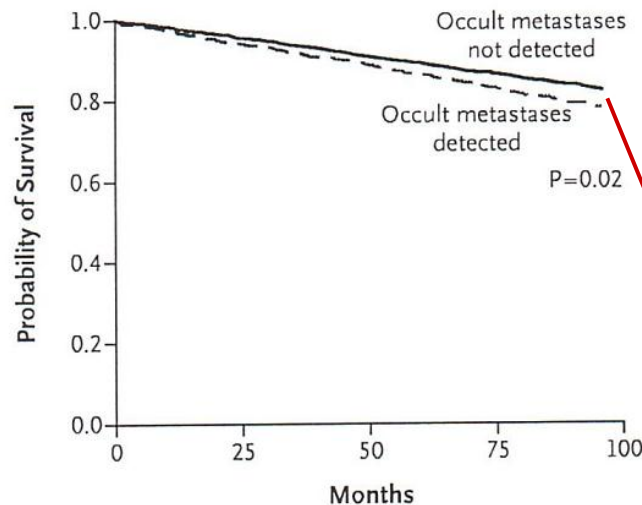Occult metastases not detected
Occult metastases detected
P=0.02

Do all studies agree?

Effect of Occult Metastases on Survival in Node-Negative Breast Cancer (NSABP-B32)
Donald L. Weaver, *et al.* NEJM 2011: 412-421.

B Disease-free Survival

Probability of Survival vs Months

Occult metastases not detected
Occult metastases detected
P=0.02

	MV HR for death	95% CI
Occult vs no-occult met's	1.40	1.05 – 1.86
pN0(i+) vs pN0	1.27	1.04 – 1.54
pN1mi vs pN0	1.60	1.32 – 1.96
Chemotherapy vs not	0.88	0.68 – 1.13
Endocrine therapy vs not	0.53	0.42 – 0.66
Other systemic R/ vs not	0.35	0.09 – 1.39

KM curves show unadjusted data.

**I.e., the size of prognostic impact cannot be determined, unless shown separately for patients without AST.**
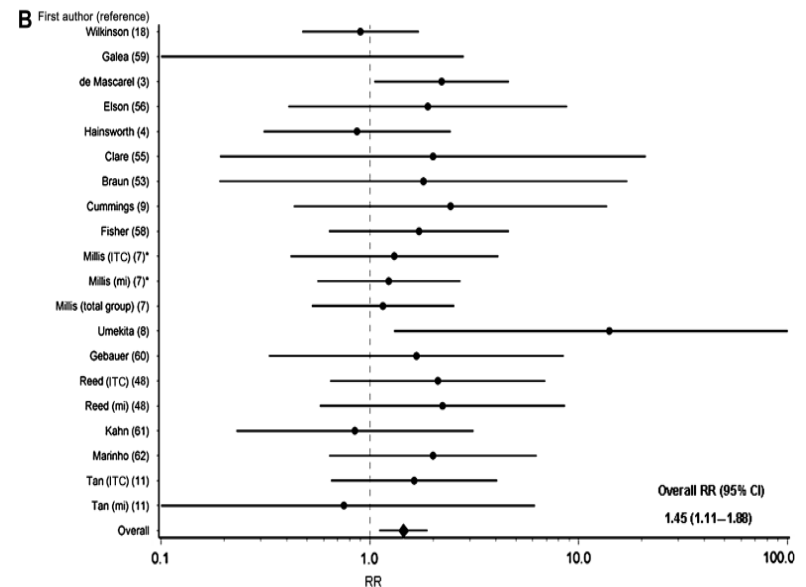
The overall evidence from the pre-SN era

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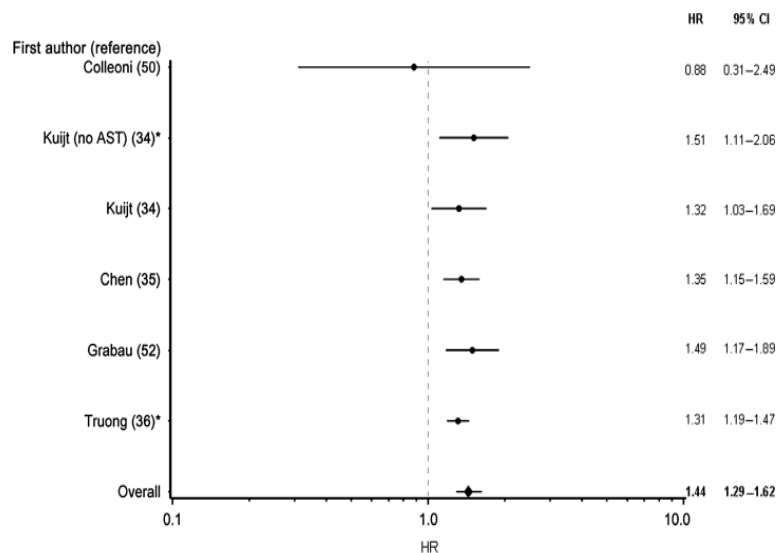
Cohort studies:
HR: 1.44 (95%CI 1.29 - 1.62)

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 <u>absolute size</u> of the prognostic impact
  - ✓ <u>which also depends</u> on other risk factors, such as histological grade.

