

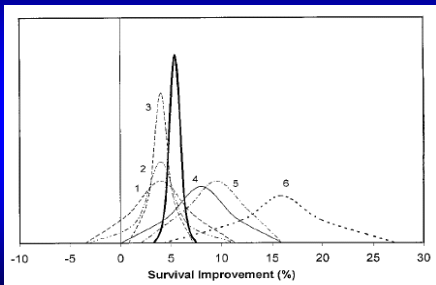
Sentinel Node Biopsy: The Past, The Present, and The Future

Thomas B. Julian, M.D., F.A.C.S.
Associate Professor of Human Oncology
Drexel University College of Medicine
Director of Breast Surgical Oncology
The WestPenn Allegheny Health Care System
Senior Surgical Director, Medical Affairs, NSABP
Pittsburgh, PA
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AD vs. no AD

Survival

Randomized Trials

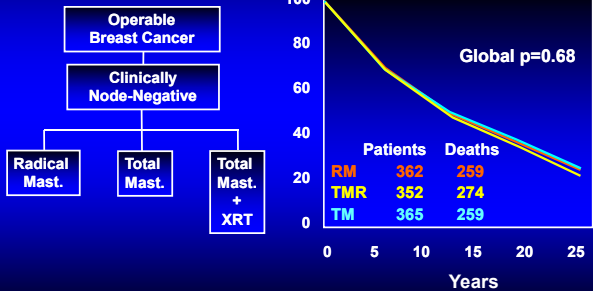


All trials reported higher survival in the AD group

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

NSABP B-04

Overall Survival



Fisher B: NEJM, 2002

Sentinel Node Concept

- Metastasis to regional lymph nodes is **not a random event** but instead there is **orderly progression** of tumor cells within the lymphatic system.
- Primary draining or **sentinel node** is the first to contain metastases.
- Biopsy of this **sentinel node** can accurately predict axillary involvement

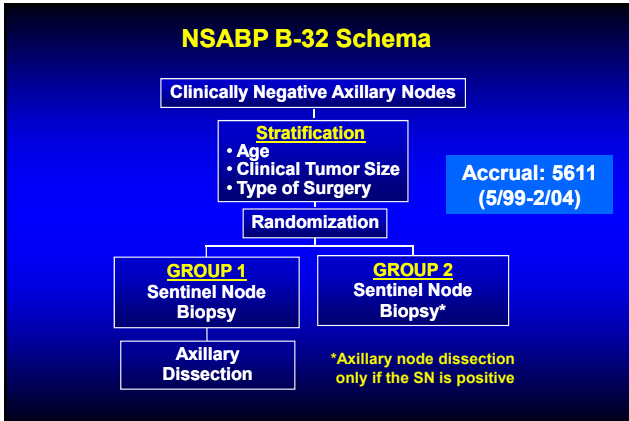


Sentinel Node Detection Techniques



SLNB: Rapid Clinical Adoption

- Over the past decade, SLNB alone has gained acceptance as the **preferred method for staging the axilla** in patients with **negative SLN(s)**
- **Clinical guidelines** (St. Gallen, NCCN) include **SLNB alone** as an acceptable method for staging the axilla in pts with operable BC
- **Significant reduction in morbidity** compared to ALND (particularly in **arm numbness/paresthesia and lymphedema**)
- **Low rates of axillary recurrence** after a (-) SLNB
- Outcome results from **large RCTs not disclosed until now**



ASCO 2010 Abstract LBA 505

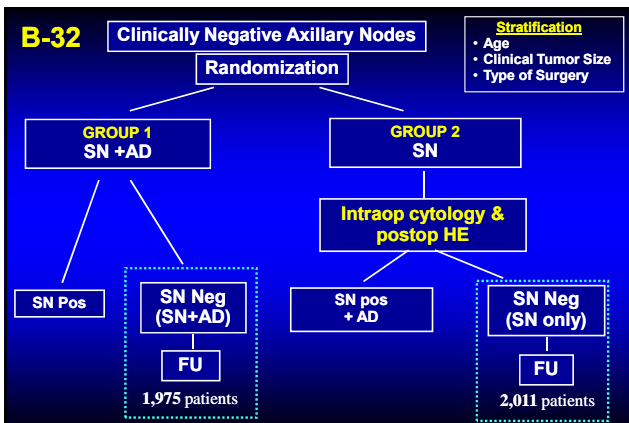
NSABP PROTOCOL B-32

A Randomized, Phase III Clinical Trial to Compare Sentinel Node Resection to Axillary Dissection in Clinically Node-Negative Breast Cancer Patients

