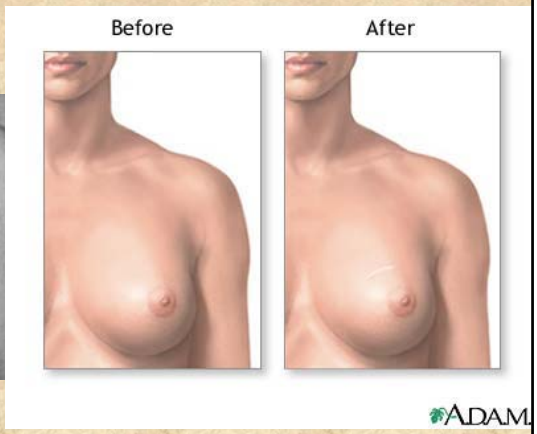
Sentinel Node Biopsy in Breast Cancer

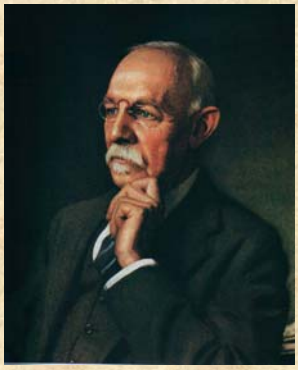
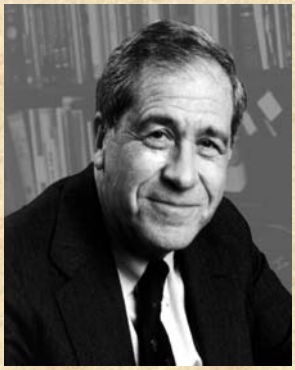
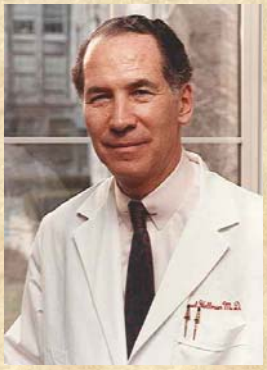
Should it be the “standard of care”?