Use of Adjuvant chemotherapy in the AMAROS study

Straver et al. J Clin Oncol 2009: 28:731-737

	Odds ratio for receiving chemotherapy	95% CI
Age		
Per additional year	**0.85**	**0.83-0.88**
Grade		
I	**1**	
II	**1.73**	**0.99-3.01**
III	**7.05**	**3.56-13.96**
Size of SN metastasis		
Single ITC	**1**	
Clusters of ITC	**1.85**	**0.27-12.49**
Micro	**4.90**	**0.80-29.98**
Macro	**9.83**	**1.65-58.79**
Multifocality		
Yes/no	**4.91**	**2.02-11.90**

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
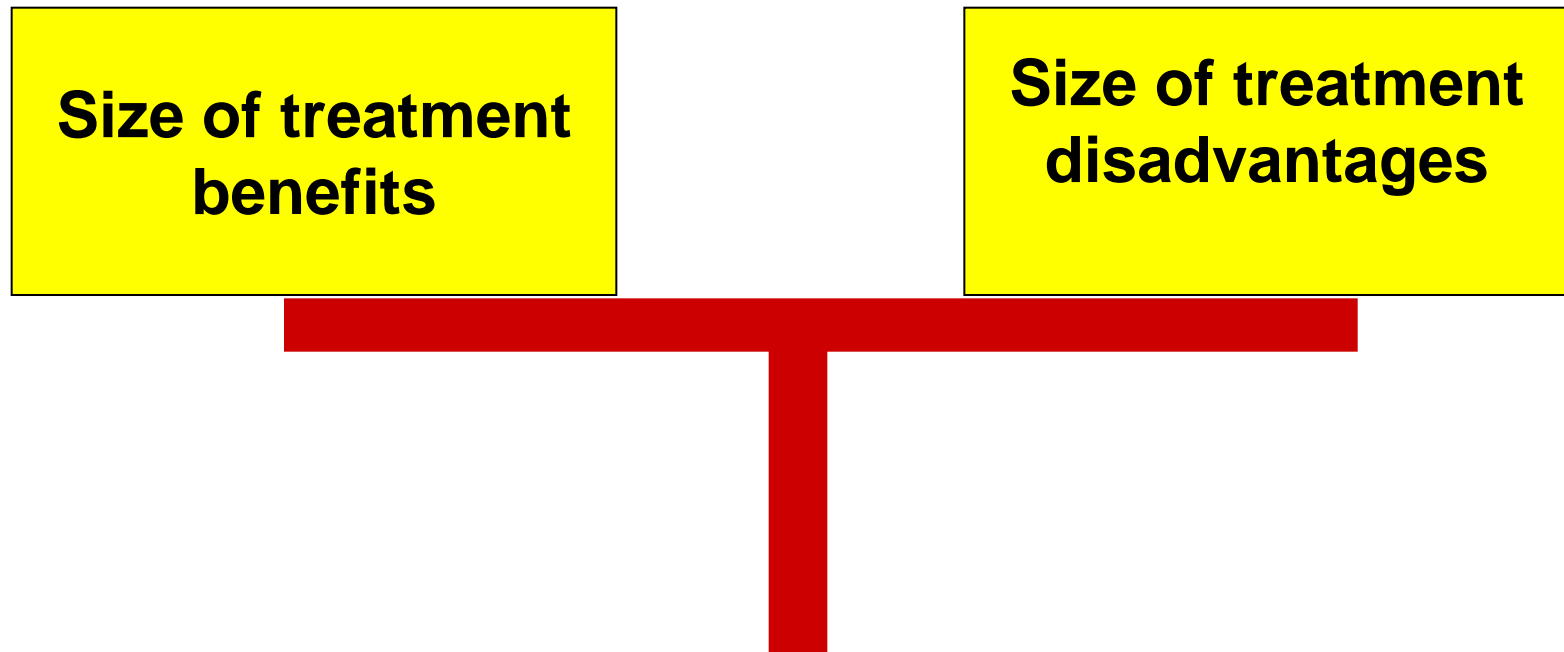
ITC and micrometastases: overall chance on second echelon node metastases

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

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)		
ALND vs no ALND	0.87	0.62 – 1.23

Recurrence	ALND (n=420)	SN only (n=436)
Local	3.6%	1.8%
Regional	0.5%	0.9%
Total	4.1%	2.8%

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

Source	No pts	% T1	AST % chemo / endocr.	Ax RT %	SN status	Median FU (mo)	Axillary recurrence %
2009 Bulte[23]	20	71*	21 / 23 *	NR	20"micro"	46 (11-64)	0
2009 Bilimoria[65]	1,988	63	71/ 41	NR	530"micro"; 1,458macro	64 (60-72)	0.6 / 1.2
2007 Takei[35]	120	30	92	54	Not specified	34 (2-83)*	0
2007 Hwang [66]	196	72	56 / 27	64	67itc; 90micro; 39macro	30 (1-62)	0
2007 Park[67]	287	78	NR	15	Not specified	23 (6-87)	2.1 (5.0)^
2006 Schulze[12]	6	100*	3 / 68*	-	1itc; 4micro; 1macro	49 +/- 17*	0
2006 Pejavar[68]	16	80*	30/34*	100	Not specified	24-60*	0
2006 Haid[69]	10	77*	32 / 93*	-	2itc; 6micro; 2macro	47 (7-90)	0
2005 Fan[42]	38	71	NR	63	27micro; 11macro	29 (6-76)	2.6
2005 Jeruss[43]	73	57*	85 / 70*	-	73 "micro"	27 (1-98)	0
2005 Langer[46]	27	72*	20 / 76@	-	27 "micro"	42 (12-64)	0
2005 Swenson[50]	67	82*	42/58*	-	32 itc; 31micro; 4 macro	33 (2-73)	1.5
2005 Chagpar[70]	15	89*	33	-	2itc; 12micro; 1macro	40 (1-54)	0
2004 Vegt[55]	10	85*	NR	100	4micro; 6macro	35 (17-59)	0
2003 Fant[71]	31	81	100	3	27"micro"; 4macro	28 (21-48)	0
2003 Guenther[72]	46	67	100	2	23itc; 16"micro"; 7macro	32 (4-61)	0