Definitive Analysis of the Primary Outcomes

DN Krag, SJ Anderson, TB Julian, A Brown, SP Harlow, JP Costantino, T Ashikaga, D Weaver, EP Mamounas, N Wolmark

Lancet Oncology, 9/2010



B-32: SN Detection Methods

Tchnetium sulfur colloid

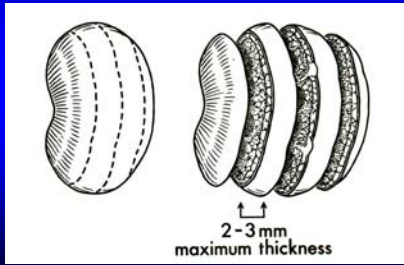


Blue dye



Palpation (~2% cases)

B-32: Standardized Path Protocol



Intraop- Cytology
Postop- HE

B-32: Core Trainers

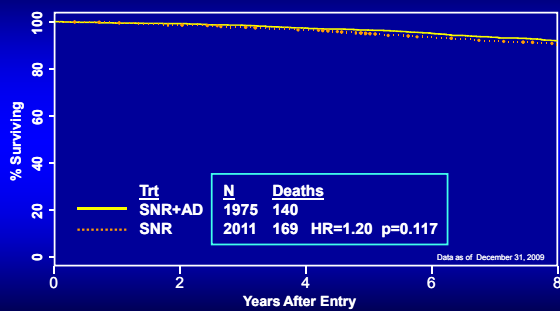


B-32 Analysis Plan

- 3,989 - SN neg (71% of 5611)
- 99.9% - follow-up information
- 95 months - average time on study
- Primary endpoints OS, DFS, Regional Control
- Study powered to detect 2% difference OS

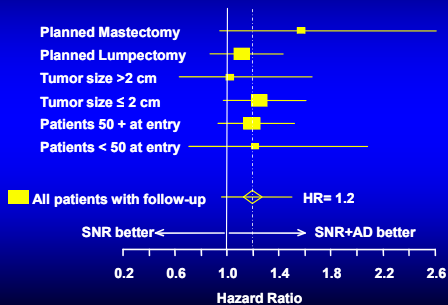
NSABP Protocol B-32

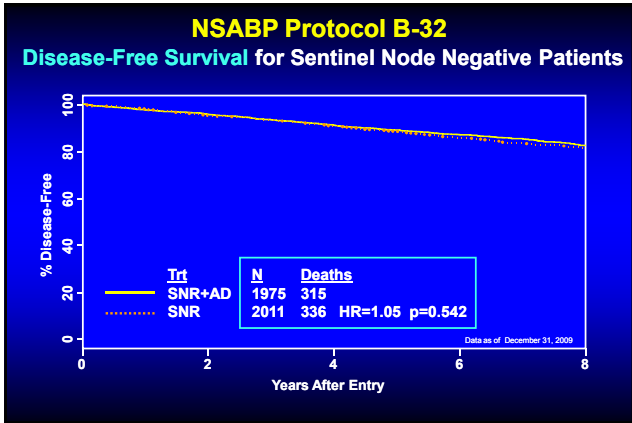
Overall Survival for Sentinel Node Negative Patients

