The Evolution of Sentinel Node Biopsy

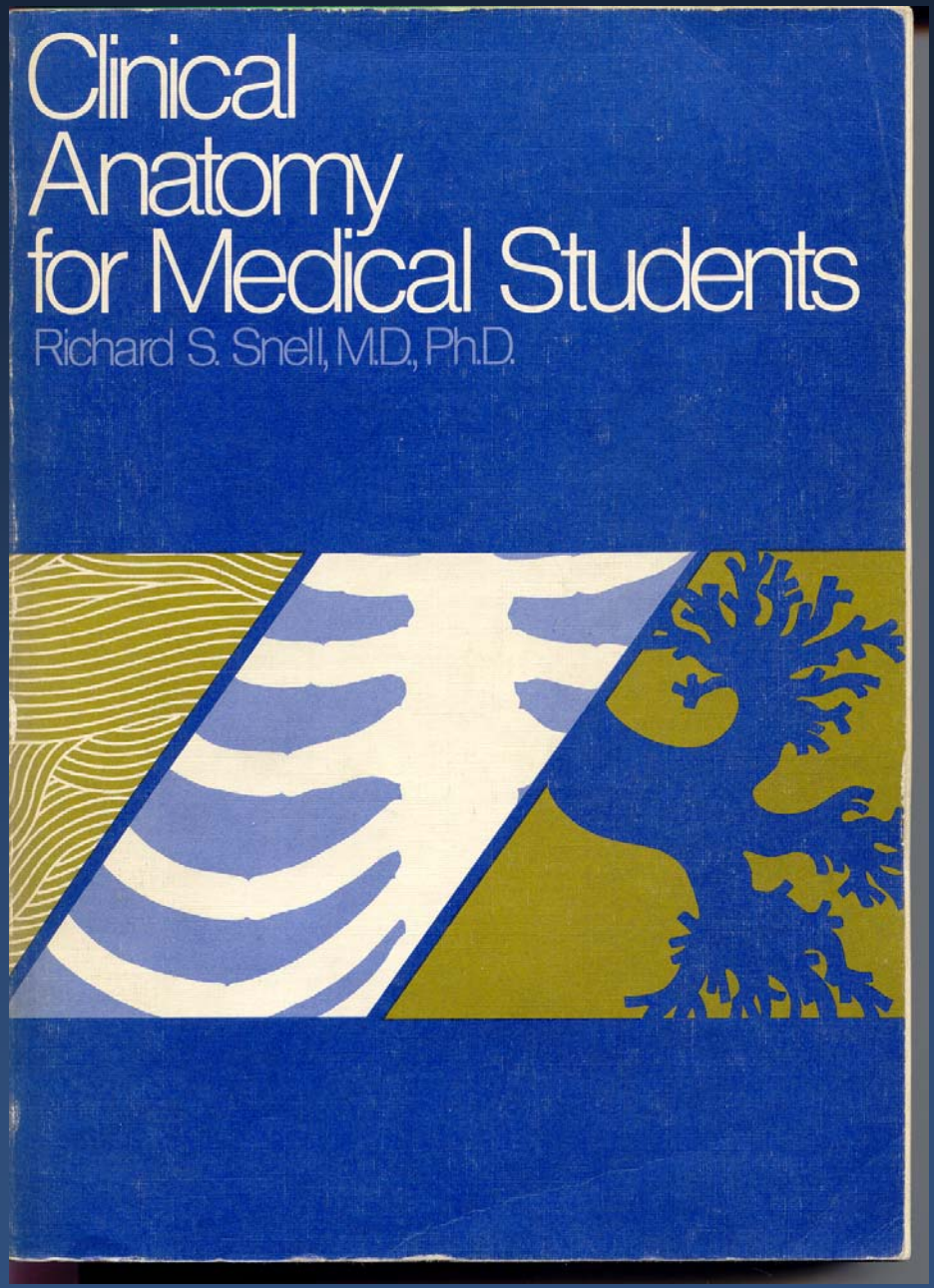
David McCready MD MSc FRCSC
Professor of Surgery
Gattuso Chair in Breast Surgical Oncology
University of Toronto

Breast Cancer Treatment

- The future of oncology is to provide maximum disease control with minimum morbidity

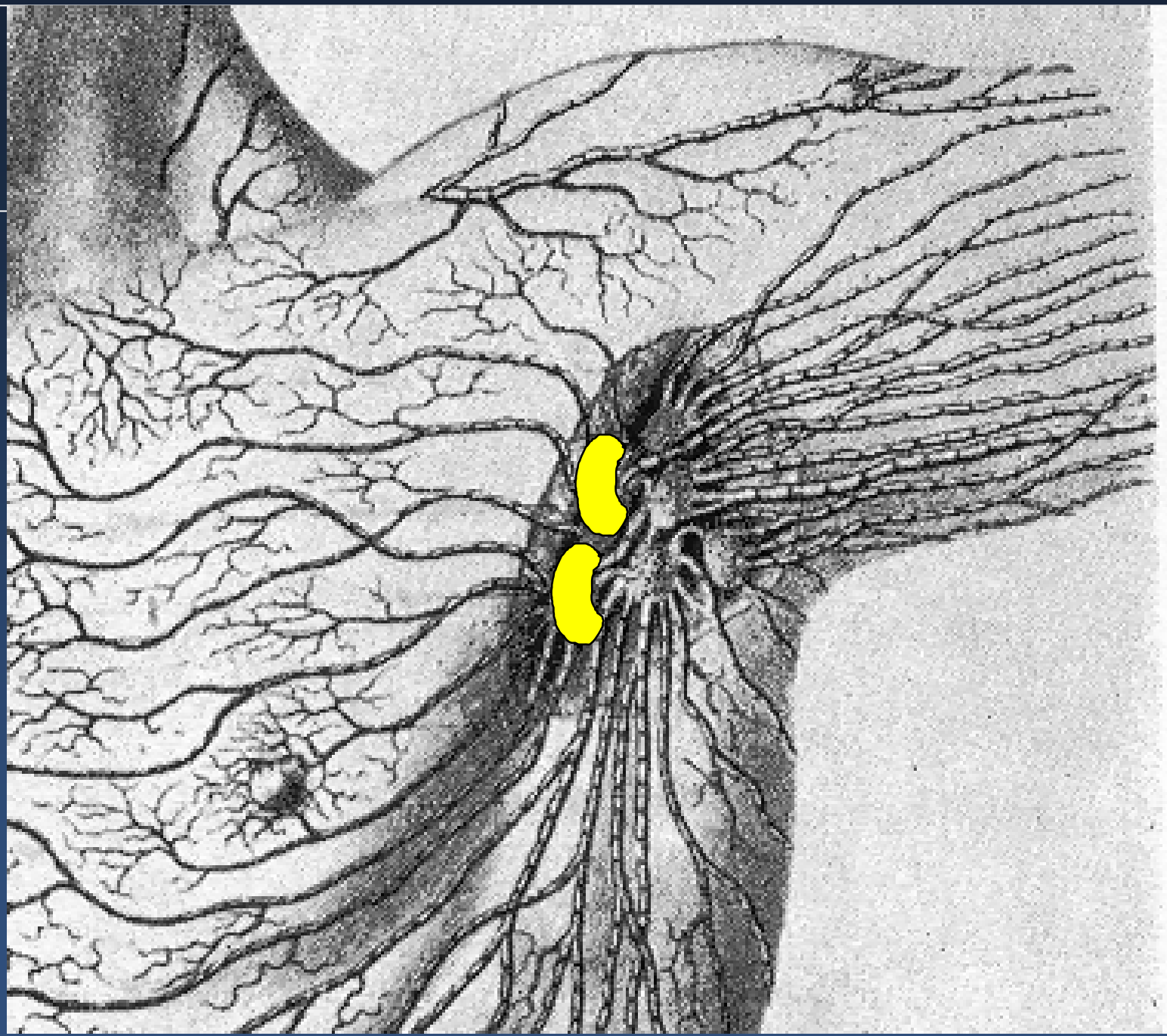
Major Points

- Sentinel node mapping works
- Enhanced pathology improves staging accuracy
- Technical factors / surgeon can affect accuracy
- Small deposits of disease probably have some prognostic value
- Node positivity rates are going up and this can be used as a quality indicator



Lymphatic System

"The lymphatic system is often de-emphasized by anatomists on the grounds that it is difficult to see on a cadaver."



Diseases of the Breast
Cushman Davis Haagensen, 1956

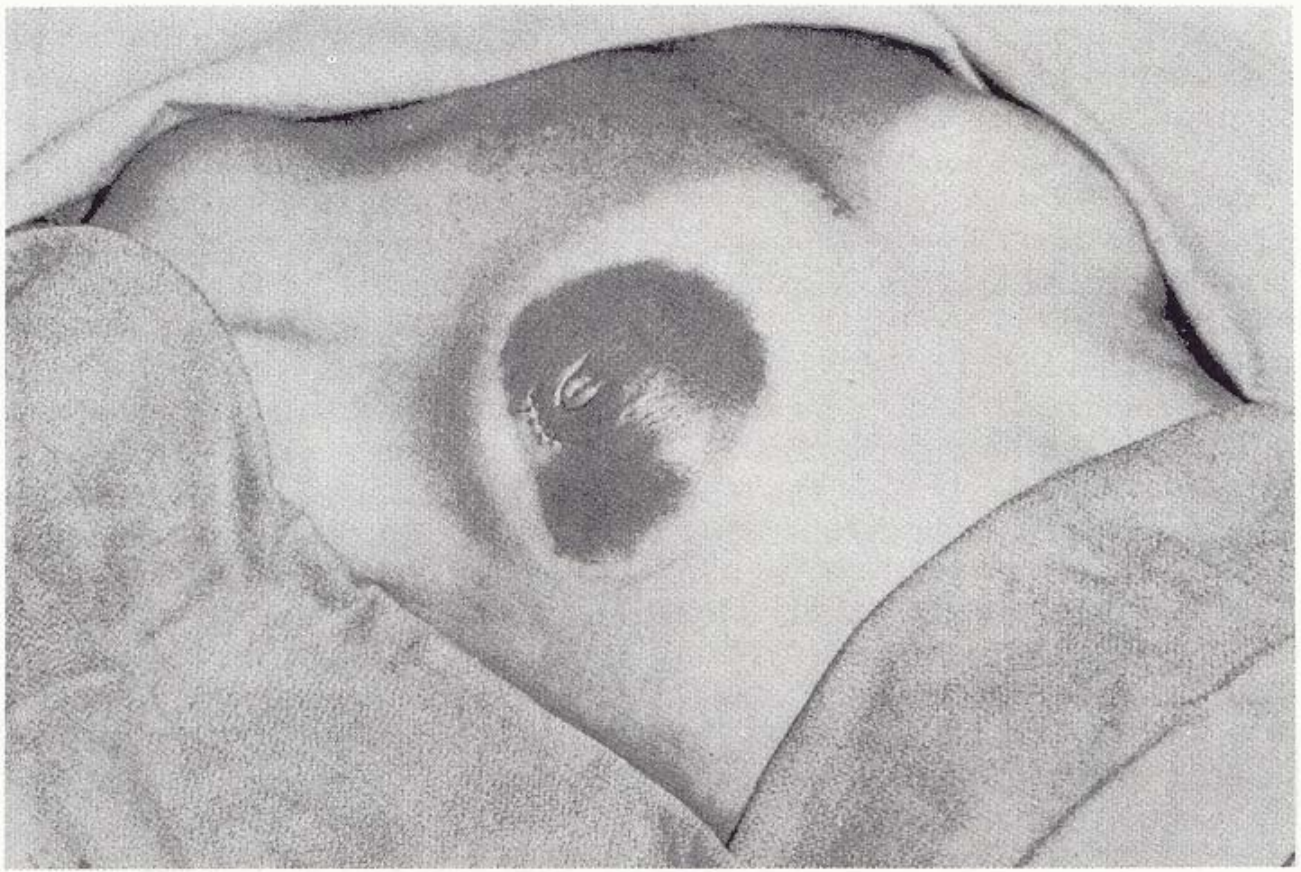


Figure 1–31. Preoperative subareolar injection of Direct Sky Blue. The skin over the central portion of the breast is stained blue.