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
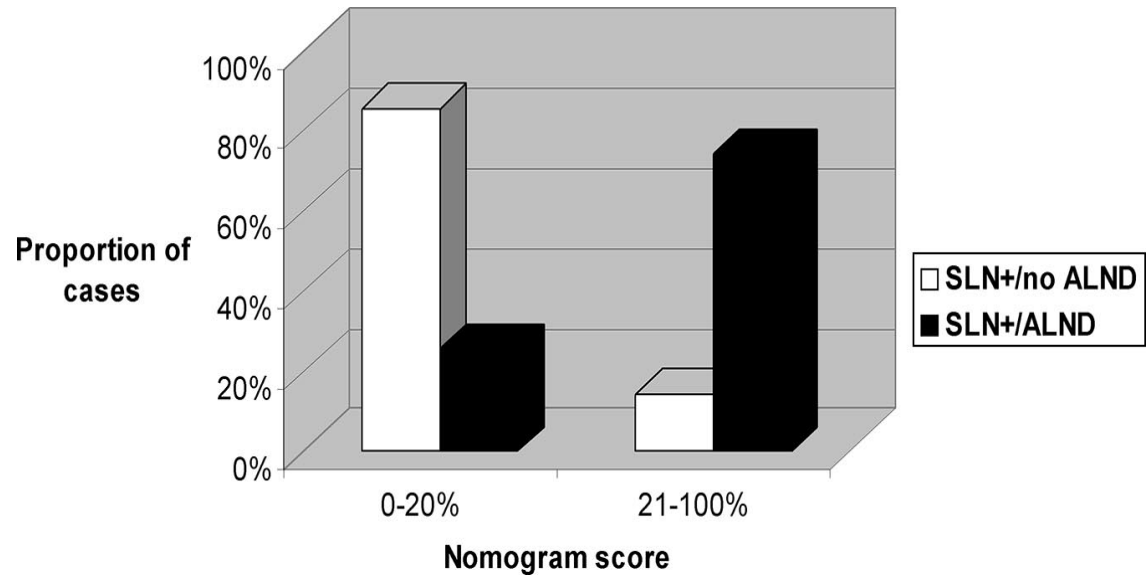
N=97,314

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

Julia Park, MS et al. Ann Surg 2007:462–468
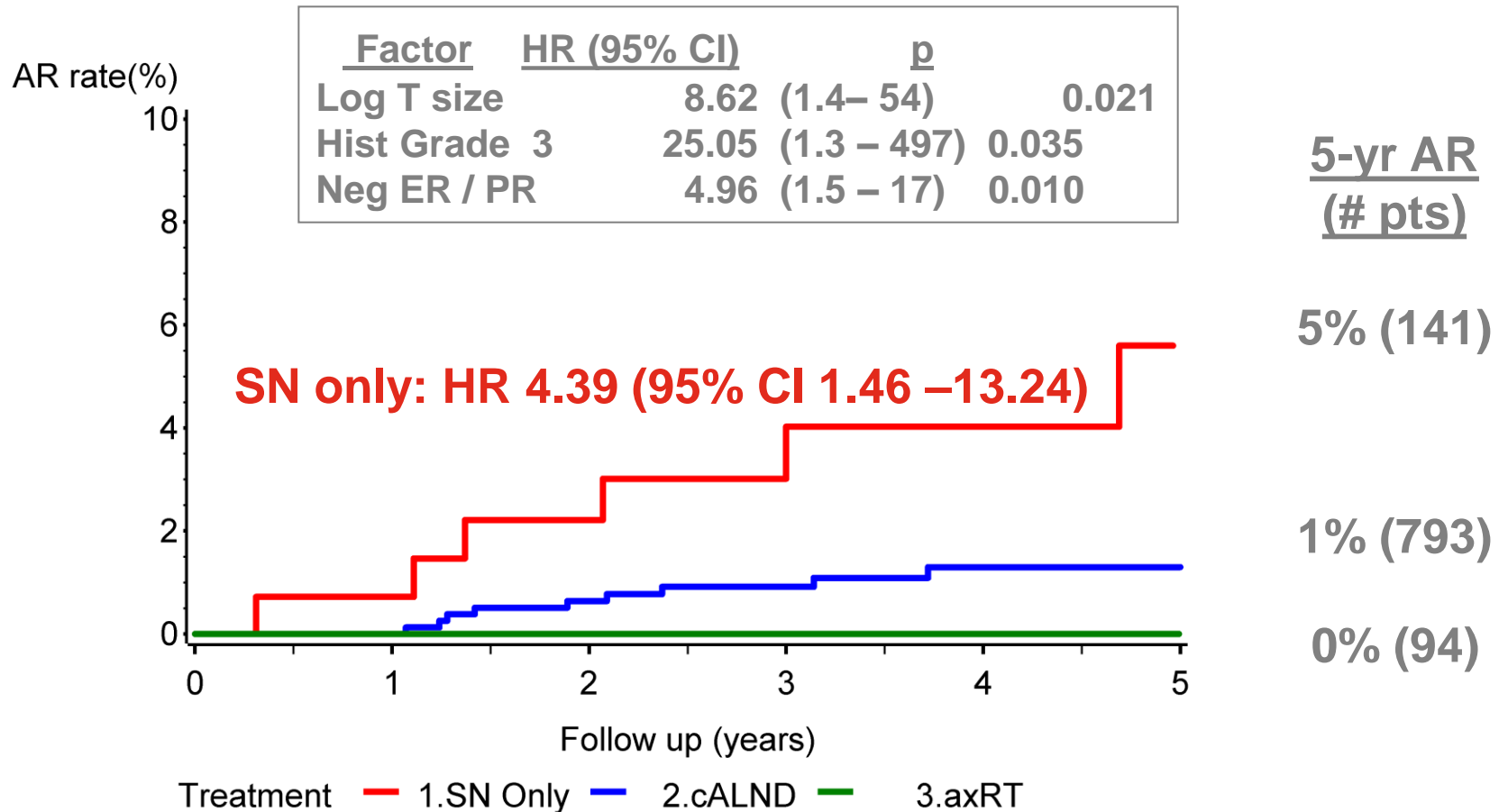

Patients without cALND:

- **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

Pepels et al. Ann Surg Oncol 2012

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?

