National Cancer Institute

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Sentinel Node Biopsy After Neoadjuvant Chemotherapy: The Pros

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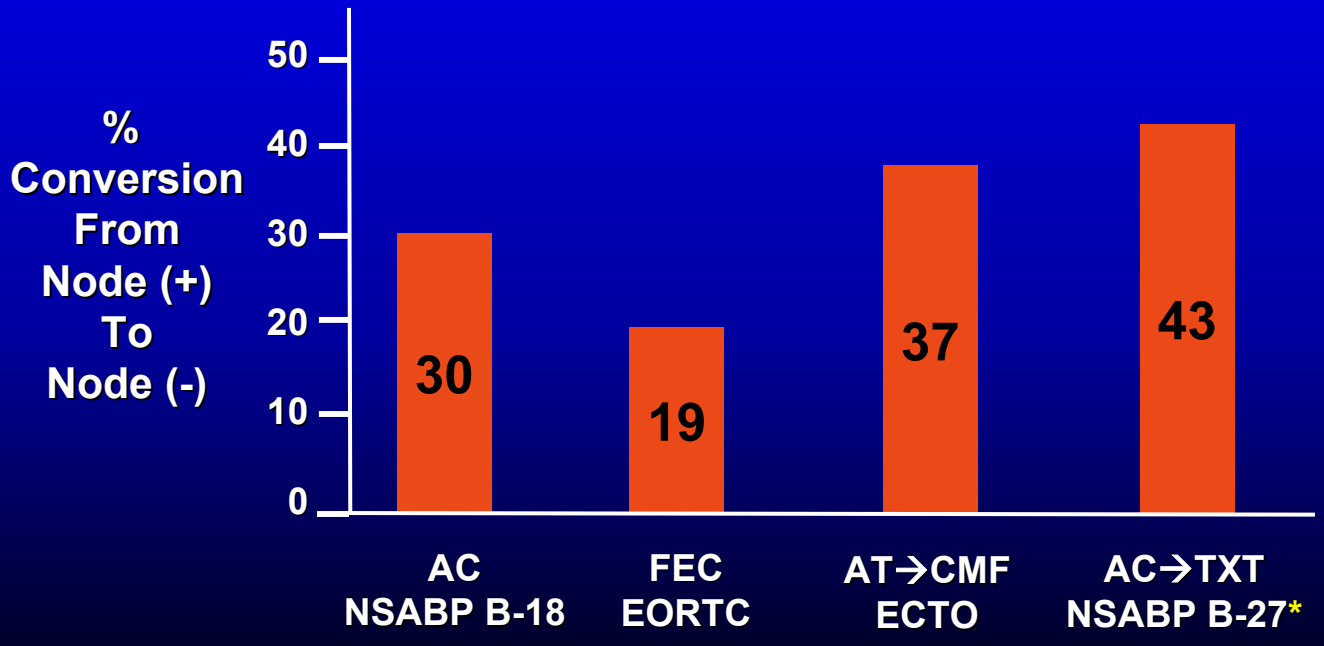
National Institutes of Health

Original Clinical Rationale for Neoadjuvant Chemotherapy

- Convert inoperable BC to operable BC
- Convert operable BC patients requiring mastectomy to candidates for BCS

Axillary Node Down-Staging with NC



*Assuming 30% nodal down-staging with neoadjuvant AC

Effect of NC on Axillary Nodal Metastases

- NC downstages axillary nodes in about 20-40% of the patients
- This was of no particular clinical significance when axillary dissection was the sole method for staging the axilla

Effect of NC on Axillary Nodal Metastases

- The advent of sentinel node biopsy introduced another potential benefit from neoadjuvant chemotherapy
- Potential for decreasing the extent of axillary surgery with SNB vs. AND if the axillary nodes are down-staged with NC

SNB After NC
Two Main Reasons Given by Those Who Oppose It

1. It does not work as well as it does before systemic therapy
2. By doing SNB after NC, we lose information that is important for further patient management

SNB After NC
Two Main Reasons for Opposing It

1. It does not work as well as it does before systemic therapy
2. By doing SNB after NC, we lose information that is important for further patient management