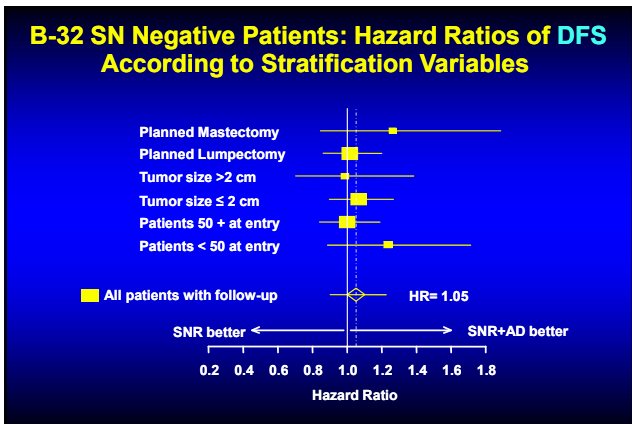


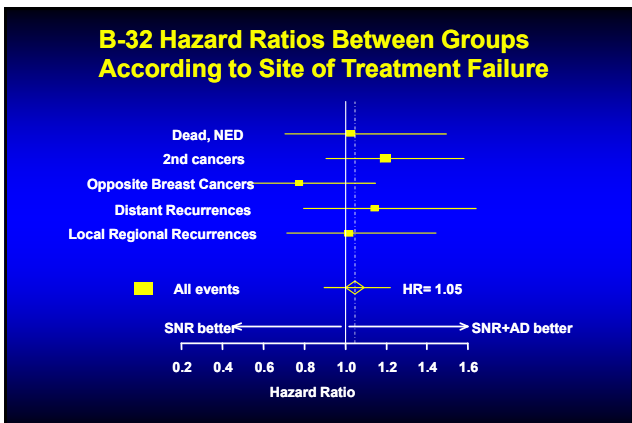
* 300 deaths triggered the definitive analysis
 * 309 reported as of 12/31/2009

B-32 SN Negative Patients: Hazard Ratios of OS According to Stratification Variables









Local and Regional Recurrences as First Events

	Group 1	Group 2
Local	54 (2.7%)	49 (2.4%)
Axillary	2 (0.1%)	8 (0.3%)
Extra-axillary	5 (0.25%)	6 (0.3%)

Residual Morbidity at End of Follow-up

- Lower in SN group
- Not nonexistent

	Group 1 SN + AD	Group 2 SN
Shoulder abduction deficit	19%	13%
Arm volume difference >5%	28%	17%
Arm numbness	31%	8%
Arm tingling	13%	7%

Ashikaga et al JSO in press

All differences p<0.001

B-32: Conclusion

- No significant differences were observed OS, DFS, or Regional Control
- Morbidity decreased
- * When the SN is negative, SN surgery alone with no further AD is appropriate, safe, and effective therapy for breast cancer patients with clinically negative lymph nodes.

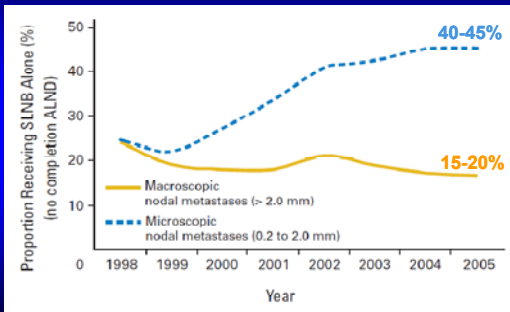
SNB: Areas of Remaining Controversy and Future Directions

- Significance and management of IHC+ SNs and SNs positive for micrometastases
- Role of SNB in patients with DCIS
- Role of SNB in patients receiving neoadjuvant chemotherapy

Extensive Pathologic Evaluation of SNs and Minimal SN Involvement

- Multiple serial sectioning and IHC staining yield additional metastases in 10-30% of pts with negative SNs on routine H&E staining
- The clinical significance of identifying minimal SN involvement by the more sensitive techniques is a subject of controversy
- This question can only be definitively answered in large prospective trials of SNB +/- AND
- Retrospective outcome studies are subjected to selection bias regarding the use of AND/XRT or adjuvant systemic therapy

Rates of SLNB Alone in Pts With (+) SLN NCDB 1998-2005



Bilimoria C et al. J Clin Oncol 2009

2010 AJCC Breast Cancer Staging

- **pN0**: No regional LN metastases identified histologically
- **pN0(i-)**: No regional LN metastases identified histologically, negative IHC
- **pN0(i+)**: Malignant cells in regional LN(s) no greater than 0.2 mm (detected by H&E or IHC including ITCs)
- **pN0(mol-)**: No regional LN metastases histologically, negative molecular findings (RT-PCR)
- **pN0(mol+)**: Positive molecular findings (RT-PCR) but no regional LN metastases detected by histology or IHC
- **pN1mi**: Micrometastases (greater than 0.2 mm and/or more than 200 cells but none greater than 2.0 mm).