Size of treatment benefits

Size of treatment disadvantages

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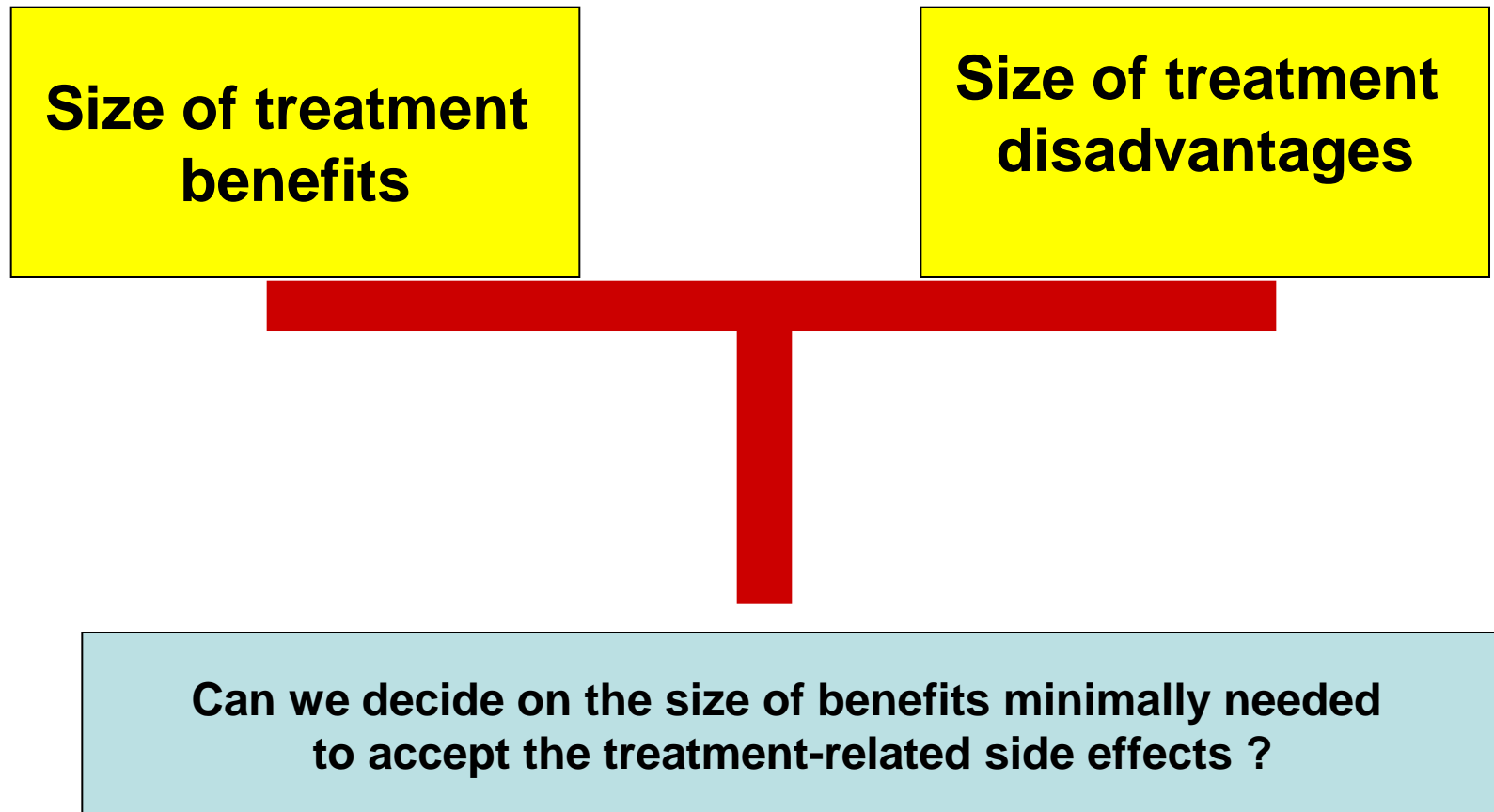
Case with limited macrometastases

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 ?

Risk Factors for Non-Sentinel Lymph Node Metastases in Patients with Breast Cancer. The Outcome of a Multi-institutional Study

Bolster M, et al. Annals of Surgical Oncology 2006: 181–189

TABLE 4. *Observed and predicted proportion of positive non-SNs in relation to primary tumor and SN characteristics*

pN(sn)	Lymph and/or blood vessel invasion	Tumor size (cm)	Patients (n)	Positive non-SNs (n)	Observed proportion of positive non-SNs (%)	95% CI	Predicted proportion of positive non-SNs (%)	95% CI
pN0(i+)	No	< 1.0	24	0	.0	0–14		
		1.1–3.0	14	1	7.1		9.7	4–23
		3.1–5.0	4	0	.0		24.9	9–53
	Yes	1.1–3.0	14	3	21.4		17.6	7–37
		3.1–5.0	3	2	66.7		39.8	17–68
pN1mi	No	1.1–3.0	27	8	29.6		25.0	14–41
		3.1–5.0	4	1	25.0		50.8	27–75
	Yes	1.1–3.0	8	2	25.0		39.9	22–61
		3.1–5.0	3	3	100.0		67.3	40–87
pN1+	No	1.1–3.0	50	15	30.0		30.0	20–42
		3.1–5.0	5	4	80.0		57.1	33–79
	Yes	1.1–3.0	20	9	45.0		46.1	30–63
		3.1–5.0	4	2	50.0		72.6	47–89

SN, sentinel lymph node; 95% CI, 95% confidence interval; pN1+, pN1a and higher pN positive stages.

Enter Your Information   Clear   Calculate ▸

Frozen Section Performed?   ☐ YES
Was a frozen section analysis performed during pathological examination? This does not have to be the method that detected the cancer in the sentinel lymph nodes, but it is necessary to know as a variable for this calculator.

Pathological Size   [   ] (0.1 to 9.0 cm)
Size of the primary tumor, in centimeters.

Tumor Type and Grade   [▾]
Indicate if tumor type is ductal or lobular, as noted in the pathology report. If ductal, indicate the nuclear grade -- I: slight or no variation in the size and shape of the nucleus; II: moderate variation in the size and shape of the nucleus; III: marked variation in the size and shape of the nucleus.

Number of Positive Sentinel Lymph Nodes   [   ] nodes (1 to 7)
Indicate the number of sentinel lymph nodes found to have cancer when biopsied.

SLN Method of Detection   [▾]
Select the method used to detect cancer spread to the sentinel lymph nodes.