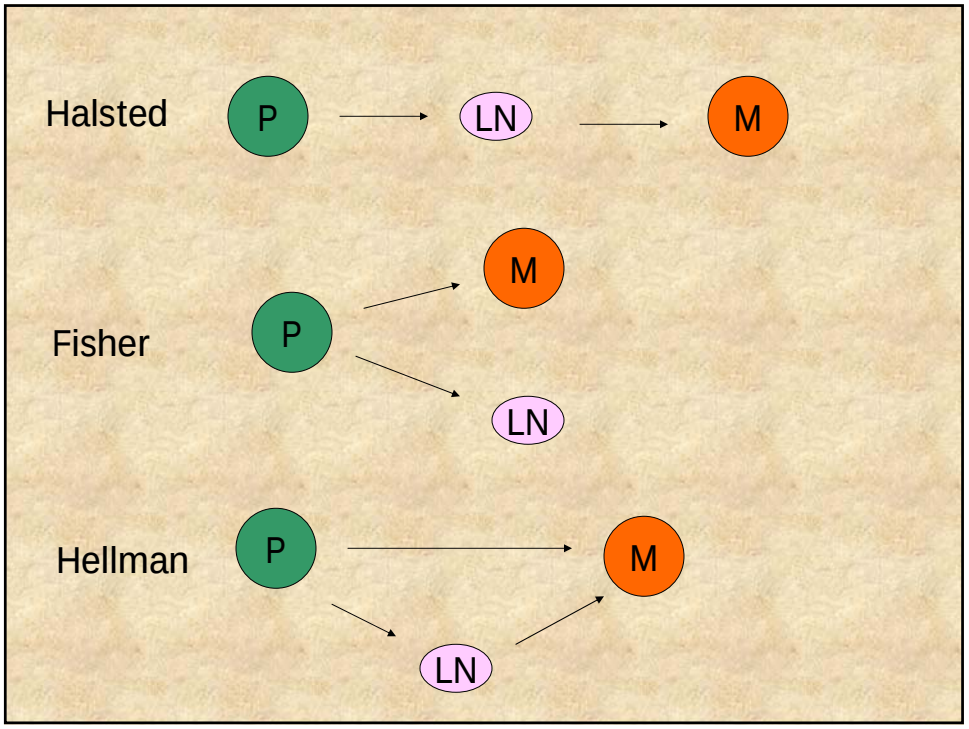
Greg McKinnon MD FRCSC

Evolution of breast cancer surgery

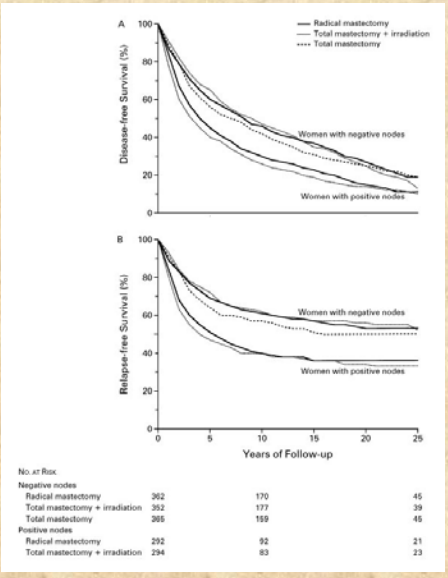


Nodes and Survival

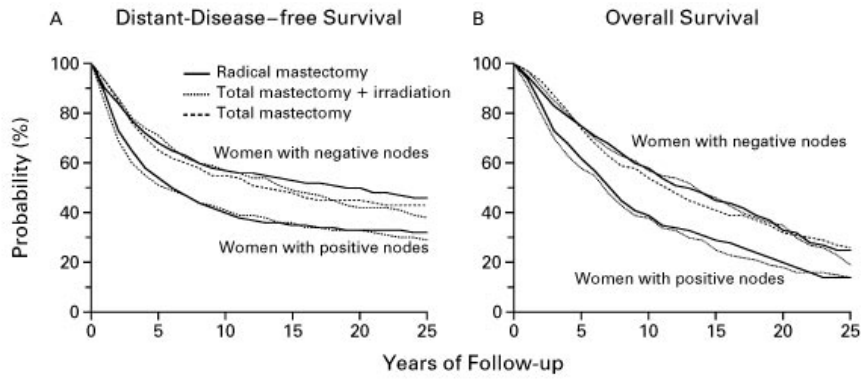


NSABP B-04: Disease-free Survival



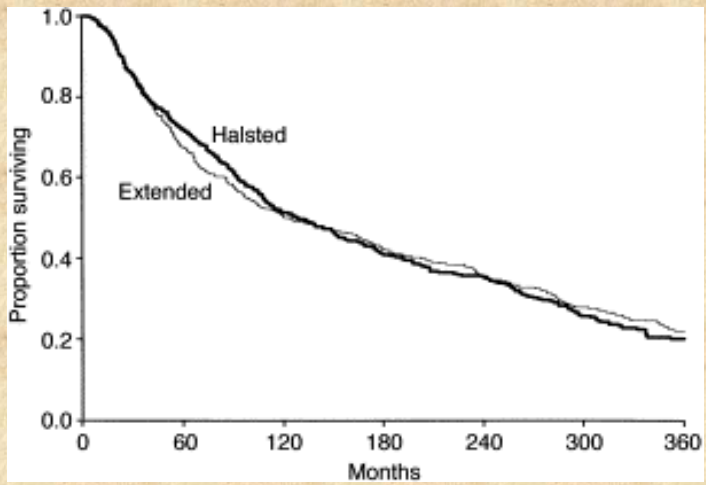
Fisher B et al, NEJM 347:567, 2002

NSABP B-04: Overall Survival



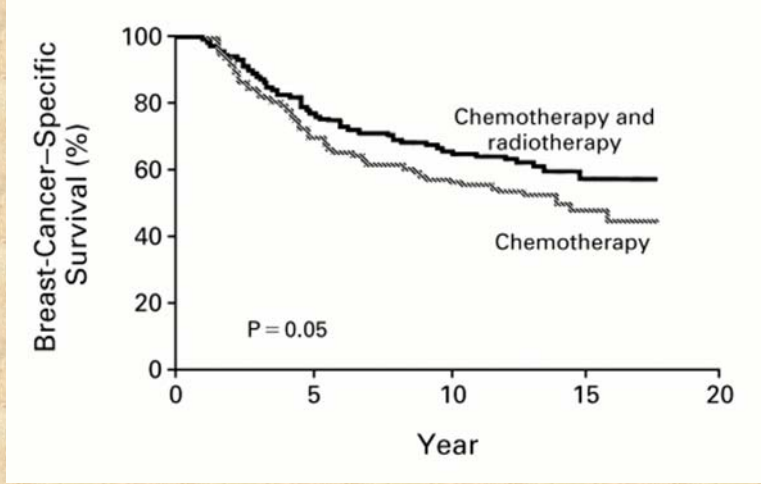
Fisher B et al, NEJM 347:567, 2002

30-year RCT: Halsted versus Extended Dissection (Inc. internal Mammary nodes) n = 716



Veronesi et al: Eur J Cancer. 1999 Sep;35(9):1320

Effect of Regional Radiotherapy
n = 318 p = 0.05



Ragaz et al, NEJM 337:956, 1997

Effect of regional radiotherapy on mortality

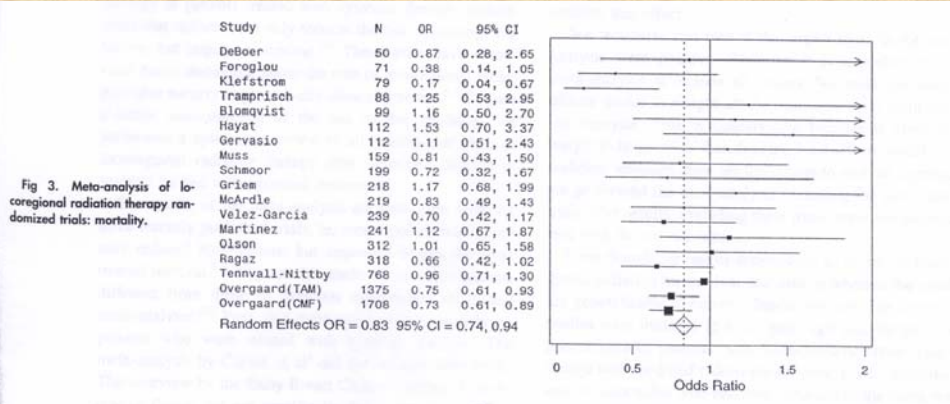


Fig 3. Meta-analysis of loco-regional radiation therapy randomized trials: mortality.