SNB After NC

- Is SNB after NC as feasible and accurate as before systemic therapy?
  - Does response to NC cause scarring that could affect the lymphatic drainage making SN identification more difficult and/or less accurate?
  - Is NC equally effective in down-staging SNs and non-SNs

SNB After NC
Feasibility and Accuracy

- Information from:
  - Single institution trials
  - Multicenter Trials
  - Meta-Analyses

SNB After NC
Single Institution Experience

- Limited early experience with SNB after NC
- Initial small studies have shown variability in:
  - Rates of SN identification (72-100%)
  - Rates of false negative SN (0%-33%)

SNB After NC: Single Institution Series

Author	# Pts (Node +)	Success Rate (%)	FN Rate (%)	Accurate
Breslin, 2000	51 (25)	84	12	Yes
Nason, 2000	15 (9)	87	33	No
Stearns, 2002	34 (13)	85	14	Yes*
Fernandez, 2001	40 (16)	85	25	No
Haid, 2001	33(18)	88	0	Yes
Miller, 2002	35 (9)	86	0	Yes
Reitsamer, 2003	30 (15)	87	7	Yes
Brady, 2002	14 (11)	93	0	Yes
Schwartz, 2003	21 (11)	100	9	Yes
Balch, 2003	32 (19)	97	5	Yes
Aihara, 2004	20 (12)	85	8	Yes
Piato, 2003	42 (18)	98	17	Yes
All	398 (182)	89.1	10.8	

*Not in IBC

SNB After NC: Single Institution Series

Author	# Pts (Node +)	Success Rate (%)	FN Rate (%)	Accurate
Kang, 2004	54 (27)	72	11	Yes
Jones, 2005	36 (18)	81	11	No
Kinoshita, 2006	77 (27)	94	11	Yes
Shimazu, 2004	47 (33)	94	12	Yes
Julian, 2004	42 (19)	95	0	Yes
Lang, 2004	53 (24)	94	4	Yes
All	309 (160)	88.7	8.1	

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

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

Mamounas EP: J Clin Oncol, 2005

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

Conclusion:
SNB is a reliable tool for planning treatment after NC

Comparison of False Negative Rates Between SN Multicenter Studies

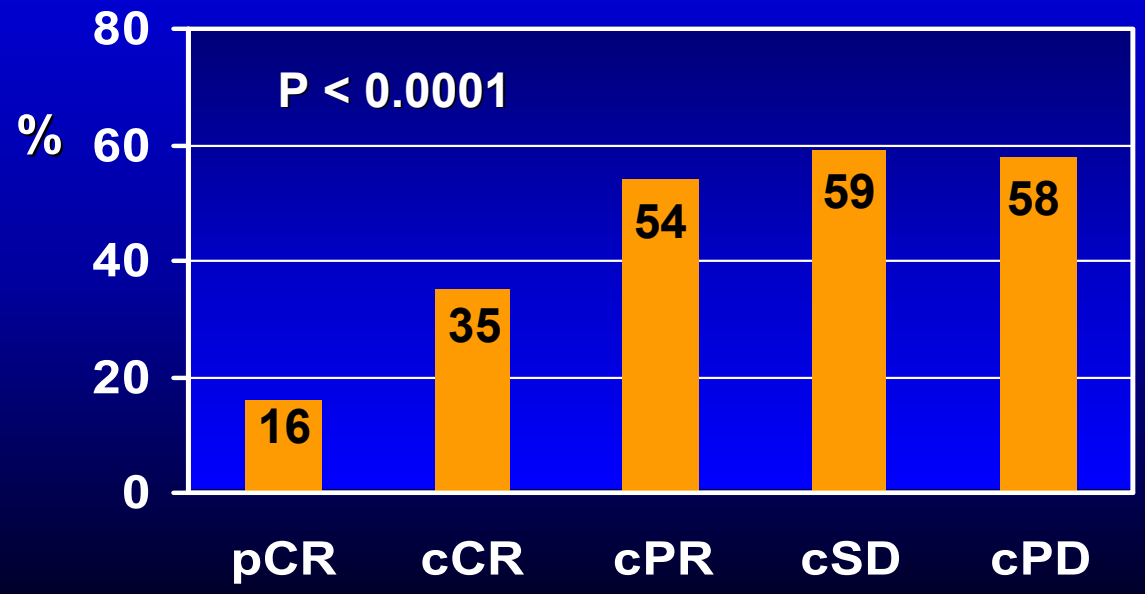
Study	FNR	(SN-/N+)
Multicenter SB-2 Trial	11%	(13/114)
Italian Randomized Trial	9%	(8/91)
Ann Arundel	13%	(25/193)
University of Louisville	7%	(24/333)
NSABP B-32 Randomized Trial	10%	(75/766)
NSABP B-27 (After NC)	11%	(15/140)
Meta-Analysis (After NC)	12%	(65/540)