SLN Method of Detection   [▾]
Select the method used to detect cancer spread to the sentinel lymph nodes.
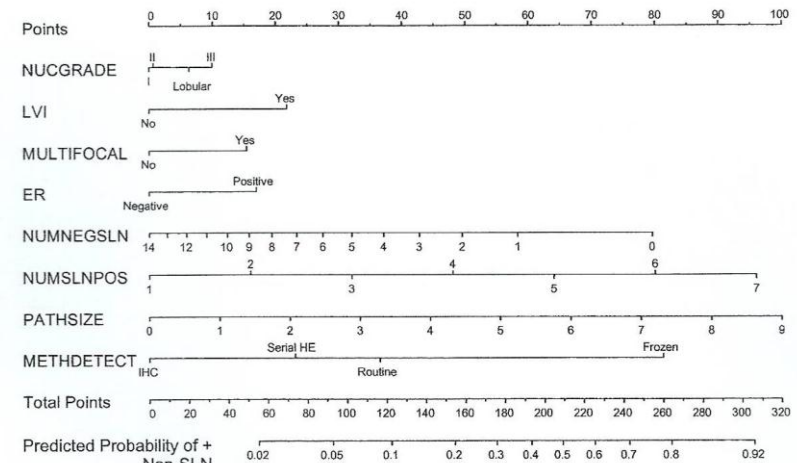
Number of Negative Sentinel Lymph Nodes   [   ] nodes (0 to 14)
Indicate the number of sentinel lymph nodes that were found not to have cancer when biopsied.

Lymphatic or Vascular Structure Involvement (Lymphovascular Invasion)   ☐ YES
Check box if one or more tumor cells were found in blood or lymphatic vessels.

Multifocality?   ☐ YES
Check box if patient has cancer cells that have separated from the main tumor mass.

Estrogen Receptor Positive?   ☐ YES
Select YES if breast cancer cells tested positive for estrogen receptors.

[Clear]   [Calculate ▸]

Examples of existing nomograms and calculators for prediction of non-SN involvement

1146   K. J. VAN ZEE ET AL.

Points
NUCGRADE
LVI
MULTIFOCAL
ER
NUMNEGSLN
NUMSLNPOS
PATHSIZE
METHDETECT
Total Points
Predicted Probability of + Non-SLN

CALCULATOR

Enter Tumor Size (cm):   [   ]

Size of Sentinel Lymph Node Metastasis (mm):
○ Isolated Tumor Cells (less than or equal to 0.2mm)
○ Micrometastasis (greater than 0.2mm to 2mm)
○ Macrometastasis (greater than 2mm)

Angiolymphatic Invasion:
○ Yes
○ No
[Calculate]
Clear / Start Over

Results:

Note: 0 = 0% predicted probability of NSLN metastasis, 1 = 100% predicted probability of NSLN metastasis. A computed value between 0 and 1 should be multipled by 100 to convert a probability to a percentage.

Value of Memorial Sloan-Kettering Cancer Center nomogram in clinical decision making for sentinel lymph node-positive breast cancer

I. van den Hoven[1], G. P. Kuijt[1], A. C. Voogd[2], M. W. P. M. van Beek[3] and R. M. H. Roumen[1]

[1]Department of Surgery, Máxima Medical Centre, Veldhoven, [2]Eindhoven Cancer Registry, Eindhoven, and Maastricht University Medical Centre, School GROW, Maastricht, and [3]Laboratory for Pathology and Medical Microbiology, Eindhoven, The Netherlands
Correspondence to: Dr I. van den Hoven, Department of Surgery, Máxima Medical Centre, PO Box 7777, NL-5500 MB Veldhoven, The Netherlands (e-mail: i.vandenhoven@mmc.nl)

ROC Curve

AUC = 0.68
CI [0.60 – 0.76]
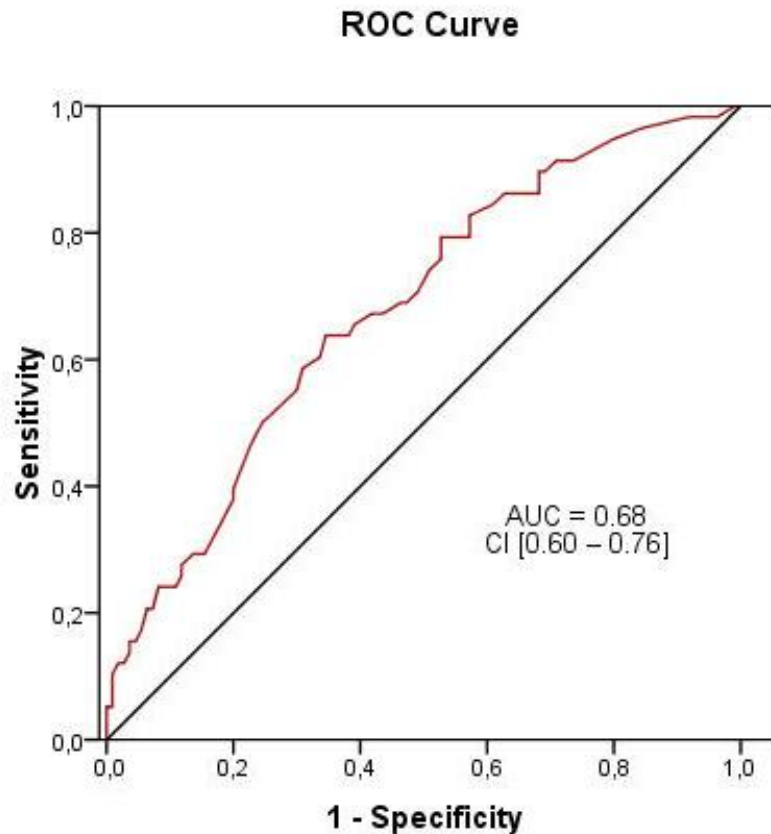
For low predicted probability cut-off values of no more than 5, 10 and 15 per cent:

- **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.**

ORIGINAL ARTICLE – BREAST ONCOLOGY

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, MD[1], Gerrit P. Kuijt, MD[1], Adri C. Voogd, PhD[2], and Rudi M. H. Roumen, MD, PhD[1]
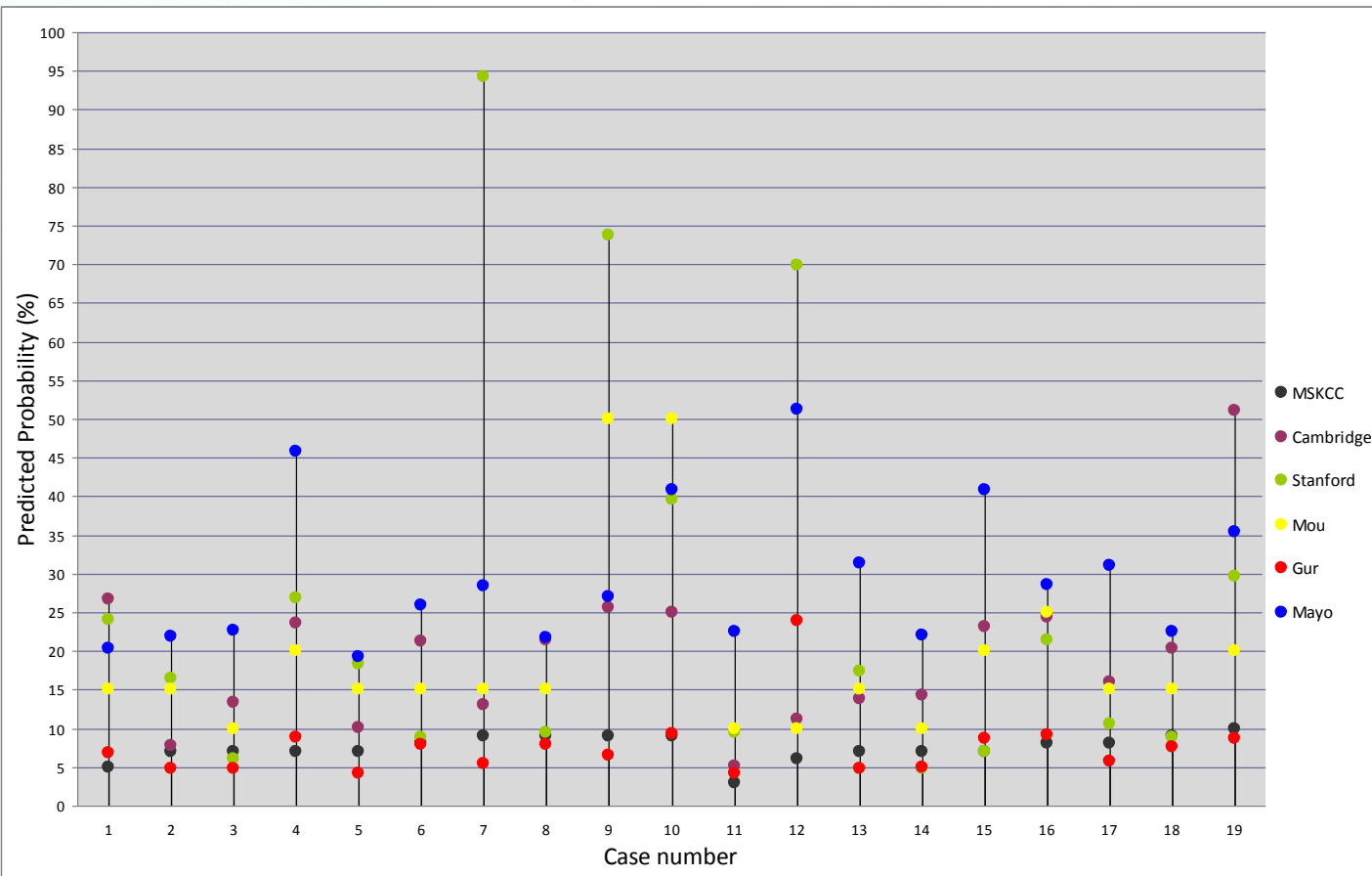
Moreover,
prediction of axillary recurrence

- ≠ 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

Model	Low predicted non-SN risk ≤10%		High predicted non-SN risk > 10%	
	Patients (No.)	5 year regional recurrence rate (%)	Patients (No.)	5 year regional recurrence rate (%)
MSKCC	300	2.8	166	3.4
Stanford	465	3.2	21	0
Tenon	438	2.3	48	10.1
Bolster	384	2.2	102	6.3

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

Degnim AC, et al. *Cancer* 2003;98:2307-15.

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

*Cserni G. In: Kahan Zs, Tot T (eds): Breast cancer, a heterogeneous disease entity. The very early stages. Springer Science+Business Media, 2011, 149-184.

**Van la Parra RFD et al. Meta-analysis of predictive factors.. EJSO 2011; 37:290-9.

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.**

Cserni G, et al. Multicentre validation of different predictive tools of non-sentinel lymph node involvement in breast cancer. Surg Oncol 2012; 21:59-65.

Institutional value	Low risk (obs. NSN+)	Non low risk obs. NSN+
GOOD		
Stanford	22% (9%)	33%
F micrometastasis	66% mic (5%)	30%
SUITABLE (<20%)		
MSKCC	27% (16%)	33%
Masaryk	33% (16%)	32%
Tenon score	52% (18%)	39%
UNSUITABLE		
Louisville CPR	2%	
Mayo nomogram	0%	
MDA score	(>20%)	

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+!

Cserni G. et al. *Orv Hetil* 2009; 150: 2182-8.

STANFORD NOMOGRAM

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

Tumor size / ITC vs MIC vs MAC / LVI

CALCULATOR

Enter Tumor Size (cm): [   ]
Size of Sentinel Lymph Node Metastasis (mm):
○ Isolated Tumor Cells (less than or equal to 0.2mm)
○ Micrometastasis (greater than 0.2mm to 2mm)
○ Macrometastasis (greater than 2mm)
Angiolymphatic Invasion:
○ Yes
○ No
[Calculate]
Clear / Start Over

Results:

Note: 0 = 0% predicted probability of NSLN metastasis, 1 = 100% predicted probability of NSLN metastasis. A computed value between 0 and 1 should be multipled by 100 to convert a probability to a percentage.