Whelan et al:J Clin Oncol. 2000 Mar;18(6):1220-9

Effect of AND on Survival:Meta-analysis

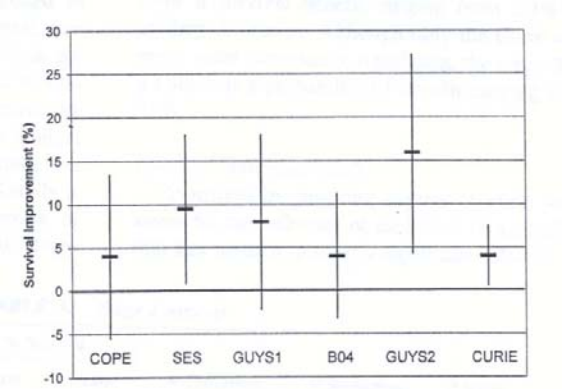


FIG. 1. Comparison of six randomized trials. Vertical bars are 95% confidence intervals, and the horizontal line through each bar represents the estimated survival benefit for each study. COPE, Copenhagen study; SES, SouthEast Scotland Study.

Orr: Ann Surg Oncol. 1999 Jan-Feb;6(1):109-16

- Regional control

Risk of axillary recurrence in node-negative patients following dissection of the axilla.

N = 3128

# nodes removed	risk of axillary recurrence
0	19%
1-2	10%
3-4	5%
>5	3%

Graversen et al:Eur J Surg Oncol. 1988 Oct;14(5):407-12.

Regional Recurrence after Radiotherapy to the Axilla

Table 2
Efficacy of radiation in preventing axillary recurrences for patients with clinically negative axilla

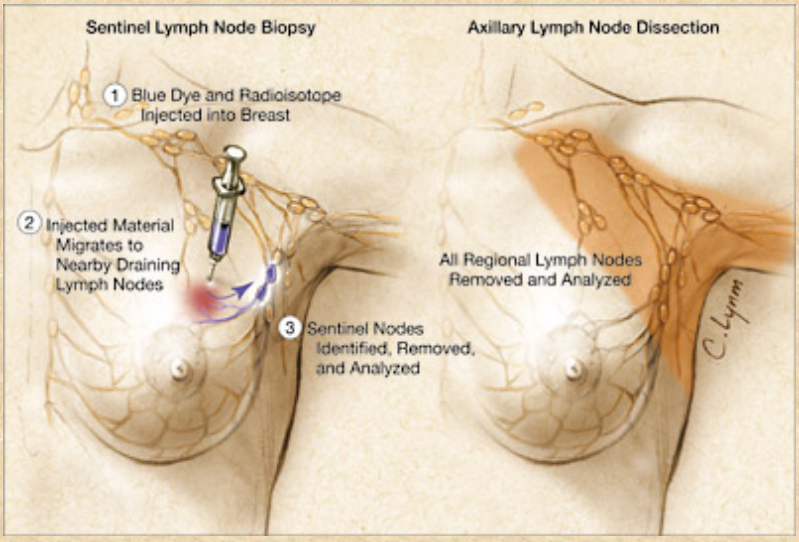
Series	Number of patients	Radiation of level III/SCF	Follow-up	Regional recurrence rate
Haffty [23]	327	Yes	5-year rate	3%
Recht [27]	9	Yes	77 months	2.1%
Wazer [28]	73	Yes	54 months	1%
Wong [29]	92	No	50 months	1%
Halverson [24]	75	Varied	Not provided	2.7%
Zurrida [30]	221	Yes	42 months	0.5%
Hoebers [25]	105	Yes	5-year rate	2%
Kuznetsova [26]	456	Yes	52 months	0%

Buchholtz et al:Surg Clin North Am. 2003 Aug;83(4):911-30

Conclusions 1

- Regional control is important and easily achieved
- Survival is probably affected
- **Nodes still matter**

SNB versus Routine AND: Which is better?



What is the false negative rate of SNB?

Failure v.s. False negative

- Failure rate = FN/TN + FN
- False negative rate = FN/FN + TP

False negative rate = FN/FN + TP Calculated according to completion AND

Table 1
False-negative rates in series with sentinel lymph node surgery followed by completion axillary dissection

Series	Total no. of cases	No. of cases with +LN	False-negative rate
Krag [7]	443	114	11.4%
Tafra [10]	535	140	13%
Veronesi [11]	376	180	6.7%
McMasters [8]	2148	Not reported	8%
Begkvist [3]	450	184	11%
O'Hea [9]	60	23	13%
Dupount [4]	555	114	4%
Hill [6]	458	47	10.6%
Giuliano			
Early series [1]	174	42	11.9%
Later series [5]	107	42	0%

Abbreviations: No, number; +LN, positive lymph nodes.