2010 AJCC Breast Cancer Staging

- **Stage 0:** Tis N0 M0
- **Stage IA:** T1* N0 M0
- **Stage IB:** T0 N1mi M0
T1* N1mi M0
- **Stage IIA:** T0 N1** M0
T1* N1** M0
- **Stage IIB:** T2 N0 M0
T3 N0 M0

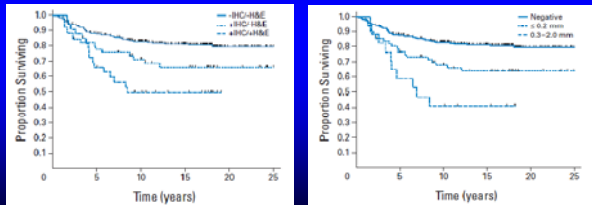
* T1 includes T1mi (microinvasion \leq 1mm)
 ** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified as Stage IB

Prognostic Significance of Occult Micrometastases in Axillary Nodes

Author	Type/Period	Results
Dowlatshahi (1997)	Review of all reported series 1948-1960	Definite survival disadvantage with occult metastases
Sakorafas (2004)	Review of all reported series 1966-2003	Micrometastases associated with worse prognosis
Kulijt (2005)	Eindhoven Ca Reg (1975-1997) (n=10,111)	Pts with micrometastases have worse survival
Maibenco (2006)	SEER Data (T1 tumors) 1988-2001 (n=43,921)	Slightly elevated risk of death with solitary (5.0%) or multiple (3.6%) micrometastases
Chen (2007)	SEER Data 1992-2003 (n=209,720)	Pts with micrometastases have intermediate prognosis between node (-) and node (+)

MSKCC Occult Axillary Metastases in BC 20-Year Follow-Up

- 368 pts diagnosed between 1976-78
- No systemic therapy
- Negative ALNs were examined per SLN protocol



Tan L et al. J Clin Oncol 2006.

Prognostic Implications of ITCs and MMs Moffitt Cancer Center Study

- Between 1997-2004, 2,381 patients underwent SLNB
 - 2108 were pN0(i-)
 - 122 were pN1mi (97 underwent AND)
 - 151 were pN0(i+) (107 underwent AND)
- DFS and OS was worse for pts with pN1mi compared to those with pN0(i-)
- DFS and OS were not different between pts with pN0(i+) and those with pN0(i-)

Cox C et al. J Am Coll Surg 2008.

Prognostic Implications of ITCs and MMs John Wayne Cancer Institute Study

- Between 1992-1999, 790 patients with stage I-II invasive BC were accrued in a prospective study:
 - 486 (62%) negative SLN
 - 84 (11%) ITCs (67 underwent AND)
 - 54 (7%) micrometastases (48 underwent AND)
 - 166 (21%) macrometastases
- Mean follow up: 72.9 months
- Patients with pN0(i+) or pN1mi did not have significantly worse 8-year DFS or OS compared with SN-negative patients

Hansen, et al. J Clin Oncol 2009

Prognostic Implications of ITCs and MMs Anne Arundel SN Multicenter Study

- Between 1996-2005, 1,259 patients were accrued
 - 893 (71%) negative SLN
 - 25 (2%) ITCs (13 underwent AND)
 - 57 (5%) micrometastases (41 underwent AND)
 - 284 (23%) macrometastases
- Mean follow up: 4.9 years
- Distant recurrence rates: 6%, 8% 14% and 21%
- Presence of **MMs was associated with worse DFS** compared to pts with negative nodes ($p < 0.02$)

Reed J, et al. J Am Coll Surg 2009.

Micrometastases and Isolated Tumor Cells as Prognostic Factors: the MIRROR Study

• Patients with favorable primary tumor characteristics
No indication for adjuvant systemic therapy
• Sentinel node procedure
• pN0, pN0(i+) or pN1mi

• >35 yrs
• 1-3 cm/grade I-II
• <1 cm/any grade

pN0
No adjuvant therapy

pN0(i+) or pN1mi
No adjuvant therapy

pN0(i+) or pN1mi
Adjuvant therapy

- Patients selected from the Netherlands Cancer Registry (1997-2005)
- Primary endpoint: 5-year disease-free survival (DFS)

de Boer et al. SABCS 2008. Abstract 23.