First Edition: 1956, Third Edition: 1986

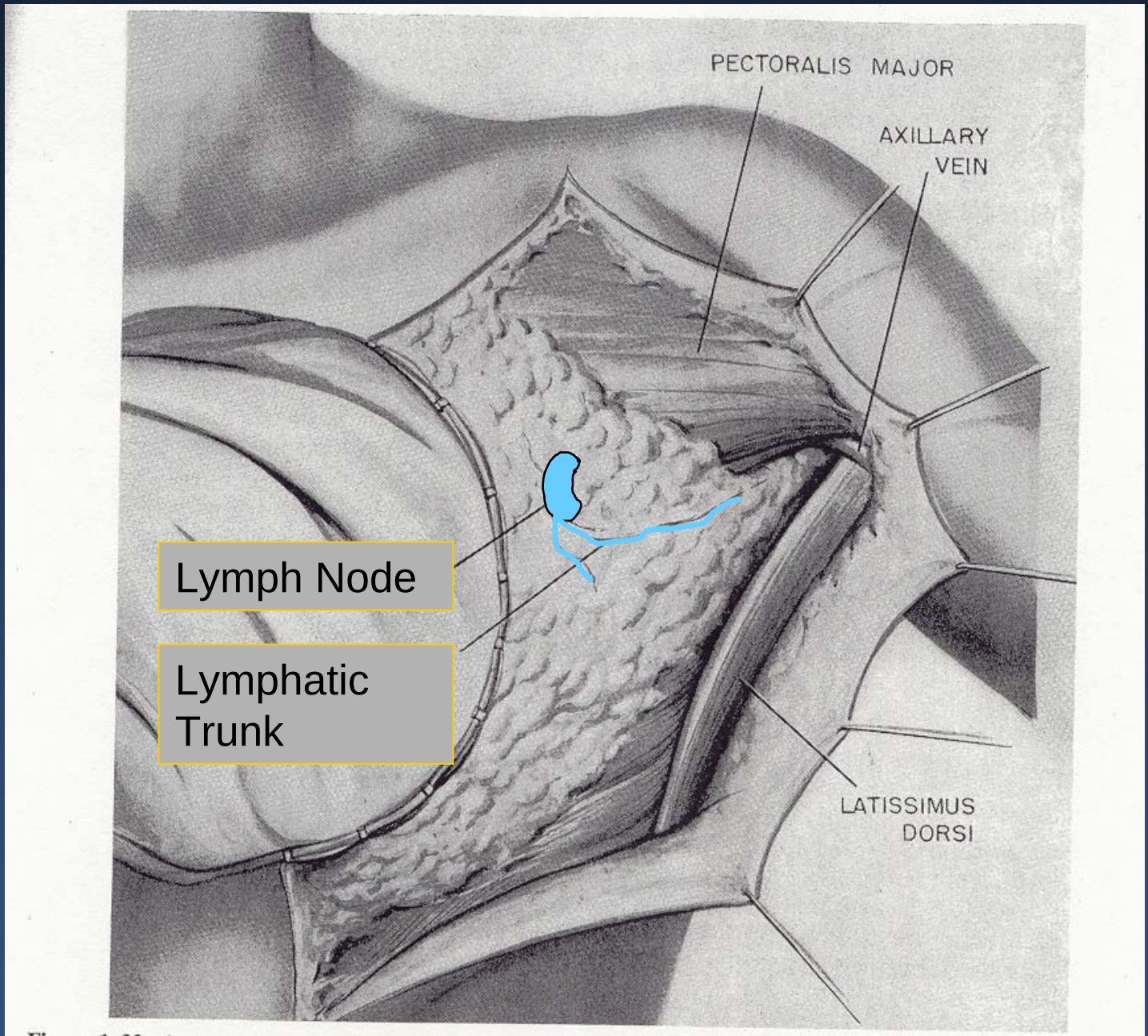


Figure 1–32. A prepectoral lymph node high up on the upper outer surface of the breast revealed by preoperat subareolar injection of Direct Sky Blue.

program in evidence-based care
a cancer care ontario program

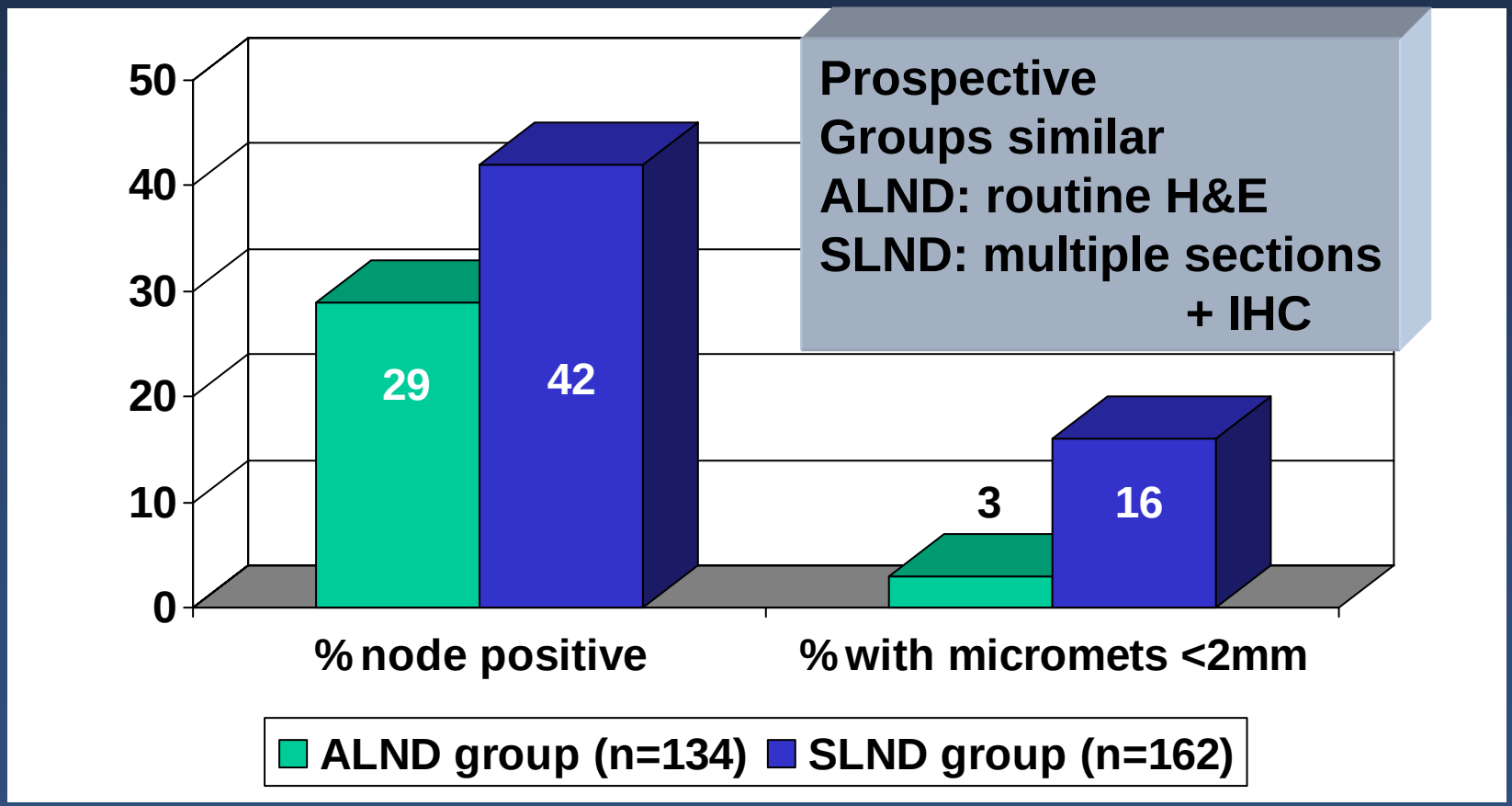
programme de soins fondé sur des preuves
un programme de action cancer ontario

Surgical Management of Early-Stage Invasive Breast Cancer

- Removal and examination of level I/II axillary lymph nodes should be the standard practice in most cases of early breast cancer
- This should ideally result in the identification of at least 10 nodes

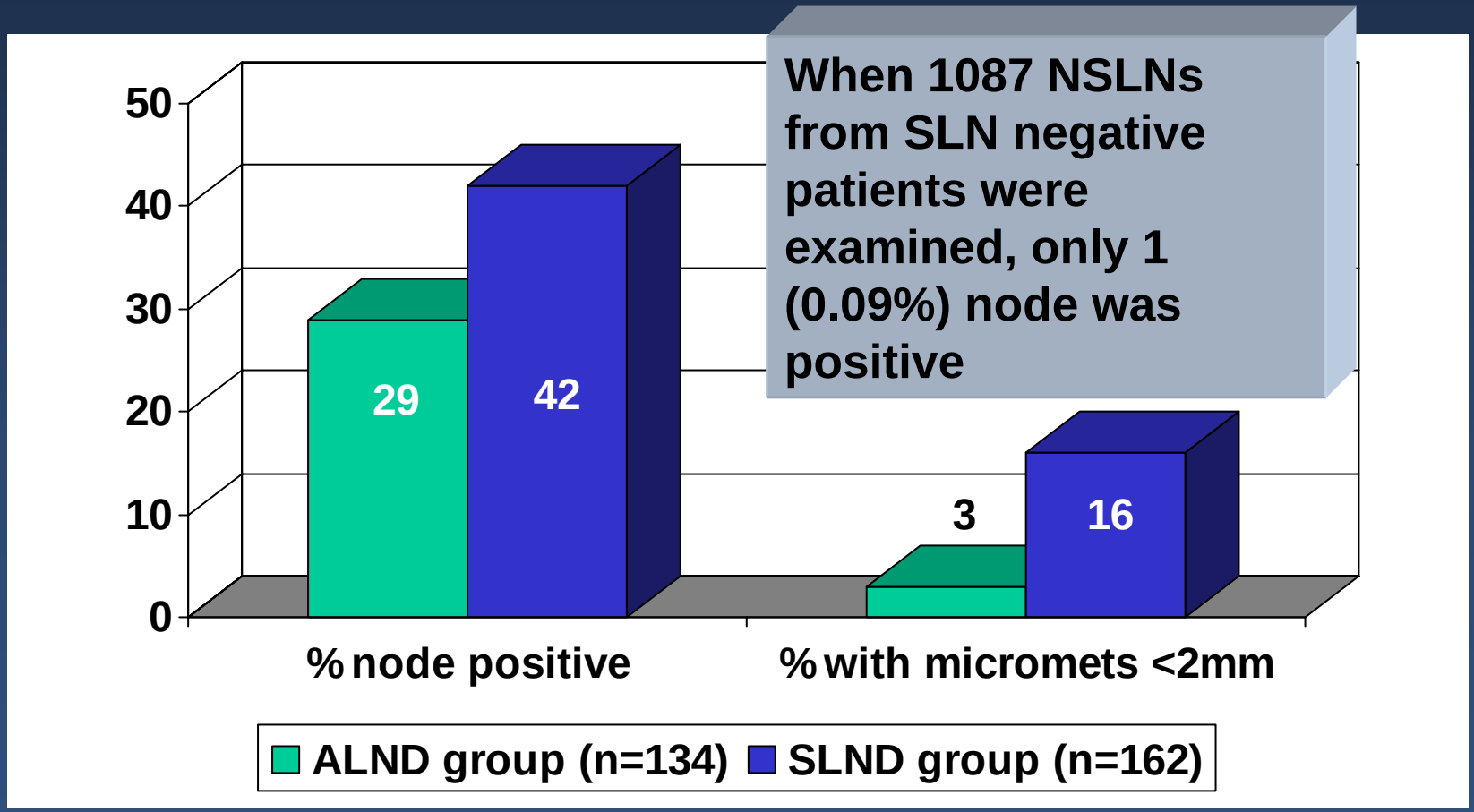
Improved Axillary Staging of Breast Cancer with Sentinel Lymphadenectomy

Armando E. Giuliano, M.D., Paul S. Dale, M.D., Roderick R. Turner, M.D., Donald L. Morton, M.D., Sheila W. Evans, R.N., M.S., and David L. Krasne, M.D.