Kohrt HE, et al. BMC Cancer, 2008;8:66.

French micrometastasis nomogram

Pure vs mixed type / Method of metastasis detection / Tumor size / LVI
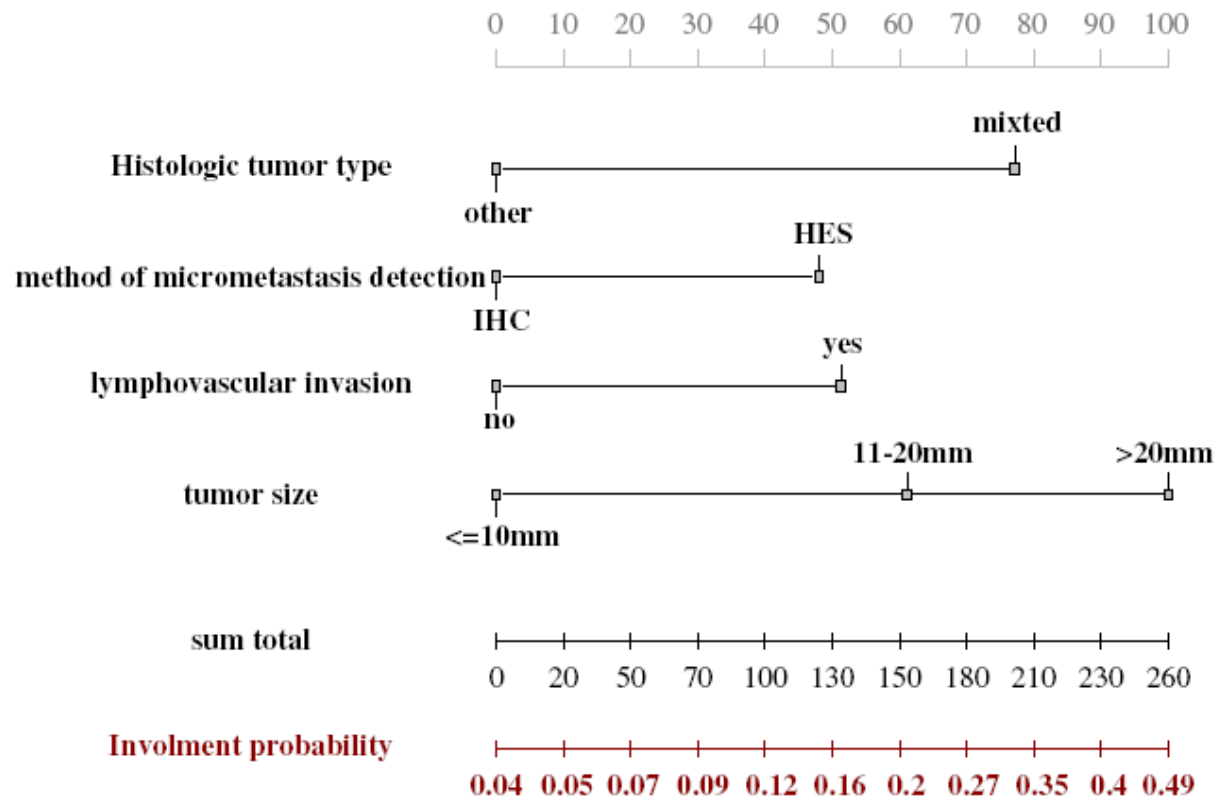
Houvenaeghel G, et al. EJSO 2009; 35: 690-5.

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)

*Cserni G, et al. Patients' choice on axillary lymph node dissection following sentinel lymph node micrometastasis… Pathol Oncol Res 2012 in press

- **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.**

Cserni G et al. Multi-institutional comparison of NSN predictive tools in breast cancer patients with high predicted risk of further axillary metastasis. *Pathol Oncol Res* 2012 in press

# 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**
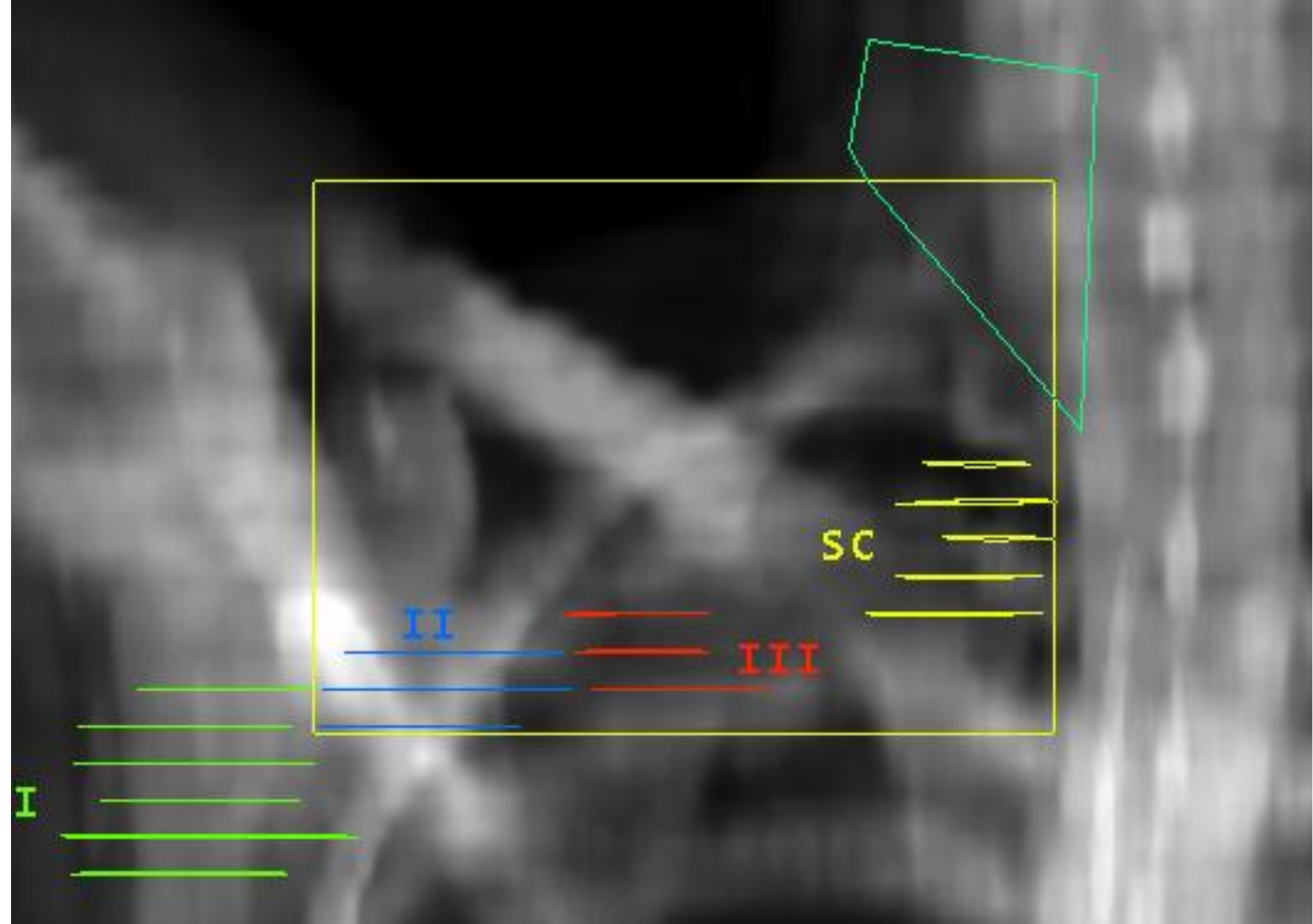- **1 SNs positive, with micrometastasis (1.3 mm)**