Krag DN: Surg Oncol 1993
Veronesi U: N Engl J Med 2003
McMasters KM: J Clin Oncol 2000
Mamounas EP: J Clin Oncol 2005
Tafra L: Am J Surg 2001
Xing Y:Br J Surg 2005
Julian JB: SABCS 2004

SNB After NC: Optimal Candidates

- Optimal candidates should have low risk for a positive non-SN
- SNB inaccuracy rate is a function of:
  - False Negative Rate
    - »Anatomic variability
    - »Surgeon's performance
  - Rate of axillary node positivity

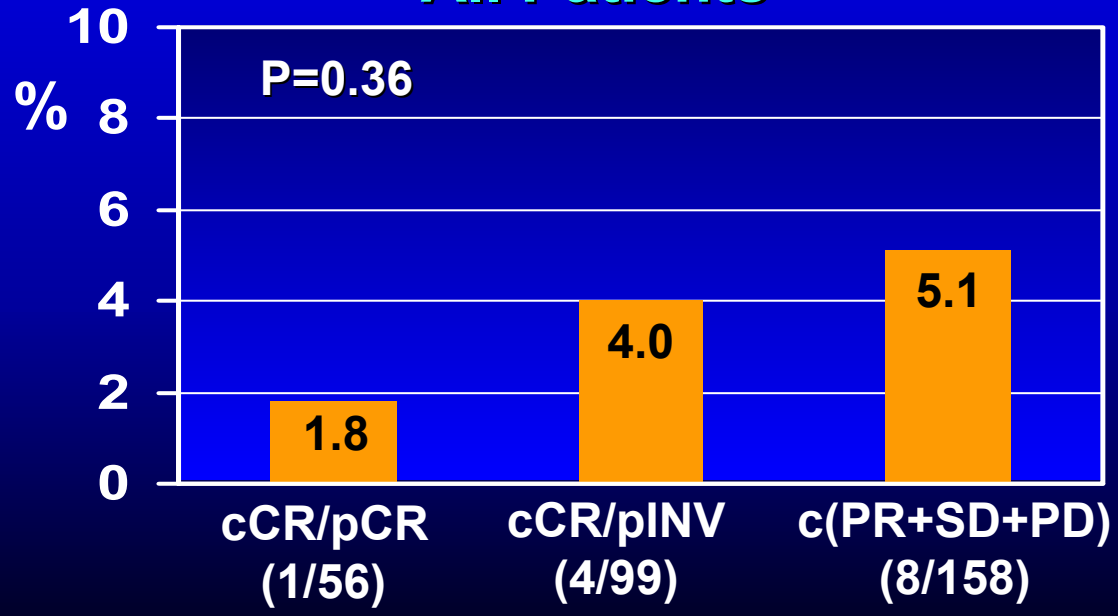
NSABP B-27:Rate of Positive Nodes According to Tumor Response



Bear HD: J Clin Oncol 2003

NSABP B-27: SN Inaccuracy Rate According to Tumor Response

All Patients



Mamounas EP: J Clin Oncol 2005

SNB After NC
Two Main Reasons for Opposing It

1. It does not work as well as it does before systemic therapy
2. **By doing SNB after NC, we lose information that is important for further patient management**