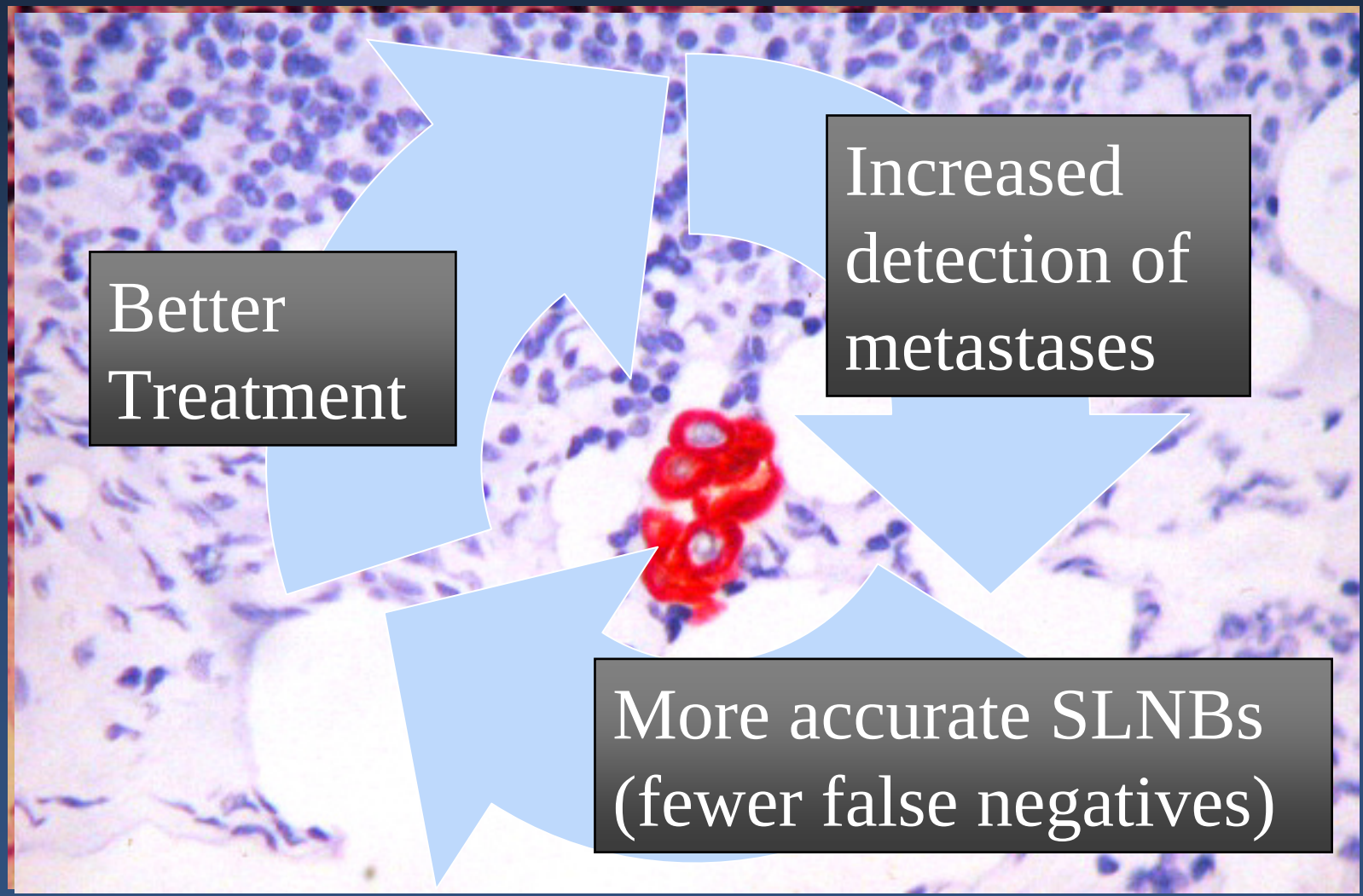


Improved Axillary Staging of Breast Cancer with Sentinel Lymphadenectomy

Armando E. Giuliano, M.D., Paul S. Dale, M.D., Roderick R. Turner, M.D., Donald L. Morton, M.D., Sheila W. Evans, R.N., M.S., and David L. Krasne, M.D.



Enhanced Pathology of SLNs:
Serial Sections and Immunohistochemistry



BRIEF COMMUNICATION

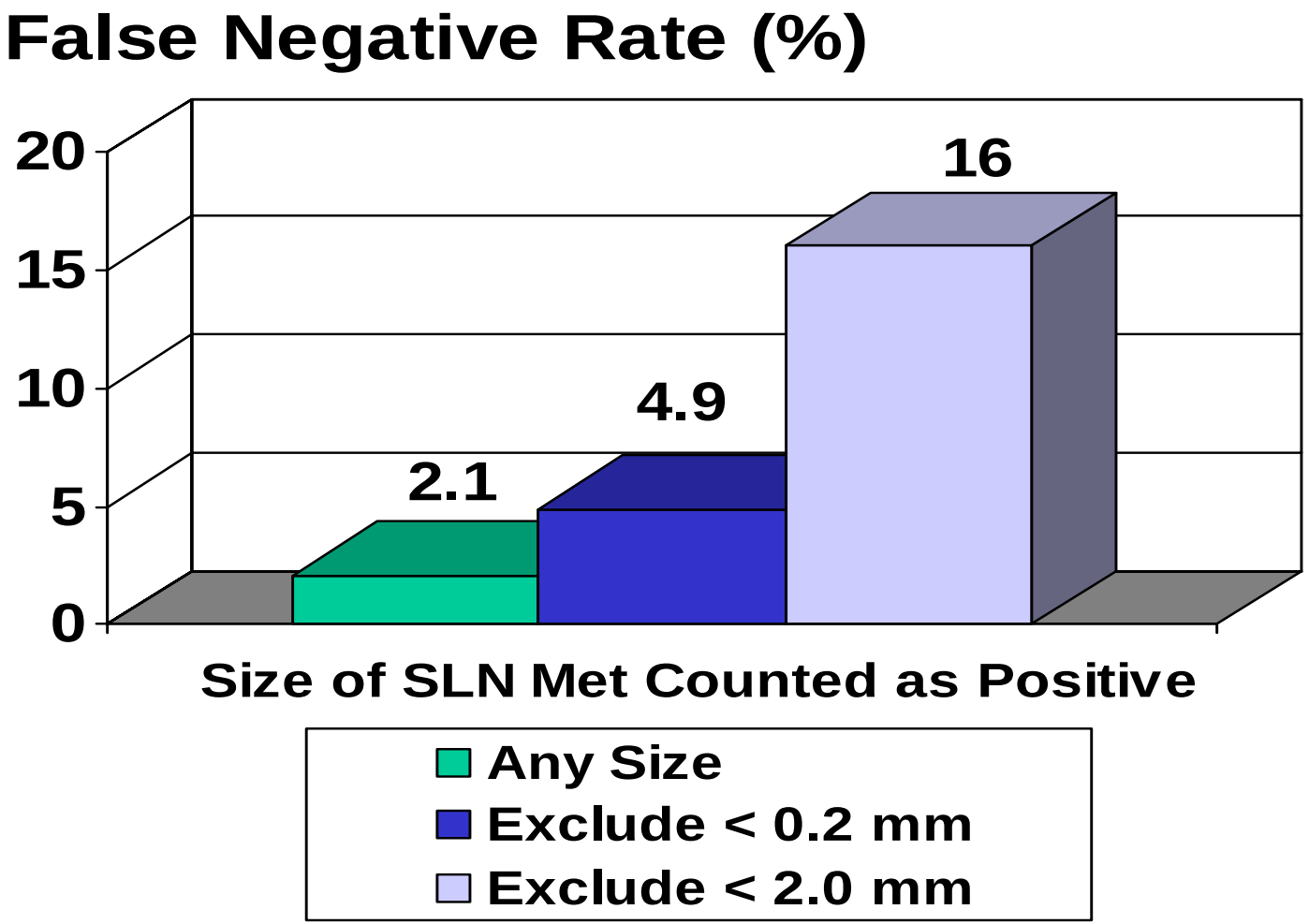
Influence of the New AJCC Breast Cancer Staging System on Sentinel Lymph Node Positivity and False-Negative Rates

David R. McCready, Wei Sean Yong, Alexander K. T. Ng, Naomi Miller, Susan Done, Bruce Youngson

- Exclusion of pN0(i+) (“ITC” nodes) or pN1(mic) lowers the SLN positivity rate
- Enhanced pathology (IHC) improves accuracy by lowering FN rate

McCready et al, JNCI, 2004;96(11):873

Breast Cancer SLN Validation Series



Should SLN Biopsy Be Adopted or Tested?