MIRROR Study: Outcomes According to SLN Status No Adjuvant Systemic Therapy

	pN0 (n = 838)	pN0(i+)/pN1mi (n = 832)	pN0(i+) (n = 505)	pN1mi (n = 327)
5-year DFS	86%	77%	77%	76%
P value*	NA	.0001	< .001	.003
Recurrence				
HR	1.00	1.49	1.50	1.52
P value*	NA	.001	.003	.009

* Compared to pN0

de Boer et al. SABCS 2008. Abstract 23.

**MIRROR Study:
Outcomes of Pts with Minimal SLN Involvement**

± Adjuvant Systemic Therapy

	pN0(+)/pN1mi		pN0(+)		pN1mi	
	- AST (n = 832)	+ AST (n = 958)	- AST (n = 505)	+ AST (n = 296)	- AST (n = 327)	+ AST (n = 662)
5-year DFS	77%	86%	77%	83%	76%	88%
P value*	NA	< .0001	NA	< .05	NA	< .0001
Recurrence						
HR	1.00	0.57	1.00	0.67	1.00	0.50
P value*	NA	< .0001	NA	.03	NA	.0002

* Compared to - AST

AST: Adjuvant Chemotherapy:10%, Hormonal Therapy: 63%; Both: 23%

de Boer et al. SABCS 2008. Abstract 23.

**2010 ASCO: ACOSOG Z0010 Trial
Abstract CRA 505**

- 5,539 pts were entered in a prospective, multicenter observational study to determine the clinical significance of SN and BM micromets
- Lumpectomy + SNB + bilateral iliac crest BM aspiration
- SN and BM were evaluated by central IHC and results were not reported to the investigator or treating clinician
- SNs were successfully identified in 5,184 pts (94.5%)
- Histologic SN mets were found in 23.9%
- IHC detected additional 350 pts (10.5%) with SN mets
- BM mets were identified by IHC 3% of the pts

Cote R et al Proc ASCO 2010 CRA 504

**2010 ASCO: ACOSOG Z0010 Trial
5-Year Overall Survival by SN and BM Status**

Group	% Alive in 5 Years	P value
SN Histology Status		
Positive	92.8 (91.3-94.3)	0.0002
Negative	95.6 (95.0-96.3)	
SN IHC Status		0.53
Positive	95.1 (92.7-97.7)	
Negative	95.8 (95.0-96.5)	
BM IHC Status		0.015
Positive	90.2 (84.6-96.2)	
Negative	95.1 (94.3-95.8)	

Cote R et al Proc ASCO 2010 CRA 504

Meta-Analysis of Non-SN Positivity Associated with Minimal SLN Involvement

- 25 studies reporting on non-SN involvement associated with low-volume SN involvement (789 pts H&E (+) SNs, 345 pts IHC (+) SNs)
- The weighted mean estimate for non-SN metastases after low-volume SN involvement is around 20 %
- The incidence is around 9 % if the SN involvement is detected by IHC alone

Coemi G, et al. Br J Surg. 2004

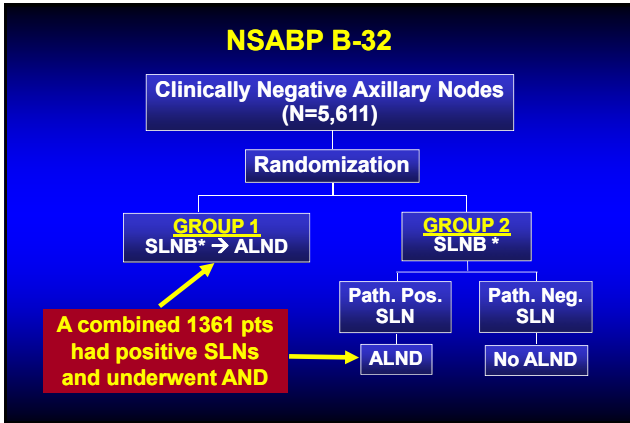
Rates of Non-SLN Involvement in Pts with Isolated Tumor Cells in the SLN Systematic Review

- 29 studies including 836 patients
- Overall pooled risk of NSN involvement: 12.3%
- 64% of pts with NSLN involvement had macromets
- Patients with ITCs in the SLN without other indications for adjuvant systemic therapy might be candidates for axillary dissection

Van Deurzen C, et al. J Nail Cs Inet 2008

Identification of Subsets at Low Risk for non-SLN Involvement Questions

- Is there a threshold of comfort where AND can be omitted ?
- Can we reliably identify subgroups at or below that threshold?
- Does omitting AND impact on overall survival or local recurrence?
- Can we manage these patients with other modalities (adjuvant chemo, adjuvant XRT)?