FN determined by patient follow-up

N = 222 patients
Median follow-up 32 months

TABLE 5. *Site and frequency of disease recurrence in SLN-positive and SLN-negative patients*

Site of recurrence	SLN positive (n = 63)	SLN negative (n = 159)
Local	3 (4.8%)	1 (.6%)
Regional	1 (1.6%)	0
Distant	2 (3.2%)	4 (2.5%)
Total	6 (9.5%)	5 (3.1%)

SLN, sentinel lymph node.

Badgewell BD, Ann Surg Oncol, 10: 376-80, 2003

FN determined by patient follow-up

- N = 67 SN negative patients
- Median follow-up = 39 months
- Axillary recurrence rate = 0

Guiliano:J Clin Oncol. 2000 Jul;18(13):2553-9.

FN determined by patient follow-up

- N = 206
- Median follow-up = 26 months
- Axillary recurrence rate of 1.4%

Chung et al:Am J Surg. 2002 Oct;184(4):310-4

FN determined by patient follow-up

- N = 685
- median follow-up 30 months
- Axillary recurrence rate: 0.1% (1)

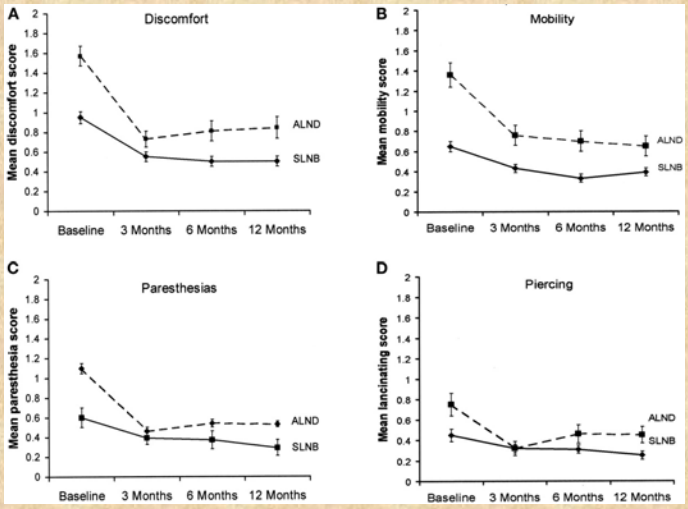
Blanchard:Arch Surg. 2003 May;138(5):482-7

Morbidity of SNB v.s. AND

- Lymphedema
- Paresthesias
- Pain

Sensory morbidity: AND v.s. SNB

171 SNB
62 AND



Temple et al:Ann Surg Oncol. 2002 Aug;9(7):654

Morbidity: SNB v.s. AND

	AND (n=213)	SNB(n=180)
Pain	23%	7.8%
Lymphedema	7.1%	1.1%
Numbness	24.4%	3.9%
Strength loss	26.3%	3.9%
↓ ROM	18%	6%

Schijven et al:Eur J Surg Oncol. 2003 May;29(4):3

Long-Term Morbidity of AND

- N = 263
- Arm circumference and questionnaire
- 49% reported sensation of lymphedema (13% severe)
- 0nset within 3 years in 77%
- 1% per year after that

Petrek et al: Cancer92, 2001

What about randomized trials of SNB?

SNB v.s. Routine AND

- N = 516
- <= 2 cm tumors
- Patients randomized to SNB or routine AND
- Intra-operative frozen sections
- Median follow-up 46 mos

Veronesi et al NEJM – 349: 546, 2003

Outcome AND vs. SNB

	AND	SNB
Recurrence		
Axilla	0	0
Supraclavicular	2	0
Breast	1	1
Contralateral breast	2	3
Distant	10	6
Death		
Breast Cancer	2	1
Other	4	1

* Median follow-up = 46 months

Veronesi et al NEJM – 349: 546, 2003

AND compared to SNB: Side Effects (24 mos)

Mobility	AND (n=100)	SN (n=100)
80 – 100 %	79	100
Swelling (circumference)		
No difference	25	93
< 1 cm	38	6
1 – 2 cm	25	1
> 2 cm	12	0

Veronesi et al NEJM – 349: 546, 2003

Outcome AND vs. SNB

	AND	SNB
Recurrence		
Axilla	0	0
Supraclavicular	2	0
Breast	1	1
Contralateral breast	2	3
Distant	10	6
Death		
Breast Cancer	2	1
Other	4	1