Clinical Assessment of Axillary Nodal Status Before NC

All this is fine

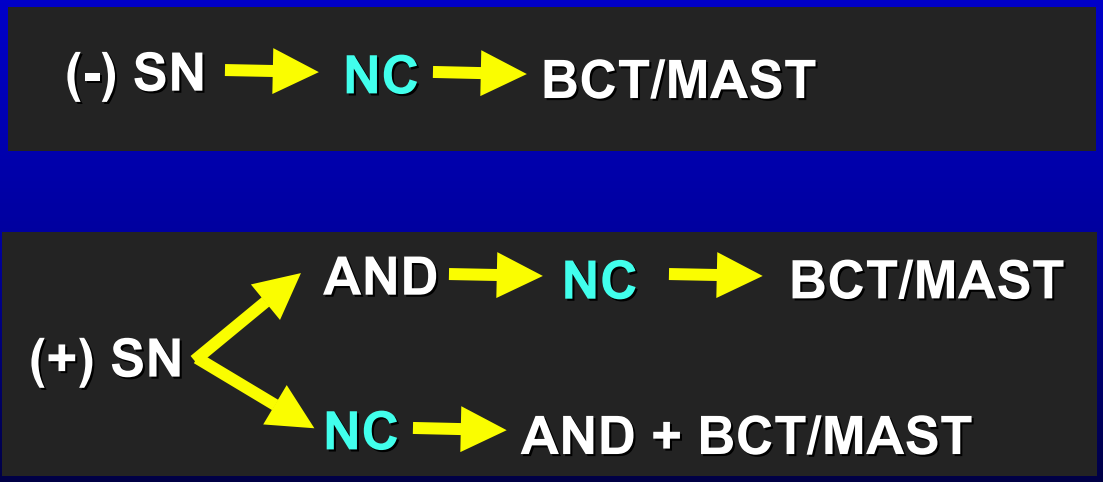
BUT

SNB **Before** NC is not!

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: Two Surgical Procedures



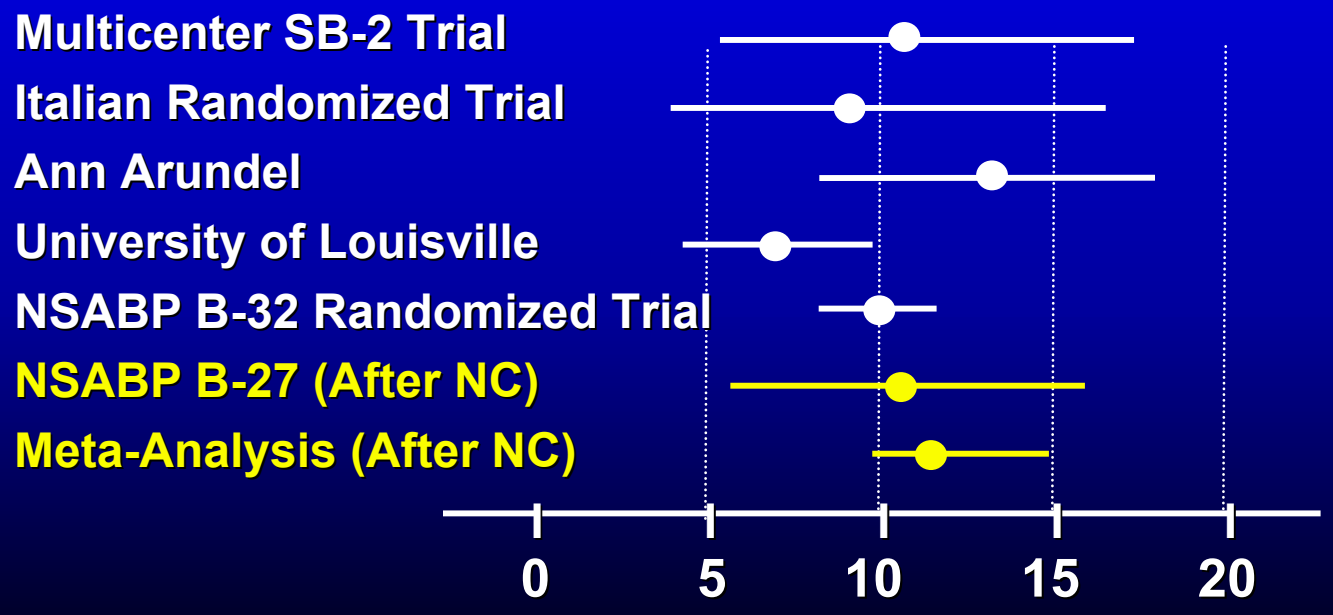
SNB Before NC: Potential Disadvantages

- 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 (-)

SNB Before NC Rather than After NC?