Adopt SLNB

- If axillary dissection is considered only a diagnostic / staging test, then one should just do the SLNB.
- The more important question is whether to use enhanced pathology / IHC.
- Join ACOSOG Z-010

Test SLNB

- If one believes that ALND may provide some therapeutic or survival value, then we should evaluate SLNB in a RCT
- Join NSABP B-32 and also test whether enhanced pathology improves outcome

Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial

David N Krag, Stewart J Anderson, Thomas B Julian, Ann M Brown, Seth P Harlow, Takamaru Ashikaga, Donald L Weaver, Barbara J Miller, Lynne M Jalovec, Thomas G Frazier, R Dirk Noyes, André Robidoux, Hugh M C Scarth, Denise M Mammolito, David R McCready, Eleftherios P Mamounas, Joseph P Costantino, Norman Wolmark, for the National Surgical Adjuvant Breast and Bowel Project (NSABP)

5611 Breast Cancer Patients

Randomize

Sentinel Lymph Node Biopsy AND Axillary Node Dissection

Sentinel Lymph Node Biopsy

Positive → **ALND**

Negative → **Observe**

Lancet Oncology 8:881, 2007

Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial

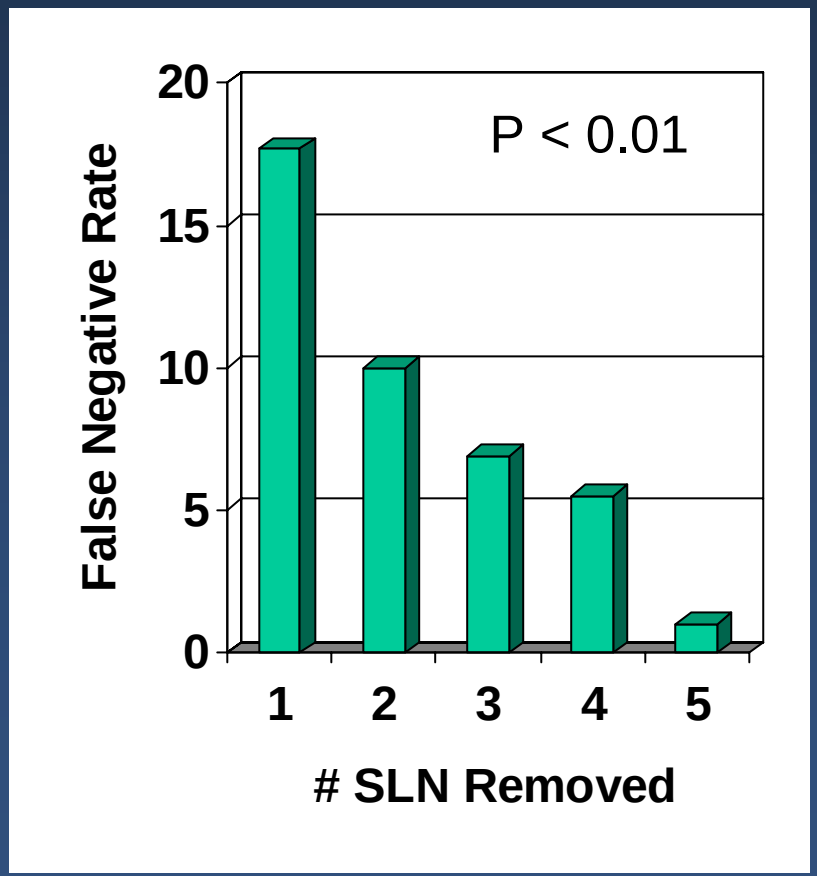
David N Krag, Stewart J Anderson, Thomas B Julian, Ann M Brown, Seth P Harlow, Takamaru Ashikaga, Donald L Weaver, Barbara J Miller, Lynne M Jalovec, Thomas G Frazier, R Dirk Noyes, André Robidoux, Hugh M C Scarth, Denise M Mammolito, David R McCready, Eleftherios P Mamounas, Joseph P Costantino, Norman Wolmark, for the National Surgical Adjuvant Breast and Bowel Project (NSABP)

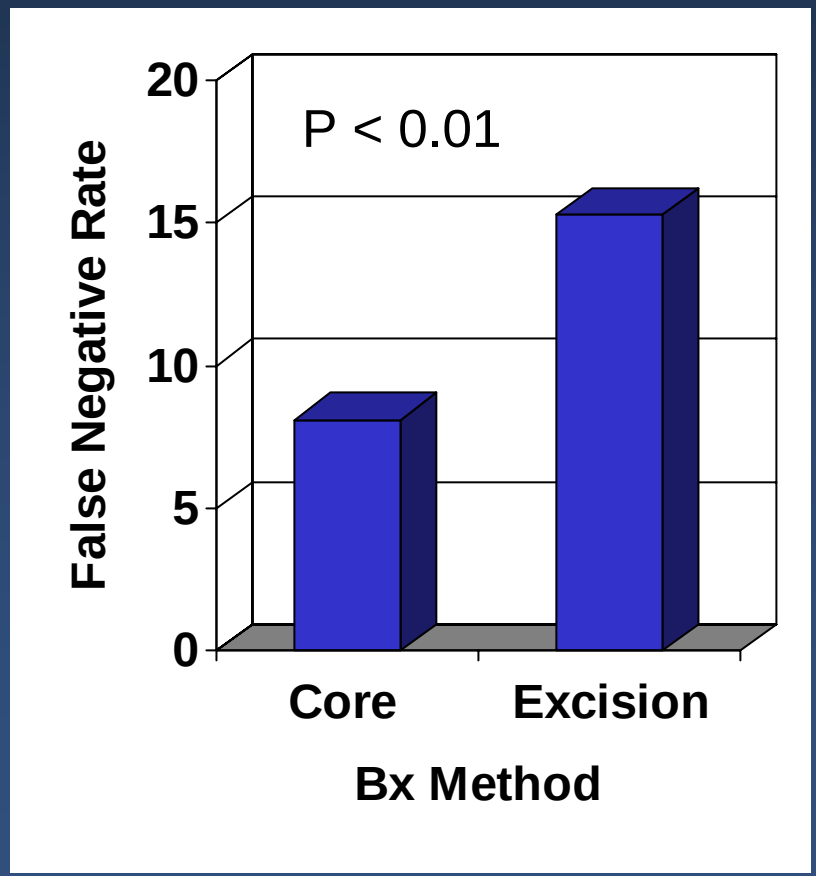
- SLNB successful in 97.2%
- Almost all (98.6%) SLN's were in axilla
- 65% hot and blue, 25% hot only, 5% blue only 5% palpation only
- No IHC
- Accuracy 97.1%
- FN rate 9.8% (CI = 7.8 - 12.2)

Lancet Oncology 8:881, 2007

NSABP B-32

- 2619 pts SLN + ALND
- 29.2 % node positive
- FN rate 9.8%, Accuracy = 97.1%, Sens 91.2%,

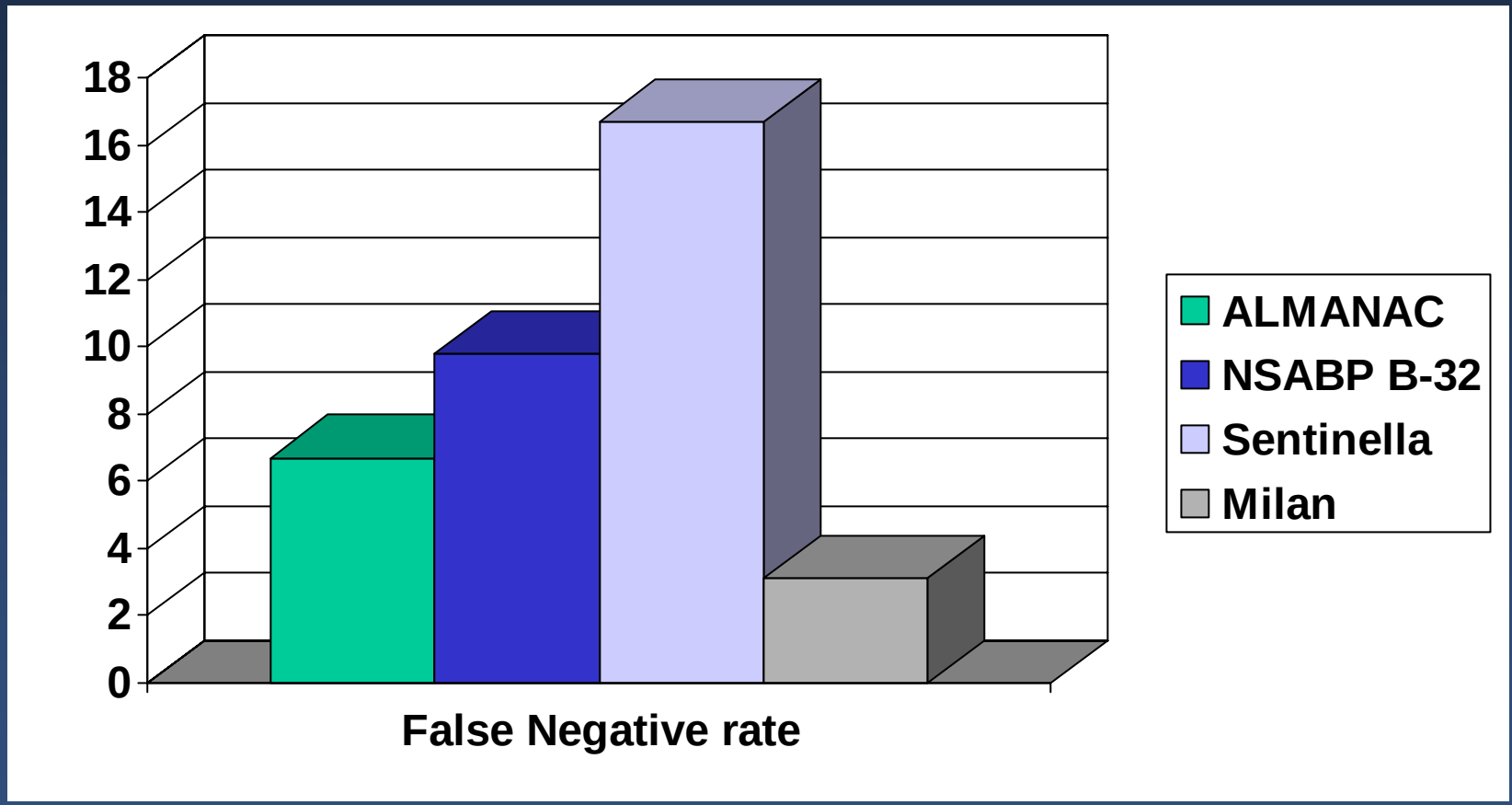




RCTs for Node Negative Patients SLNB vs ALND (± SLNB) Surgeon Training

- ALMANAC
  - Validation and randomized phases
- NSABP B-32
  - Training cases prior to surgeon entry
- Sentinella-GIVOM
  - Limited or no training
- Milan
  - Single Institution

False Negative Rates in SLN RCTs



Sentinel Lymphadenectomy Deconstructed

- Patient selection
- Mapping techniques
- Operative options
- Pathologic evaluation
- Management of the ‘positive’ SLN
- Quality assurance

Patient Selection For Sentinel Lymphadenectomy

Isolated DCIS	No
Positive nodes	No
DCIS requiring mastectomy	✓
Isolated invasive carcinoma	✓
Prior lumpectomy	✓
Multicentric carcinoma	? yes
Large (T3) invasive cancers	? yes
After preoperative chemotherapy	? yes

cancer care ontario | action cancer ontario

program in evidence-based care | programme de soins fondé sur des preuves

Sentinel Lymph Node Biopsy in Early-stage Breast Cancer: Guideline Recommendations

R. George, M. L. Quan, D. McCready, R. McLeod, R.B. Rumble, and the Expert Panel on SLNB in Breast Cancer.

A Quality Initiative of Cancer Care Ontario's Surgical Oncology Program (SOP) and Cancer Care Ontario's Program in Evidence-Based Care (PEBC)

Report Date: July 14, 2009

"SLNB is recommended as the preferred method of axillary staging for all patients with a clinical presentation of early breast cancer in the absence of clinically or pathologically positive lymph nodes."

The New England
Journal of Medicine

© Copyright, 1998, by the Massachusetts Medical Society

VOLUME 339 OCTOBER 1, 1998 NUMBER 14

Annals of Surgical Oncology, 6(5):450–454
Published by Lippincott Williams & Wilkins © 1999 The Society of Surgical Oncology, Inc.