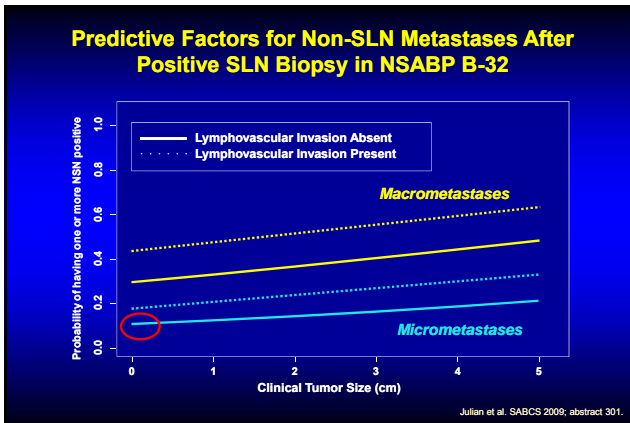
Predictive Factors for Non-SLN Metastases After Positive SLN Biopsy in NSABP B-32

Multivariate Analysis

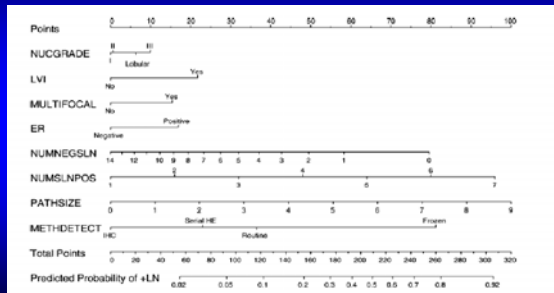
Variable	SE	P Value	Odds Ratio (95% CI)
Metastasis Type (Micro, Macro)	0.190	< .0001	3.42 (2.36-4.96)
Lymphatic Invasion (Negative, Positive)	0.175	.0004	1.85 (1.31-2.61)
Clinical Tumor Size ^a	0.079	.044	1.17 (1.004-1.37)

^a Continuous variable

Julian et al. SABCS 2009; abstract 301.

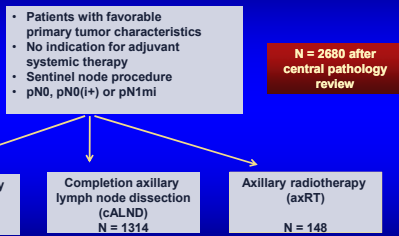


Nomogram to Predict Likelihood of Positive Non-SN with Positive SN



Van Zee et al., Ann Surg Oncol., 2003

Omission of Axillary Therapy in Patients with pN1mi or pN0i+ by SLNB: MIRROR Study



- Patients selected from the Netherlands Cancer Registry (1998-2005) (N = 3205)
- Median follow-up: 4.7 years

Tjan-Heijnen et al. J Clin Oncol 2009; 27 (suppl): 18s (abstract CRA506)

Omission of Axillary Therapy in Patients with pN1mi or pN0i+ by SLNB: MIRROR Study

Results: Multivariate Analysis

Sentinel node status	Axillary therapy	N	5-yr axillary recurrence	HR	95 % CI
pN0	cALND	125	1.6%	1.00	Reference
	SN only	732	2.3%	1.08	0.23 – 4.98
pN0 (i+)	cALND/axRT	450	0.9%	1.00	Reference
	SN only	346	2.0%	2.39	0.67 – 8.48
pN1mi	cALND/axRT	887	1.0%	1.00	Reference
	SN only	141	5.0%	4.39*	1.46 – 13.24

HR corrected for age, tumor size, grade, hormone receptor status, adjuvant systemic therapy and radiotherapy to the breast

* Statistically significant compared to cALND/axRT

Tjan-Heijnen et al. J Clin Oncol 2009; 27 (suppl): 18s (abstract CRA506)

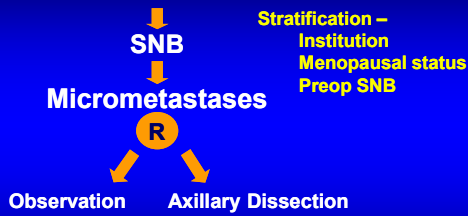
SLN Biopsy Patterns and Outcomes NCDB 1998-2005