* Median follow-up = 46 months

Veronesi et al NEJM – 349: 546, 2003

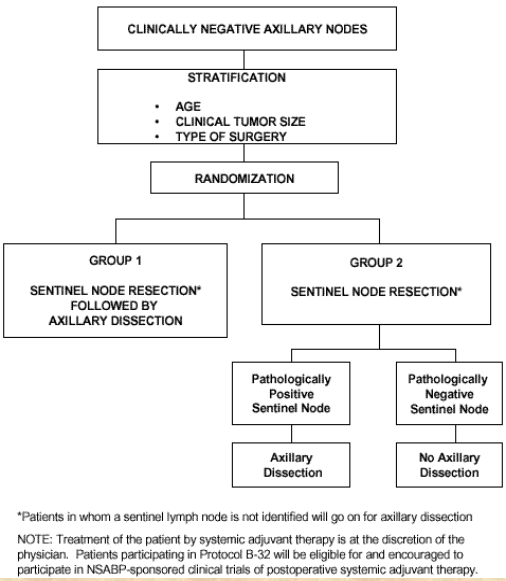
AND compared to SNB: Side Effects (24 mos)

		AND (n=100)	SN (n=100)
Pain			
	No	61	92
	Sporadic	34	7
	Continuous	5	1
Paresthesias			
	No	32	99
	Yes	68	1

Veronesi et al NEJM – 349: 546, 2003

Accrual target:5400
Now completed

NSABP B-32



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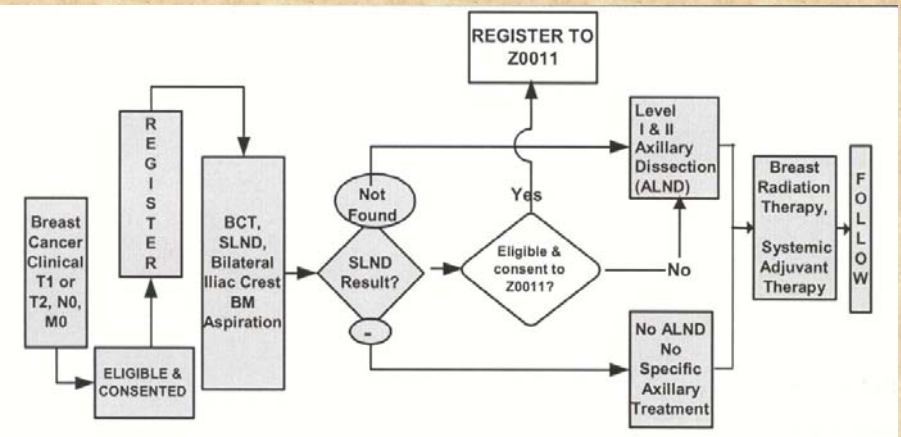

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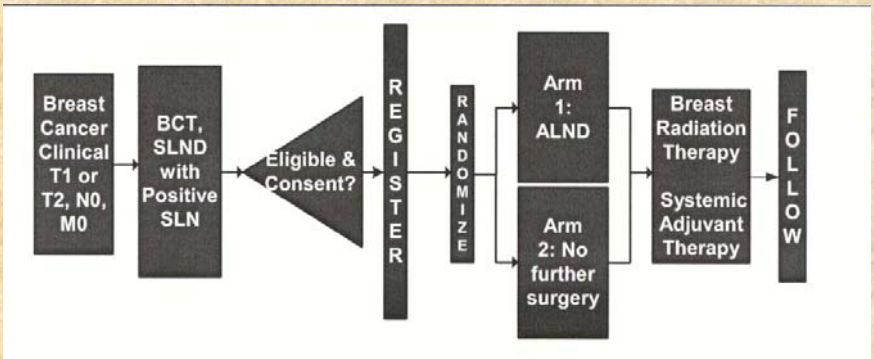


New treatments: the ideal

- Treatment A v.s. no treatment
- Treatment B v.s. treatment A

Conclusions 2

- SNB stages the axilla accurately
- Less morbid than AND
- Regional control is acceptable
- Should we wait for the randomized trials?

Conclusion 3

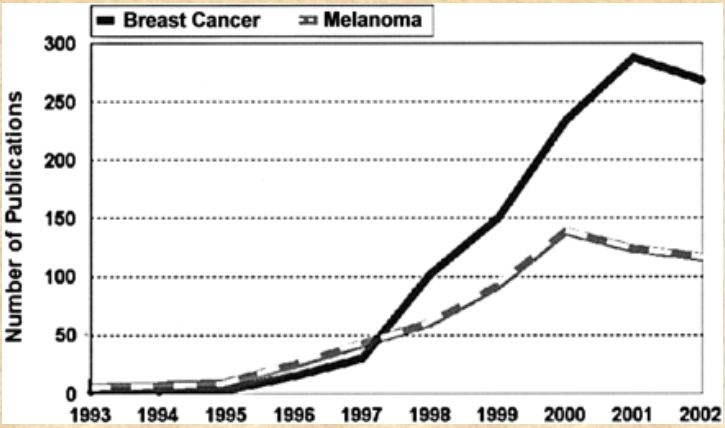
- In Canada, in 2004, it is acceptable and usually preferable to perform SNB without axillary dissection for breast cancer.

Primum non nocere

When in doubt, don't mutilate

What is the current status of SNB for Breast Cancer?