She receives breast RT (3D) and AST

Is use of modern breast irradiation technique important for your preference regarding axillary treatment ?
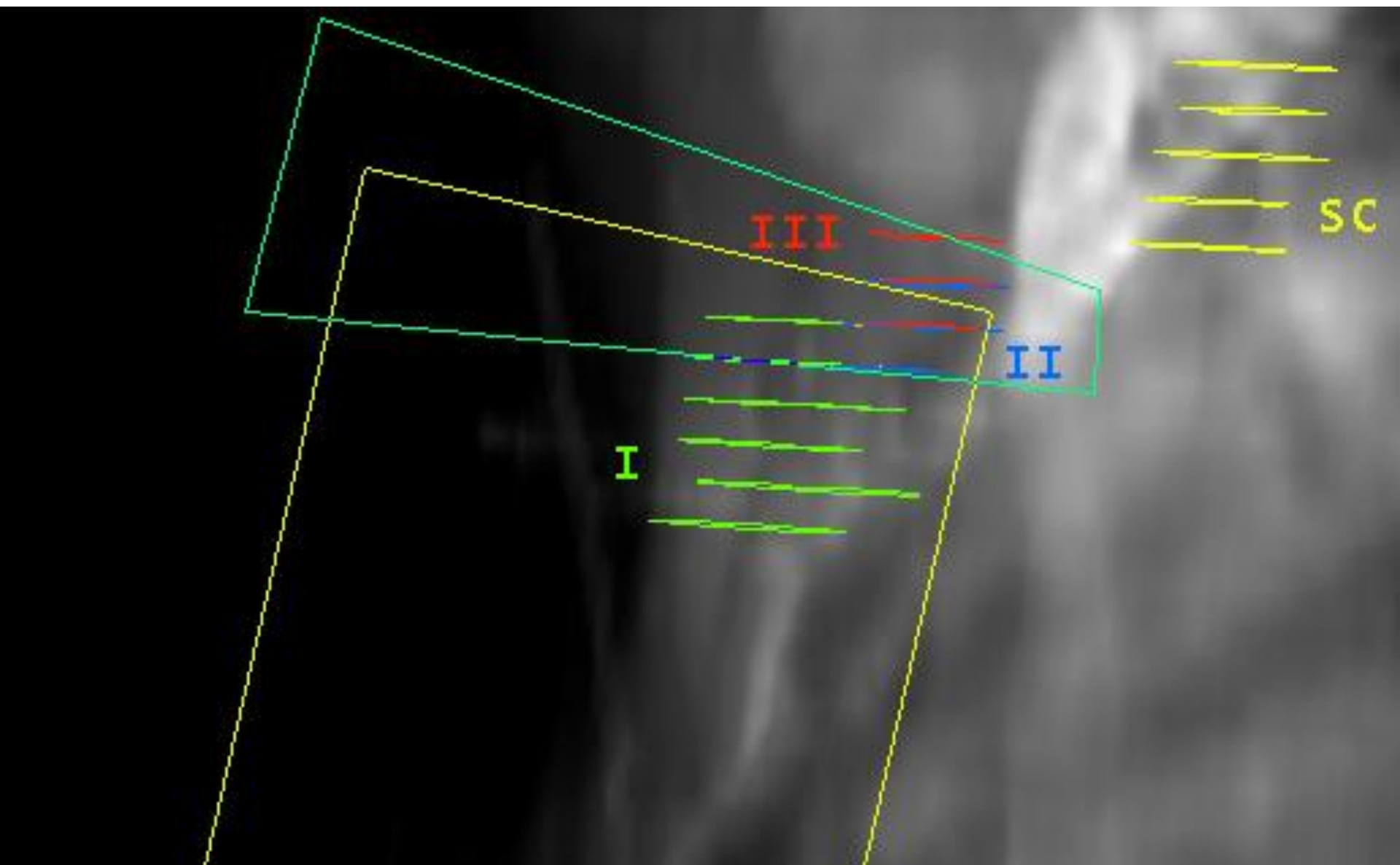
Goodman, Int J Radiat Oncol Biol Phys 50:99-105, 2001

Goodman, Int J Radiat Oncol Biol Phys 50:99-105, 2001

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 > 3cm or G 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 > 3cm, G III, LVI