- This approach assumes surgeons are comfortable performing SNB alone before NC but not after NC
- Outcome results from large randomized trials comparing SNB alone with axillary dissection are pending

SNB at Diagnosis vs. After NC
Confidence Intervals Around FNR



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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 Adjuvant Chemo?

- Consideration for adjuvant chemo after NC depends on:
  - What NC was used (anthracyclines only or anthracyclines and taxanes)
  - Clinical and path breast tumor response
  - Status of axillary nodes after NC
- Uncertain significance of negative nodes after NC and prior SNB (downstaging vs. prior removal of all (+) nodes)

SNB Before NC:
Selection of Loco-Regional XRT?

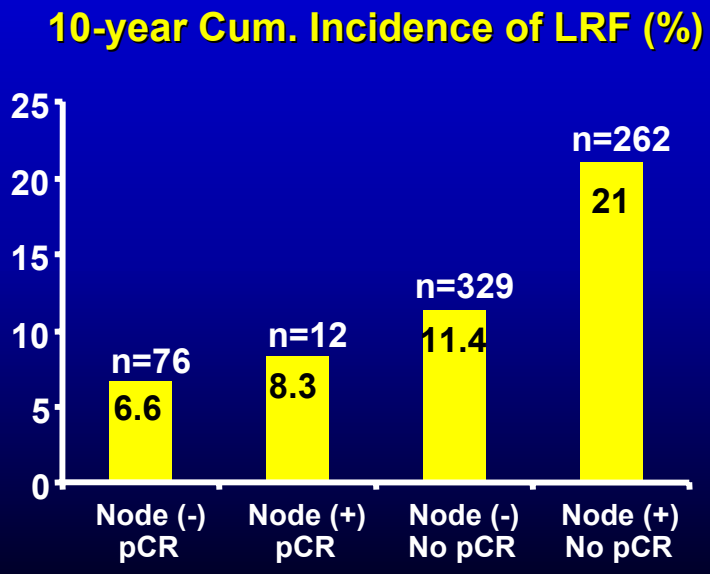
Problem:
Not much information exists on the subject!

NSABP B-18: Predictors of LRF after NC
Multivariate Analysis

Cox Model

Neoadjuvant Chemotherapy

- Number of path-positive nodes ($p<0.0001$)
- Age ($p=0.005$)
- Breast tumor response ($p=0.054$)