Intradermal Radiocolloid and Intraparenchymal Blue Dye Injection Optimize Sentinel Node Identification in Breast Cancer Patients

NSABP B-32 Technique:

- intradermal Tc-99m sulfur colloid
- peritumoral Tc-99m sulfur colloid
- peritumoral Lymphazurin

The New England
Journal of Medicine

© Copyright, 1998, by the Massachusetts Medical Society

VOLUME 339 OCTOBER 1, 1998 NUMBER 14

Annals of Surgical Oncology, 6(5):450–454
Published by Lippincott Williams & Wilkins © 1999 The Society of Surgical Oncology, Inc.

Intradermal Radiocolloid and Intraparenchymal Blue Dye Injection Optimize Sentinel Node Identification in Breast Cancer Patients

NSABP B-32 Technique:

- intradermal Tc-99m sulfur colloid — Periareolar
- ~~peritumoral Tc-99m sulfur colloid~~
- peritumoral ~~Lymphazurin~~ — Patent Blue

Operative Technique

- Drape the arm free
  - Allows easy access to harder nodes
- Small incision just inferior to hair line
- Don’t fry the Sentinel node
  - Watch the cautery
- Line of sight to the hot node
  - pick up both sides of hot line and cut between, repeat until node is seen

Criteria For SLN Removal
Multi-institutional Study on Breast Cancer

Criteria	False Negative Rate
Only hottest node	13.0 %
Hottest node and all blue nodes	8.7 %
All nodes greater than 10% of hottest and all blue nodes	5.8 %

Sentinel Nodes in Breast Cancer: Relevance of Axillary Level II Nodes and Optimal Number of Nodes that Need to Be Removed

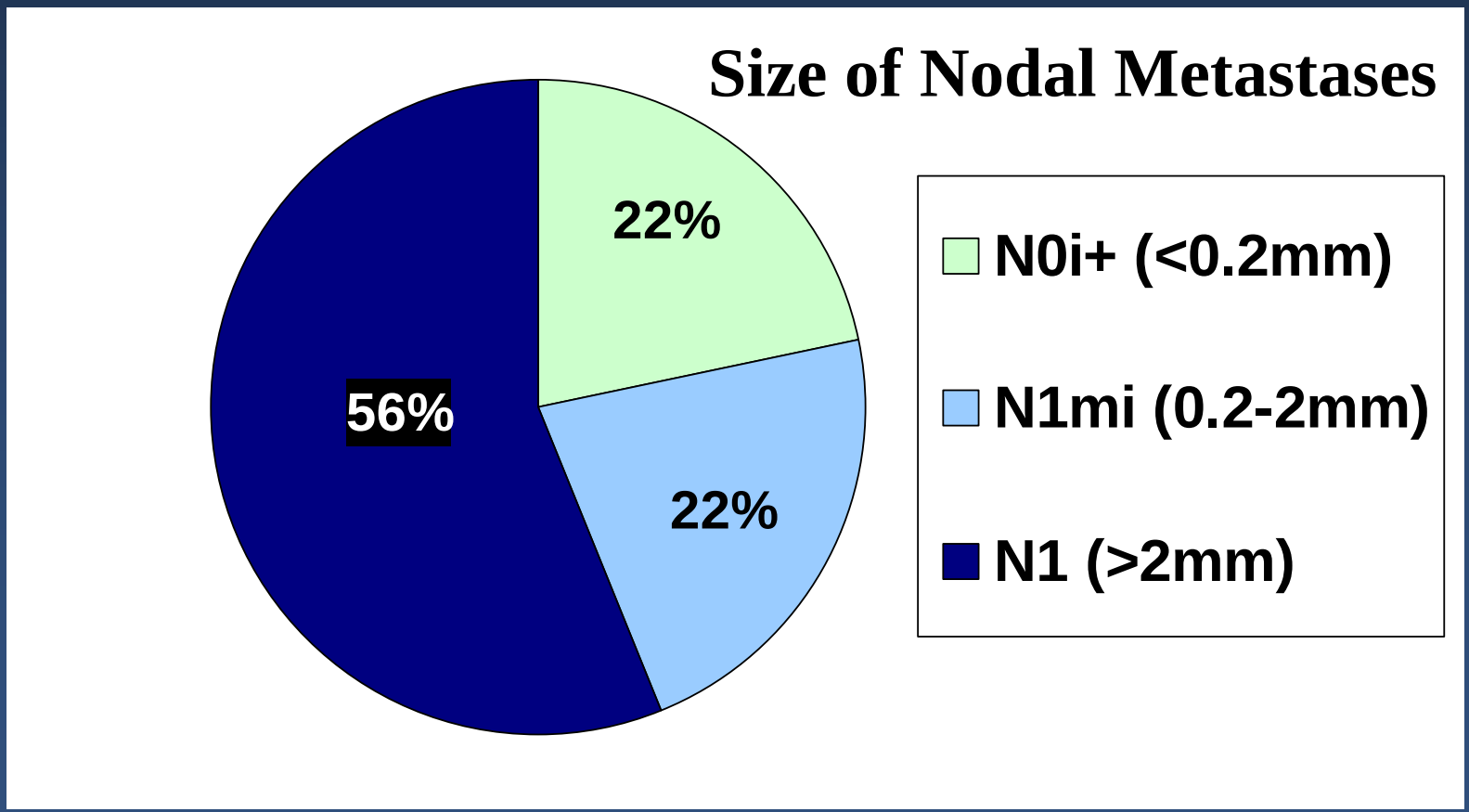
Jean-François Boileau, MD, MSc,[1] Alexandra Easson, MD, MSc,[1]
Jaime M. Escallon, MD,[1] Wey L. Leong, MD,[1] Michael Reedijk, MD, PhD,[1]
Bruce J. Youngson, MSc, MD,[2] and David R. McCready, MD, MSc[1]

- Review our recent data (97-06) and results
- Attempt to optimize procedure
  - Check the 10% rule
  - Reduce the number of SLN ’s harvested but still maintain accuracy
  - Determine whether we need to chase level II SLN ’s

Annals of Surgical Oncology, 2008

893 Sentinel Lymph Node Biopsies

- 97.4% rate of technical success (870 of 893)
- False negative rate: 4.3% (4/94)
- 287 ‘positive’ SLNs in 870 SLNBs (33 %)



All Node Positive Patients Were Accurately Staged In The First 4 SLN ’s

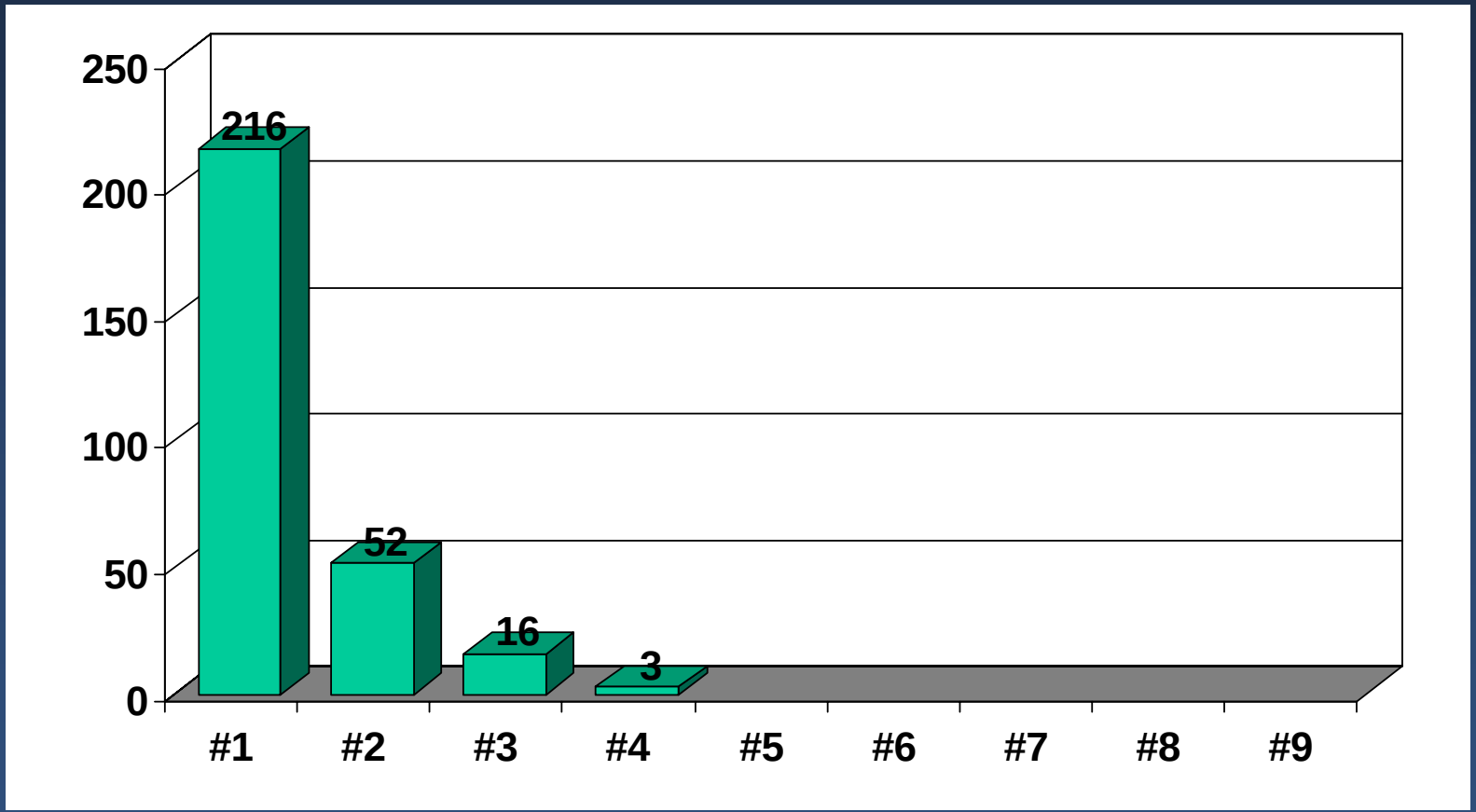


TABLE 4. *Number of undetected positive SLNBs and false negative rates with increased radioisotope threshold; lymph node metastasis >0.2 mm (N1mi or N1)*

Radioisotope threshold	Undetected positive SLNBs (*N*)	Percentage of undetected positive SLNB (%)	False negative rate (%)
10%	–	–	3.3
20%	4	2.1	5.4
30%	6	3.1	6.4
40%	8	4.1	7.4
50%	12	6.2	9.5
100%	17	8.8	12.1

N = 193 patients.