- 97,314 patients with SLN metastases in the NCDB
- 21% underwent SLNB alone
- In pts with macrometastases (n=20,075 during 1998 to 2000), there was a non significant trend toward better outcomes for SLNB+ALND vs. SLNB*:
 - Axillary recurrence HR: 0.58 (95% CI, 0.32 - 1.06)
 - Overall survival HR: 0.89 (95% CI, 0.76 - 1.04)
- In pts with micrometastases (n=2,203 during 1998 to 2000), there were no significant differences in axillary recurrence or survival between the 2 groups

*adjusted

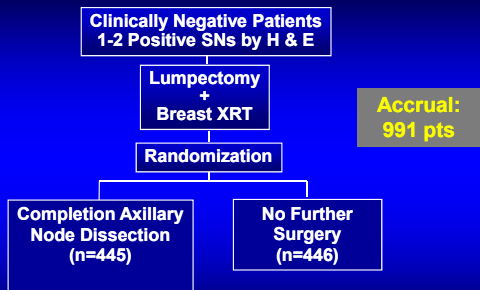
Bilimoria C. et al: J Clin Oncol 2009

IBCSG TRIAL 23-01 T ≤ 5 cm cN0



- Target sample size: 1,960
- Opened: April, 2001

ACOSOG Z0011



Accrual:
991 pts

Adjuvant systemic therapy
at the discretion of treating physician

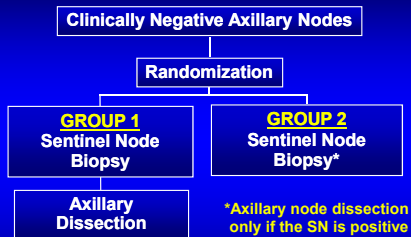
Giuliano AE et al: Proc ASCO 2010, CRA 506

ACOSOG Z0011 Results

Endpoint	SNB Alone	Completion AND	P value
Median Number of Nodes Removed	2	17	
3 or More Positive Nodes	5%	17.6%	<0.001
5-Year In Breast Recurrence	2.1%	3.7%	0.16
5-Year Axillary Nodal Recurrence	1.3%	0.6%	0.44
5-Year Overall Survival	92.5%	91.9%	0.24
5-Year DFS	83.8%	82.2%	0.13

Giuliano AE et al: Proc ASCO 2010, CRA 506

NSABP B-32 Schema



IHC and detailed pathologic examination of the SNs performed centrally and results were not disclosed

Is Axillary Radiation an Alternative to Axillary Dissection in Patients with Minimal SN Involvement?

- Randomized trials comparing the two approaches are ongoing (AMAROS)
- Low axillary recurrence rates have been demonstrated in small studies of axillary XRT:
 - Short follow-up
 - Highly selected subgroups of patients
- Most available data on local control are with axillary dissection

DCIS and SNB

- By definition DCIS does not metastasize to nodes
- Routine AND was removed from clinical trials
- Historically node positive rate < 2%
- Recent data 10-15% positive SNB rate is associated with microinvasive or invasive cancer found with the DCIS
- High percentage of positive SNB by IHC
- **Outcomes poorly understood or established**

When to perform SNB in DCIS?

- Extensive DCIS requiring a mastectomy
 - Technically unable to perform SNB after Mx
- Following a lumpectomy for DCIS in which microinvasive or invasive disease is found after lumpectomy

Neoadjuvant Chemotherapy

- NC provides significant tumor down sizing
- NC provides significant axillary down staging
- **Is SNB after NC as feasible and accurate as before systemic therapy?**
- **By doing SNB after NC, do we lose information that is important for further patient management?**

SNB Experience After NC

- Limited experience
- Early - 12 single institutions – ID rate 89%, FNR 10.8%
- Late - 6 single institutions – ID rate 89%, FNR 8.1%

SNB After NC: Single Institution Series Positive Axillary Nodes Before NC

Author	Stage	# Pts (Node +)	Success Rate (%)	FN Rate (%)	Accurate
Shen, 2006	T1-T4, N1-N3	69(40)	93	25	No
Lee, 2006	T1-T4, N1 (Palpable and FNA (+) or > 1cm thick with loss of fat hilum on US and SUV > 2.5	219 (124)	78	6	Yes
Newman, 2007	Resectable T1-3, N1 (FNA (+) under US)	40 (28)	98	11	Yes
All		328 (172)	84	11.6	