Publications on SNB



Leong S. Ann Surg Oncol 2004 11: 192

Changes to AJCC Staging

• Micrometastases are distinguished from isolated tumor cells on the basis of size and histologic evidence of malignant activity.
• Identifiers have been added to indicate the use of sentinel lymph node dissection and immunohistochemical or molecular techniques.
• Microscopic involvement of the internal mammary nodes detected by sentinel lymph node dissection is classified as N1.

SNB Consensus Conference- 2001

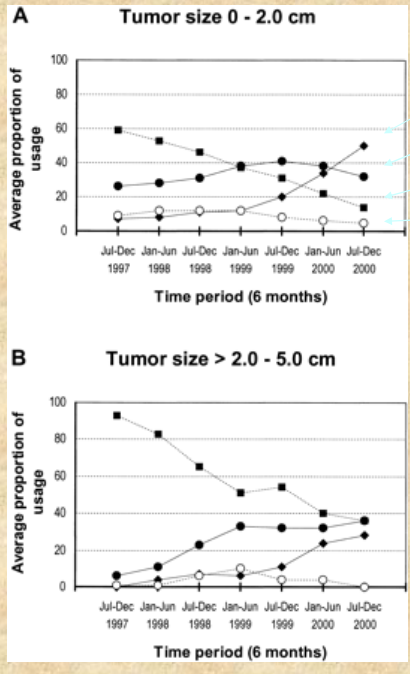
- "Panelists strongly felt that one does not need to wait for the results of these randomized trials to perform sentinel lymph node biopsy"

Schwartz et al: Cancer, 94 May 2002

SNB in U.S.

- N = 410 surgeons
- 77% performed SNB for breast cancer
- 28% performed SNB for high grade DCIS
- Expectation of care?

Lucci et al: J Am Coll Surg 2001 192:466



SNB

SNB + AND

AND

NOne

Trends in Axillary Surgery For Breast Cancer U.S.A

Edge et al:
J Natl Cancer Inst 2003; 95: 1514-1521

Surgeons "Vote With Their Feet" for Sentinel Node Biopsy for Breast Cancer Staging Tracy Hampton, PhD

JAMA. 2003;290:3053-3054.

Research
Recherche

Dr. Cantin is Associate Professor at the University of Montreal and is with the Centre hospitalier de l'Université de Montréal, Montreal, Que.; Dr. Scarth is Assistant Professor, Department of Surgery, Dalhousie University, and is with the Atlantic Health Sciences Corporation, Saint John, NB; Dr. Levine is Professor in the Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, and is the Buffet Taylor Chair in Breast Cancer Research, McMaster University, Hamilton, Ont.; and Dr. Hugi is with Providence Health Care, Vancouver, BC.

The steering committee is part of Health Canada's Canadian Breast Cancer Initiative. A list of the committee members appears at the end of the article.

A patient version of these guidelines appears in Appendix 1.

This article has been peer reviewed.

CMAJ 2001;164(2):166-73

Clinical practice guidelines for the care and treatment of breast cancer: 13. Sentinel lymph node biopsy

Jacques Cantin, Hugh Scarth, Mark Levine, Maria Hugi, for the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer

Abstract

Objective: To provide information and recommendations to women with breast cancer and their physicians regarding what is now known about sentinel lymph node (SLN) biopsy.

Options: Axillary dissection; SLN biopsy followed by backup axillary dissection; SLN biopsy.

Outcomes: Accurate determination of cancer stage, resulting in better-informed therapeutic decisions.

Evidence: Systematic review of English-language literature published from January 1991 to December 2000 retrieved primarily from MEDLINE and CANCERLIT.

Recommendations:

- Axillary dissection is the standard of care for the surgical staging of operable breast cancer.
- If a patient requests or is offered SLN biopsy, the benefits and risks as well as what is and is not known about the procedure should be outlined.
- Patients should be informed of the number of SLN biopsies performed by the surgeon and the surgeon's success rate with the procedure, as determined by the identification of the SLN and the false-negative rate (the presence of tumour cells in the axillary nodes when the SLN biopsy result is negative).
- Before surgeons replace axillary dissection by SLN biopsy as the staging procedure at their institution, they should (a) familiarize themselves with the literature on the topic and the techniques needed to perform the procedure, (b) follow a defined protocol for all 3 aspects of the procedure (nuclear medicine, surgery, pathology) and (c) perform backup axillary dissection until an acceptable success rate (as determined by the identification of the SLN and the false-negative rate) is achieved.
- A surgeon who performs breast cancer surgery infrequently should not perform SLN biopsy.
- A positive SLN biopsy result or failure to identify an SLN should prompt full axillary dissection.
- SLN biopsy is contraindicated in women who have clinically palpable nodes, locally advanced breast cancer, multifocal tumours, previous breast surgery or previous irradiation of the breast.
- Staining of tissue sections with hematoxylin and eosin, and not immunohistochemical analysis for cytokeratin, should determine adjuvant therapy.
- Participation in randomized clinical trials is encouraged.

[A patient version of these guidelines appears in Appendix 1.]

Validation: Internal validation within the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer; no external validation.

Sponsor: The steering committee was convened by Health Canada.

Completion date: Apr. 9, 2001.