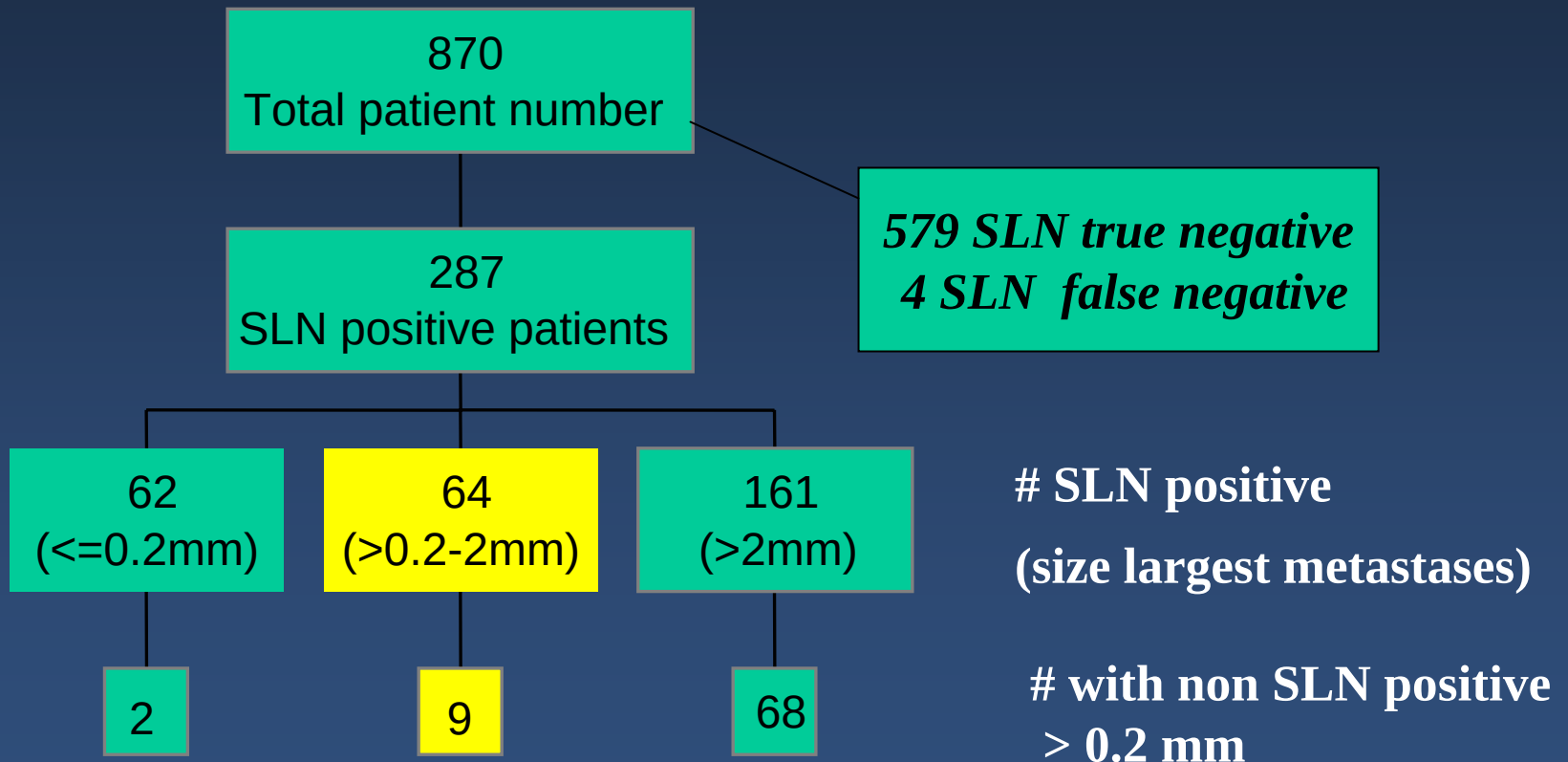
- One can safely ignore a hot ‘level 2’ node **unless**
  - it is the only node
  - the count is similar to the hottest level I node

Technical Findings

- Stick to the 10% Rule
- Stop at 4 nodes
- Ignore hot ‘level 2’ nodes
  - unless it is the only node
  - unless the counts are similar to the hottest level I node

Management of Positive SLN

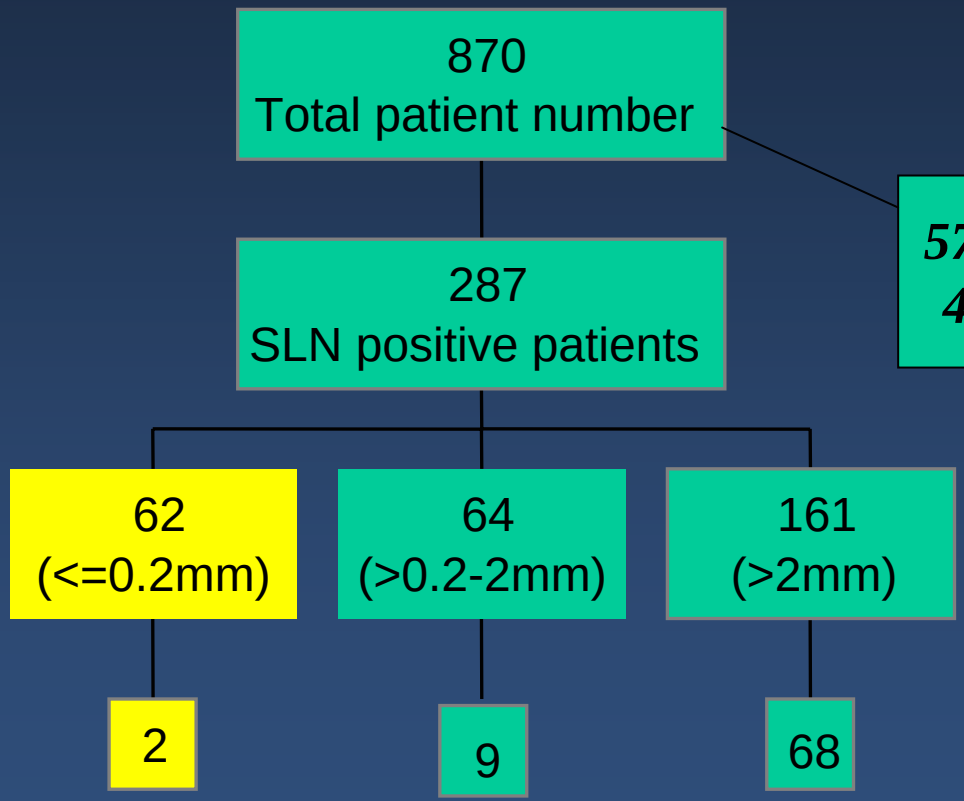
Rate of NSLN Disease at PMH



Completion ALND after finding micrometastases 0.2 - 2mm in SLN's, revealed **9 of 64 (14%)** patients had significant residual axillary disease

Management of Positive SLN

Rate of NSLN Disease at PMH



 # SLN positive

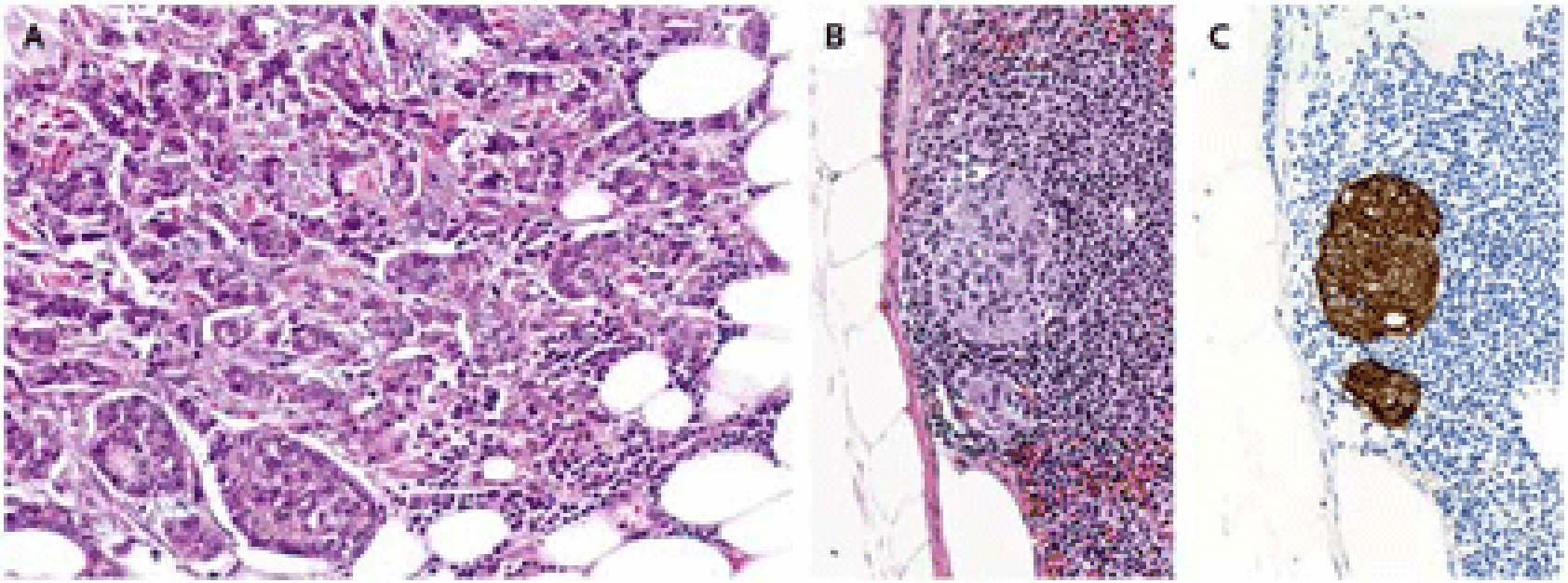
(size largest metastases)

 # with non SLN positive
> 0.2 mm

Completion ALND after 'isolated tumor cells/clusters' in SLN's, revealed **2 of 39 (5.1%)** patients had significant residual axillary disease

Case SNMM

- 0.9 cm IDC NOS, Grade 2/3
- ER ++, PR + , HER 2 neg
- LVI present
- SLN showed several nests of tumor mets < 0.02 cm on H&E in subcapsular sinus, confirmed with IHC



Case 35-2005 NEJM 2005;353:20

Table 3. Memorial Sloan-Kettering Cancer Center Nomogram for Prediction of Additional Axillary-Node Disease in the Patient.*

Variable	Patient Data
Tumor size	0.9 cm
Type and grade	Ductal; 2
Lymphatic invasion	Yes
Multifocal	No
Estrogen-receptor expression	Positive
No. of positive sentinel nodes	1
No. of negative sentinel nodes	0
Method of detection of metastases	Staining with hematoxylin and eosin, serial section

The MSK nomogram predicts a risk of additional (macro) metastases (eg 19%)

Monica Morrow Case 35-2005 NEJM 2005;353:20

Case SNMM: pT1b, pN0 (i+), M0

after Morrow

- Completion ALND ?
  - risk of additional positivive nodes — 19 %
  - risk of regional recurrence — 3 - 10 %
  - sequelae of treatment
  - potential impact of local therapy on survival
  - impact on other treatment decisions

AdjuvantOnline! predicts 10-year survival benefit of <1% if N0 and up to 5% if N1 with chemo