SNB After NC Multi-Center Studies: NSABP B-27 (n=428)

- Identification Rate: 85%
 - With blue dye: 78%
 - With isotope \pm blue dye: 88-89%
- False Negative Rate: 11%
 - With blue dye: 14%
 - With isotope \pm blue dye: 8.4%

Clinically Node (-): 12.4%
Clinically Node (+): 7.0% } P=0.51

Mamounas EP. J Clin Oncol. 2005

SNB After NC
Meta-Analysis of Single-Institution and Multi-Center Studies

- 21 studies
- 1273 patients
- Identification Rates: 72-100%
 - Pooled estimate: 90%
- False Negative Rates: 0-33%
 - Pooled estimate: 12%

SNB Before NC: Arguments in Favor

- Information on the status of SN can be obtained without the confounding effects of NC
- This may provide an advantage regarding:
 - Further surgical management of the axilla
 - Selection of optimal NC or adjuvant chemo after NC
 - Selection of optimal loco-regional XRT

SNB Before NC: Pros and Cons

- This approach can be helpful if SN is negative
- Patients with large operable breast cancer have high likelihood of positive nodes (50-70%)
- This approach does not take advantage of the downstaging effects of NC on nodes: 30-40% conversion from (+) to (-) and avoidance of AND

SNB Before NC: Selection of Optimal NC?

- May be useful in patients who will not need chemotherapy if the SN is negative (uncommon situation among typical candidates for NC)
- Usually original tumor size, age and primary tumor markers are good guides for appropriate NC

**SNB Before NC:
Selection of Loco-Regional XRT?**

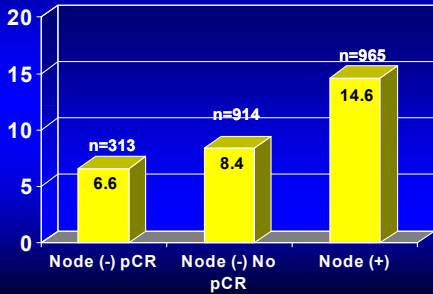
Can We Use Tumor and Nodal Response to NC in Order to Individualize the Use of L-R XRT?

**LRF Update: NSABP B-18/B-27
MVA: Predictors of LRF
(2192 pts and 229 events)**

Variable	Hazard Ratio	P-Value
Clin. Tumor Size 2.1-5 vs. 0-2 cm	0.86	
Clin. Tumor Size > 5 vs. 0-2 cm	1.36	0.01
Clin. Node (+) vs. Clin. Node (-)	1.60	0.0007
Node(-)/No pCR vs. Node(-)/pCR	1.42	
Node(+) vs. Node(-)/pCR	2.58	<0.0001

Mamounas EP: NCI Conference on Preoperative Therapy 2007

LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by
Path Nodal Status and pCR



Mamounas EP: NCI Conference on Preoperative Therapy 2007

SNB and NC

- For patients with operable BC, SNB **after** NC is feasible and accurate with similar performance characteristics to SNB before NC
- By performing SNB **after** NC, up to 40 percent of patients who present with involve axillary nodes may be spared from axillary dissection
- SNB **before** NC does not offer particular clinical advantages and reduces the number of patients who could benefit from the down-staging effect of NC in the axillary nodes

ACoSOG Z1071 and QUEBEC Schemas

T1-4 N1-2 invasive breast cancer
 (pretreatment axillary ultrasound with FNA or core biopsy documenting axillary metastases)

↓
 REGISTER*

↓
 Patients receive neoadjuvant chemotherapy
 (stratify patients by age, stage and number of cycles and type of chemotherapy)

↓
 REGISTER*

↓
 SLN and ALND

*Patients can be registered pre or post chemotherapy

Conclusions

- SNB accurately predicts axillary nodal status with decreased morbidity compared to axillary dissection
- SN micrometastases and IHC positivity are of clinical uncertainty and hence AND is controversial
- Long-term outcome data from large randomized trials have recently been presented
- The role of SNB for DCIS is very limited
- SNB following neoadjuvant therapy benefits the patient due to down staging of the axilla and avoiding needless AND. Trials pending.

Summary

CLINICAL TRIALS LEAD THE WAY