NCCN® Practice Guidelines in Oncology – v.3.2003

Invasive Breast Cancer

AXILLARY DISSECTION

In the absence of definitive data demonstrating superior survival from the performance of axillary lymph node dissection, patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with serious comorbid conditions, the performance of axillary lymph node dissection may be considered optional. The axillary dissection should be extended to include level III nodes only if there is gross disease apparent in the level I or II nodes.

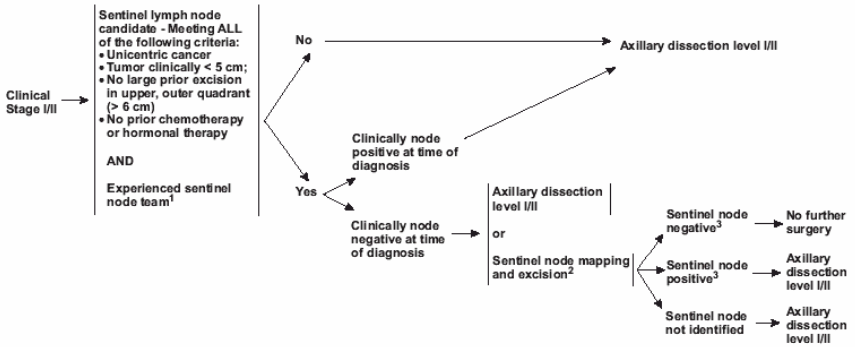
Sentinel lymph node biopsy may be considered an option (category 2B) if there is an experienced sentinel node team and the patient is an appropriate sentinel lymph node biopsy candidate (See BINV-A).

NCCN® Practice Guidelines in Oncology – v.3.2003

Invasive Breast Cancer

Guidelines Index
Breast Cancer TOC
Staging, MS, References

Surgical Axillary Staging - Stage I, IIA, and IIB



[1]Sentinel node team must have documented experience with SNB in breast cancer. Team includes surgeon, radiologists, nuclear medicine physician, pathologist, and prior discussion with medical and radiation oncologists on use of sentinel node for treatment decisions.

[2]Axillary sentinel node biopsy in all cases; internal mammary sentinel node biopsy optional if drainage maps to internal mammary nodes (Category 3).

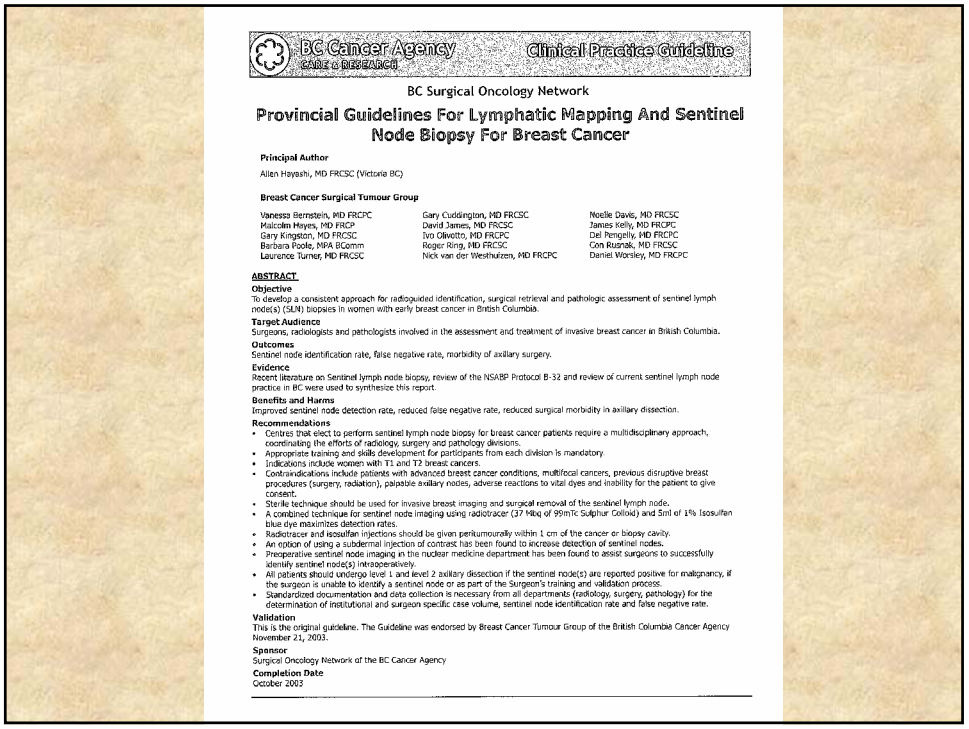
[3]Sentinel node involvement defined by multilevel node sectioning with hematoxylin and eosin staining. Cytokeratin Immunohistochemistry (ICH) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is controversial (Category 3).