Case 35-2005 NEJM 2005;353:20

VOLUME 26 · NUMBER 11 · APRIL 10 2008

JOURNAL OF CLINICAL ONCOLOGY

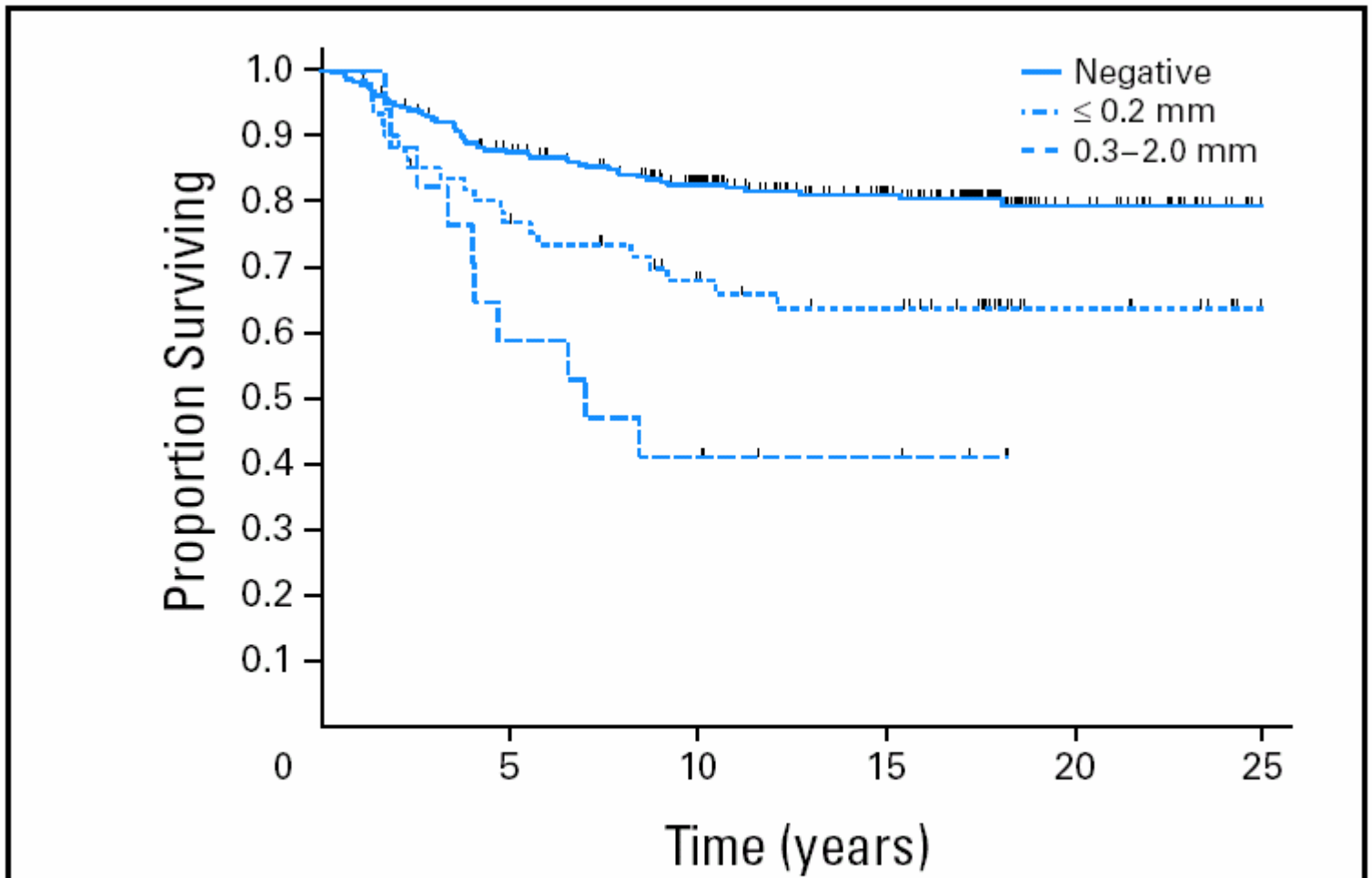
ORIGINAL REPORT

Occult Axillary Node Metastases in Breast Cancer Are Prognostically Significant: Results in 368 Node-Negative Patients With 20-Year Follow-Up

Lee K. Tan, Dilip Giri, Amanda J. Hummer, Katherine S. Panageas, Edi Brogi, Larry Norton, Clifford Hudis, Patrick I. Borgen, and Hiram S. Cody III

- 368 node negative patients: 1976-78
- Mastectomy + ALND, no systemic Rx
- SLN protocol used on ALN blocks at MSK
- 23% (83/368) upstaged
  - 73% : ≤ 0.2 mm — pN0 i+
  - 20% : 0.3 - 2.0 mm — pN1 mi
  - 6% : >2.0 mm — pN1 a

DFS by Largest Cluster Size



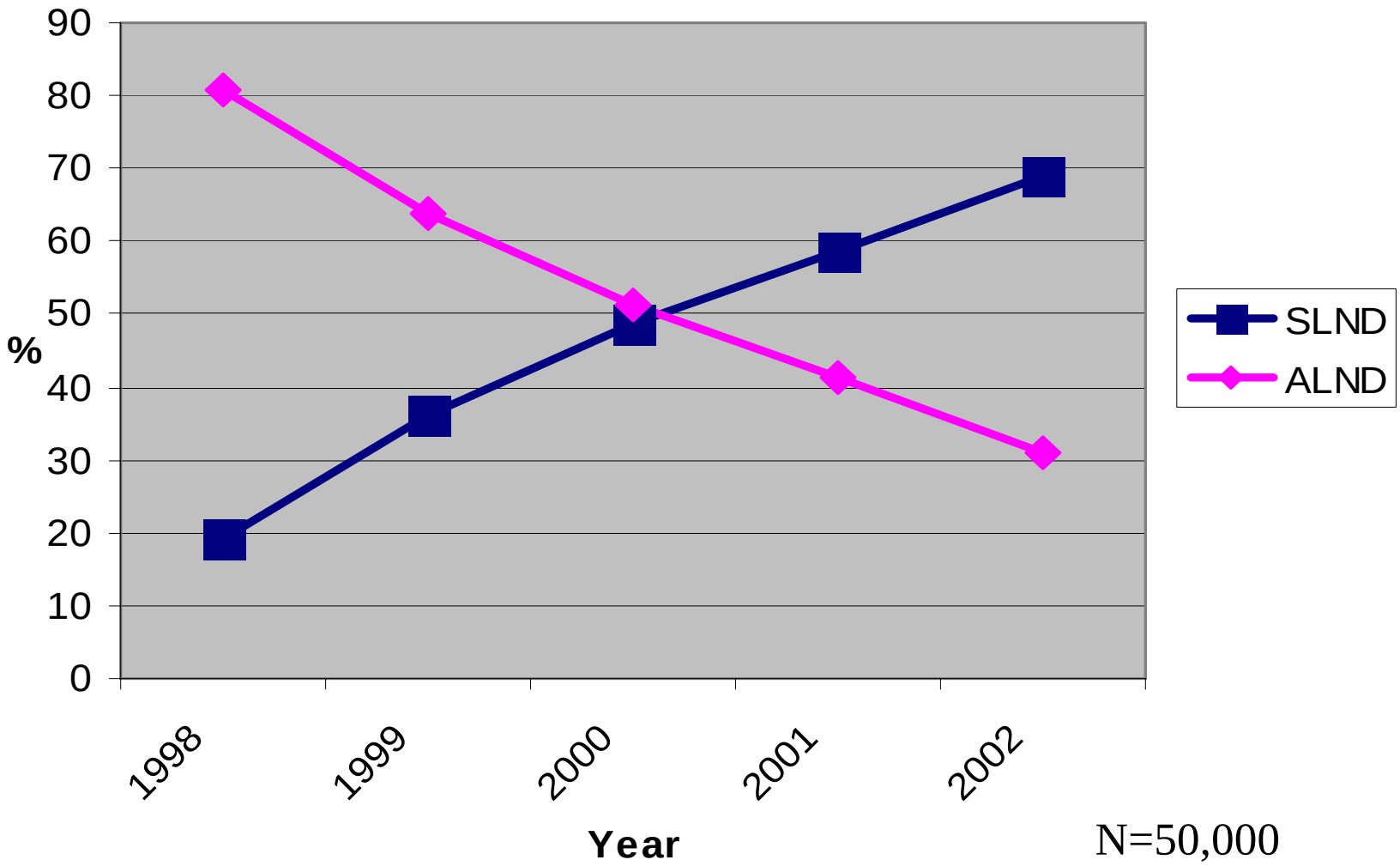
No. at risk (# events)				
Negative	241 (35)	199 (48)	140 (51)	32 (53)
≤ 0.2 mm	46 (14)	34 (19)	28 (21)	8 (21)
0.3–2.0 mm	10 (7)	7 (10)	4 (10)	0 (10)

Has the Use of SLNB Changed the Node Positivity Rate for Early Breast Cancers ?

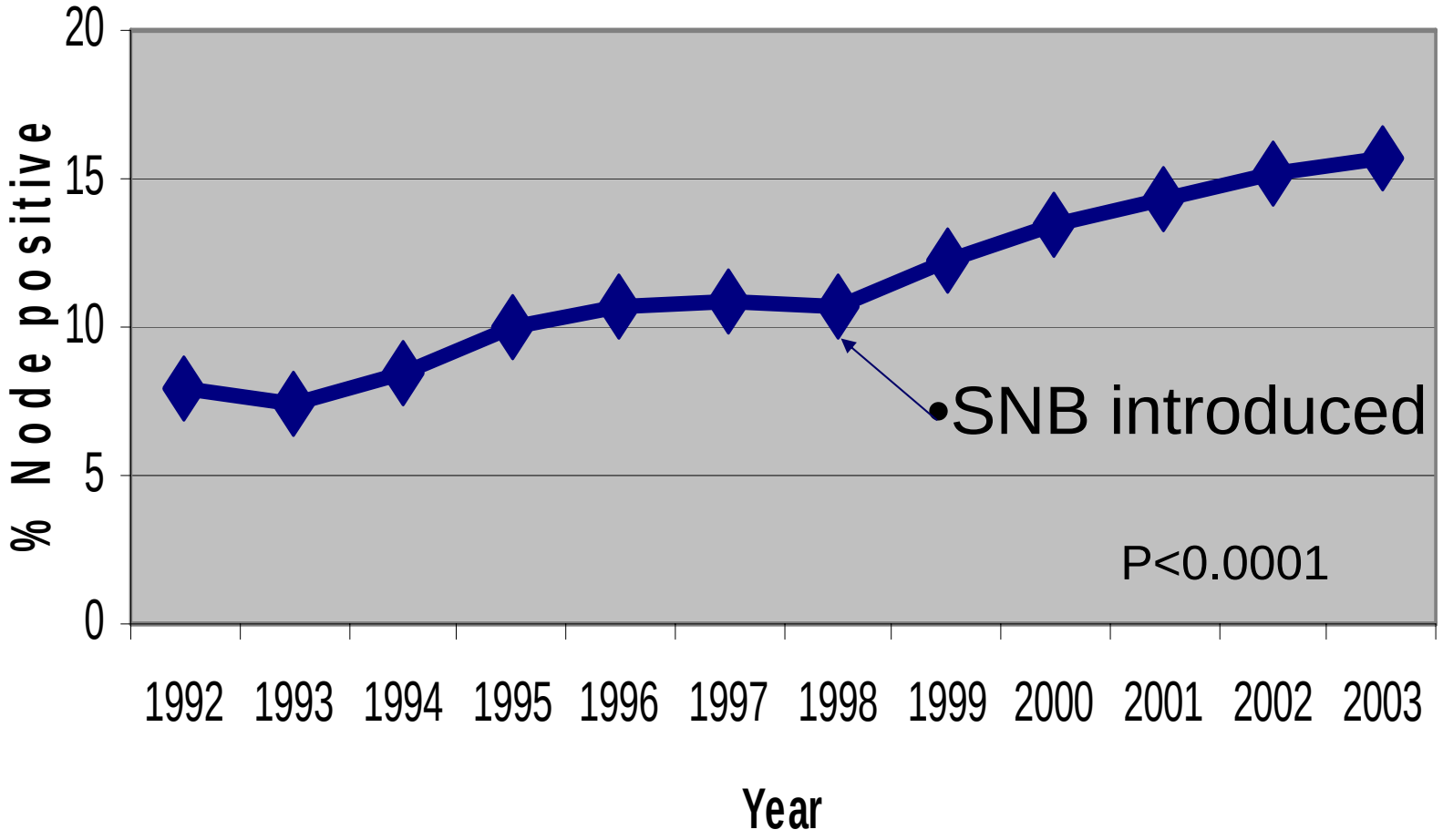
Three Scenarios for Nodal Positivity Rate:

- Rate decreases due to increased FN results
- Rate increases due to enhanced pathology, detection of unusually located nodes
- No change: enhanced pathology balanced by FN rate

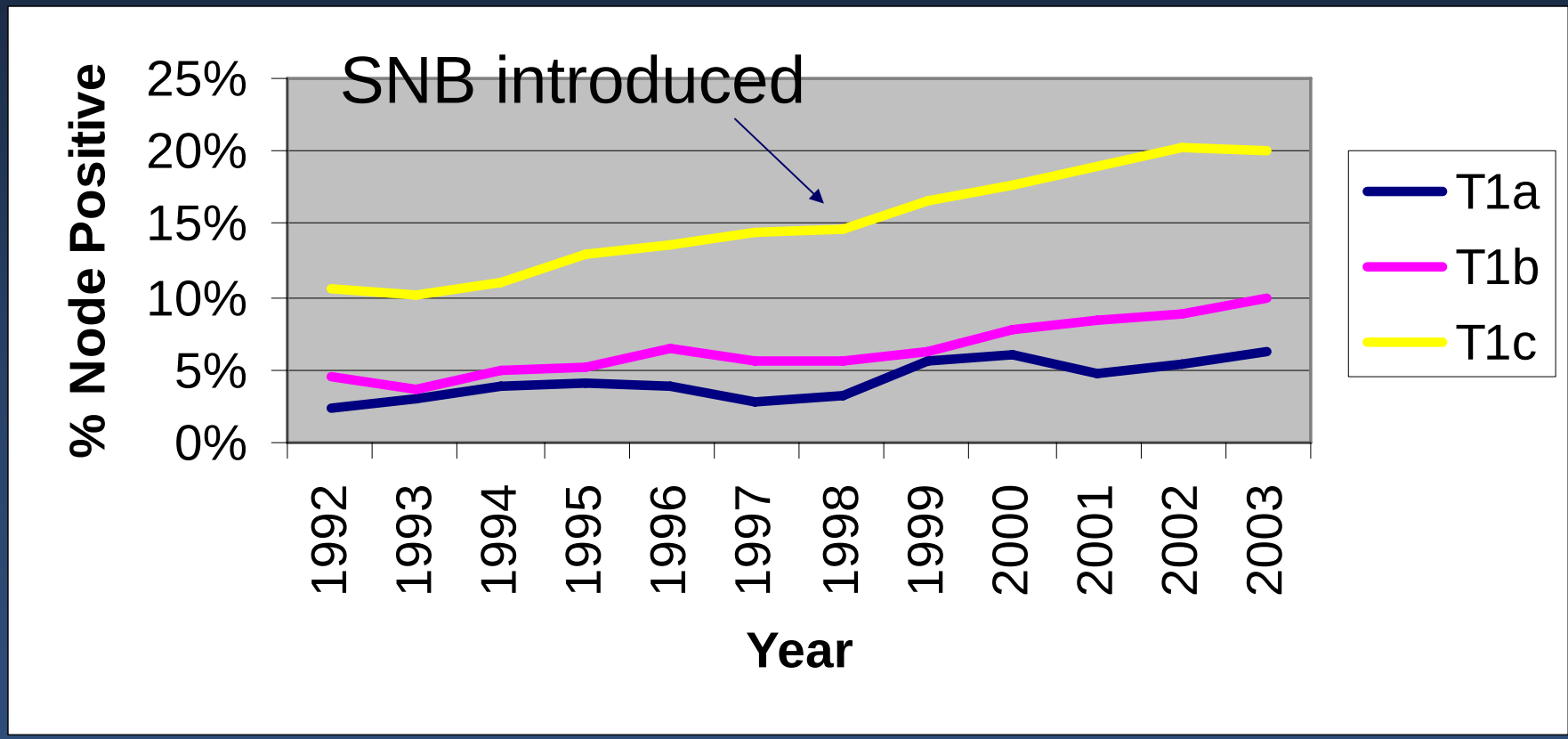
Axillary Staging for T1 Breast Cancers: SEER 1998 - 2003



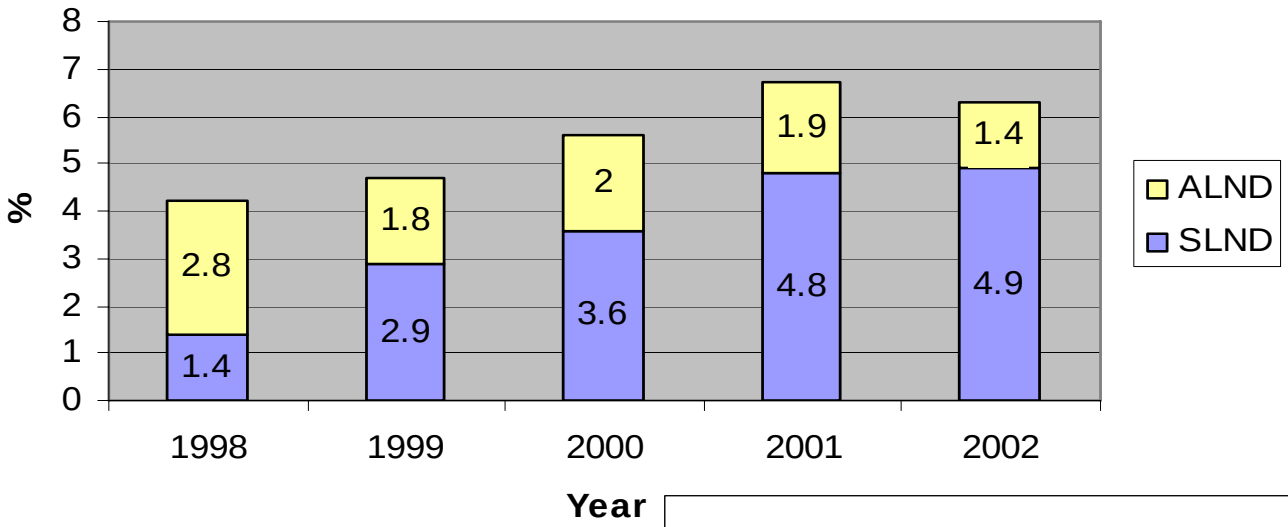
Prevalence of Node Positivity in T1 Breast Cancers



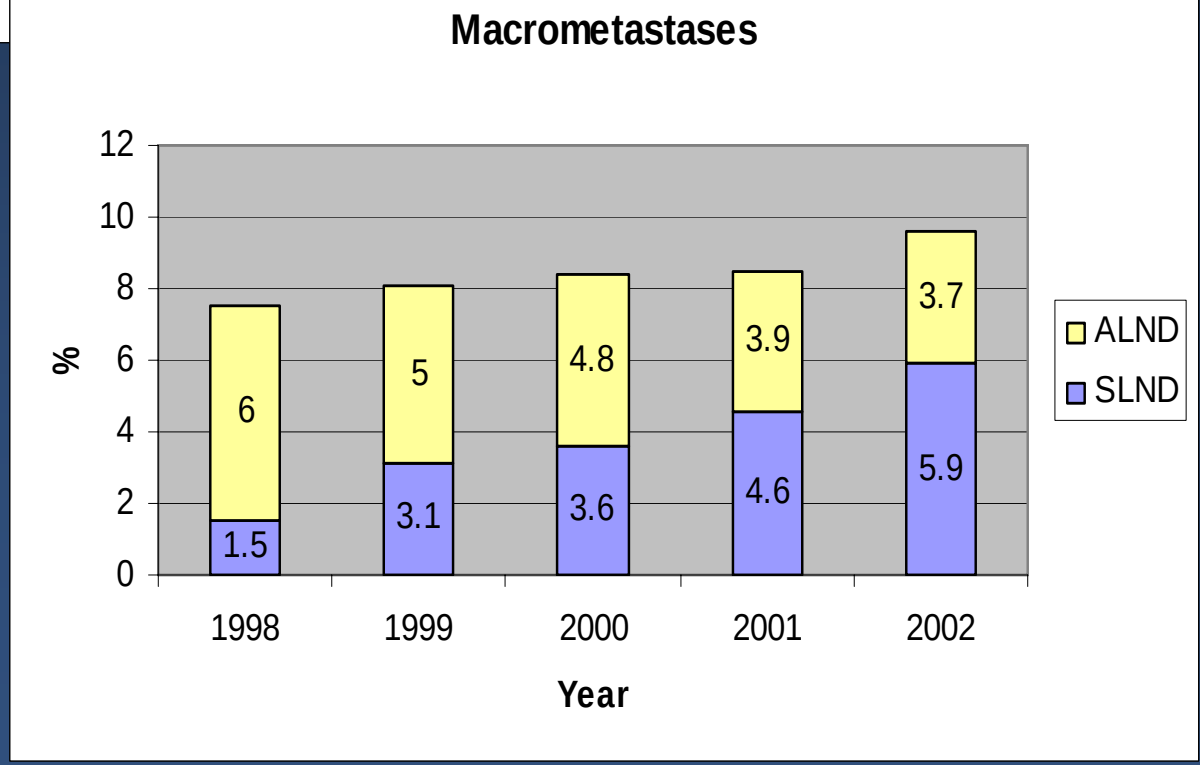
Prevalence of Node Positivity [N1(mic) and N1] in T1 Breast Cancers



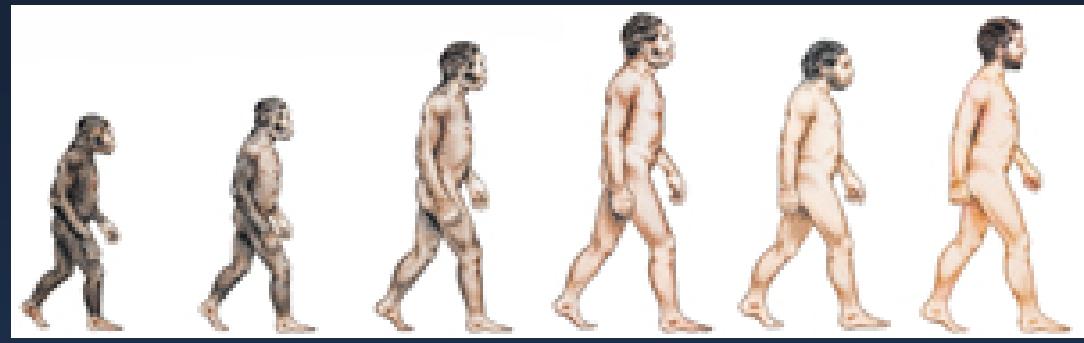
T1 Breast Cancers



- The increased node positive disease was detected by SLNB



Summary



- SLNB accurate and recommended
- IHC and multiple sections improve detection, primarily of deposits < 2 mm
- Technical factors important
- LN micrometastases probably have prognostic value
- N1 stage increasing