Return to LocoregionalTreatment (BINV-2)

Return to Breast Cancer Guideline Table of Contents

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-A



BC Cancer Agency
CARE ◇ RESEARCH
Clinical Practice Guideline

BC Surgical Oncology Network

Provincial Guidelines For Lymphatic Mapping And Sentinel Node Biopsy For Breast Cancer

Principal Author

Allen Hayashi, MD FRCSC (Victoria BC)

Breast Cancer Surgical Tumour Group

Vanessa Bernstein, MD FRCPC
Malcolm Hayes, MD FRCP
Gary Kingston, MD FRCSC
Barbara Poole, MPA BComm
Laurence Turner, MD FRCSC
Gary Cuddington, MD FRCSC
David James, MD FRCSC
Ivo Olivotto, MD FRCPC
Roger Ring, MD FRCSC
Nick van der Westhuizen, MD FRCPC
Noelle Davis, MD FRCSC
James Kelly, MD FRCPC
Del Pengelly, MD FRCPC
Con Rusnak, MD FRCSC
Daniel Worsley, MD FRCPC

ABSTRACT

Objective
To develop a consistent approach for radioguided identification, surgical retrieval and pathologic assessment of sentinel lymph node(s) (SLN) biopsies in women with early breast cancer in British Columbia.

Target Audience
Surgeons, radiologists and pathologists involved in the assessment and treatment of invasive breast cancer in British Columbia.

Outcomes
Sentinel node identification rate, false negative rate, morbidity of axillary surgery.

Evidence
Recent literature on Sentinel lymph node biopsy, review of the NSABP Protocol B-32 and review of current sentinel lymph node practice in BC were used to synthesize this report.

Benefits and Harms
Improved sentinel node detection rate, reduced false negative rate, reduced surgical morbidity in axillary dissection.

Recommendations
- Centres that elect to perform sentinel lymph node biopsy for breast cancer patients require a multidisciplinary approach, coordinating the efforts of radiology, surgery and pathology divisions.
- Appropriate training and skills development for participants from each division is mandatory.
- Indications include women with T1 and T2 breast cancers.
- Contraindications include patients with advanced breast cancer conditions, multifocal cancers, previous disruptive breast procedures (surgery, radiation), palpable axillary nodes, adverse reactions to vital dyes and inability for the patient to give consent.
- Sterile technique should be used for invasive breast imaging and surgical removal of the sentinel lymph node.
- A combined technique for sentinel node imaging using radiotracer (37 MBq of 99mTc Sulphur Colloid) and 5ml of 1% Isosulfan blue dye maximizes detection rates.
- Radiotracer and isosulfan injections should be given peritumourally within 1 cm of the cancer or biopsy cavity.
- An option of using a subdermal injection of contrast has been found to increase detection of sentinel nodes.
- Preoperative sentinel node imaging in the nuclear medicine department has been found to assist surgeons to successfully identify sentinel node(s) intraoperatively.
- All patients should undergo level 1 and level 2 axillary dissection if the sentinel node(s) are reported positive for malignancy, if the surgeon is unable to identify a sentinel node or as part of the Surgeon's training and validation process.
- Standardized documentation and data collection is necessary from all departments (radiology, surgery, pathology) for the determination of institutional and surgeon specific case volume, sentinel node identification rate and false negative rate.

Validation
This is the original guideline. The Guideline was endorsed by Breast Cancer Tumour Group of the British Columbia Cancer Agency November 21, 2003.

Sponsor
Surgical Oncology Network of the BC Cancer Agency

Completion Date
October 2003

SNB in Canada

- N = 519
- 27% perform SNB for breast cancer

Porter et al:Ann Surg Oncol. 2003 Apr;10(3):255-60

SNB in B.C.

- N = 150 surgeons
- 19% of surgeons perform SNB
- Five surgeons had abandoned routine AND

Chua et al: Can J Surg. 2003 Aug;46(4):273-8

SNB for Breast Cancer in Calgary

- Started in 1996
- 5 surgeons (3 replaced routine AND)
- 88 in 2003

- Why the difference between U.S and Canada?

Alberta Guidelines

- Multidisciplinary
- 20 SNB procedures before abandoning AND
- False negative rate <5%
- AND if cannot identify
- All women meeting criteria should be informed of the option of SNB

Alberta Guidelines: Contraindications

- Clinically positive axillary nodes
- Distant metastases
- Locally advanced or inflammatory
- Previous axillary dissection
- Previous breast surgery eg. Reduction
- Previous RT
- Pregnancy
- Allergy to dye

SNB in Lobular carcinoma

Table 2. Pathologic Results for All Lymph Nodes (Including Axillary Sentinel Lymph Nodes)

Variable	DIC (*n* = 208 patients)	LIC (*n* = 35 patients)	*P* value (chi-square)
Mean ± SD no. of lymph nodes removed	9.5 ± 3.4	9.8 ± 3.7	NS
No. of patients with involved lymph nodes (%)	85 (40.8)	11 (31.4)	NS

DIC: ductal invasive carcinoma; LIC: lobular invasive carcinoma; SD: standard deviation; NS: not significant.

Classe et al, Cancer 100, 2004

Standard?

- Community standard
- Legal standard
- Level 1 evidence?
- “Expectation of care”?

Recommendation

- SNB is an important and desirable improvement in breast surgery
- Education and not coercion is preferred
- NSABP B-32 will not solve the issue
- Begin to incorporate in practice now
- Guidelines in the future are likely to mandate including it in informed consent