Mamounas EP: Br Ca Res Treat 2003

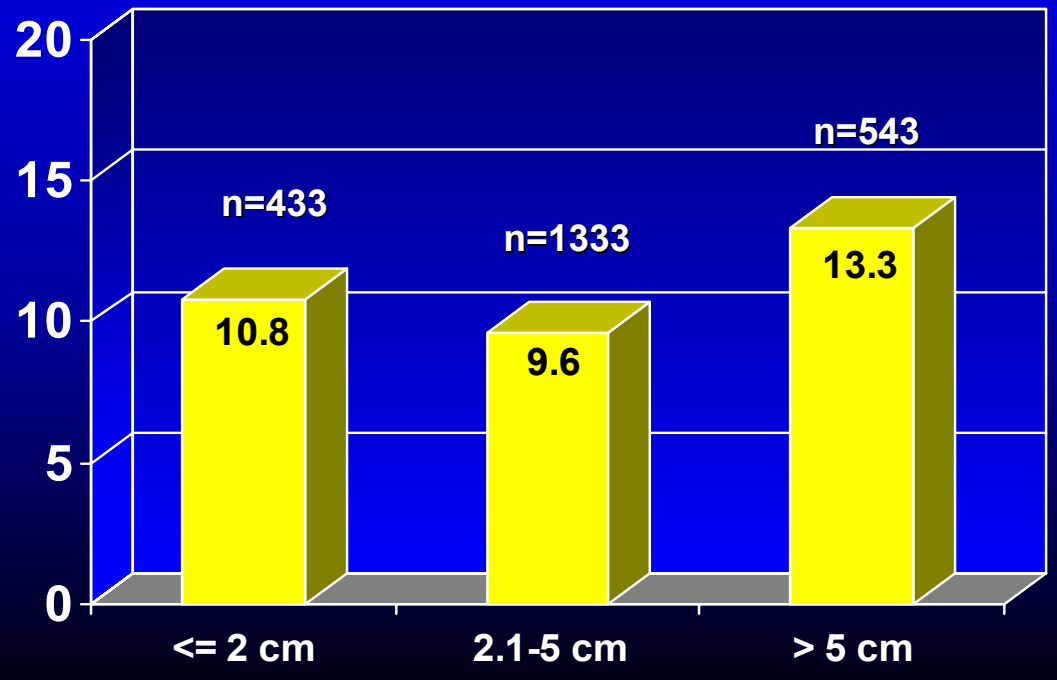
Updated LRF Analysis: NSABP B-18/B-27

- Univariate and multivariate analysis of predictors of LR failure
- Includes the preop AC arms from B-18 and B-27 and the preop AC-->T arm from B-27
- Similar results were obtained by using only the two preop AC arms or by adding the third B-27 arm (AC-->S-->T)
- Analysis is based on 2192 pts and 229 events (LRF)
- Pathologic complete response (pCR) was defined as no invasive disease in the breast and negative axillary nodes

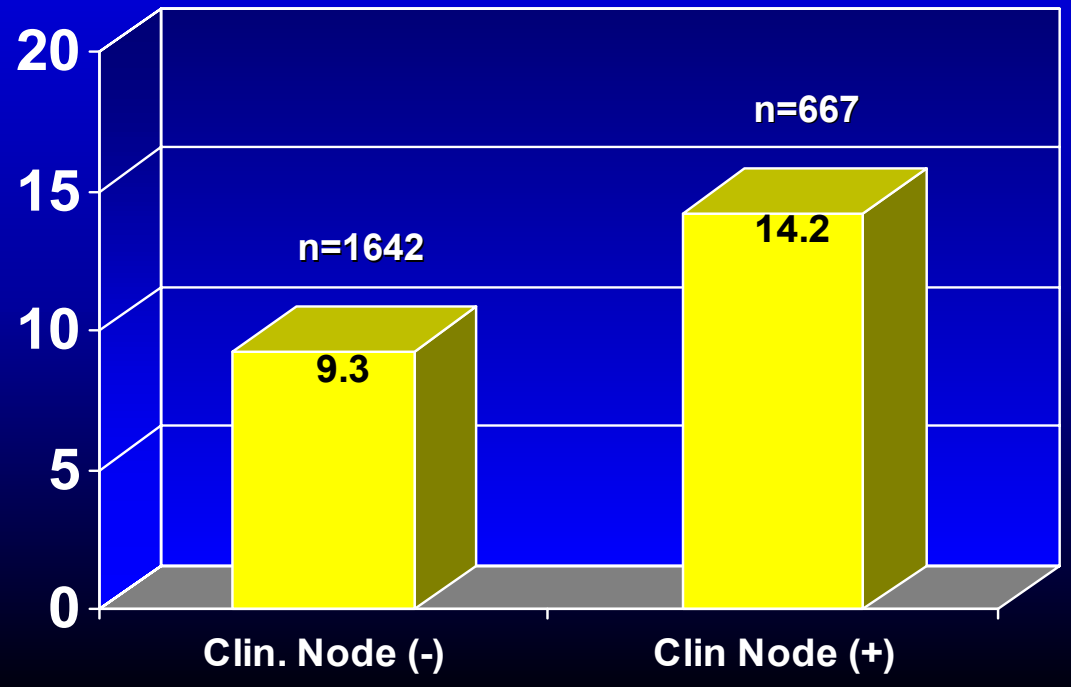
LRF Update: NSABP B-18/B-27
MVA: Predictors of LRF

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

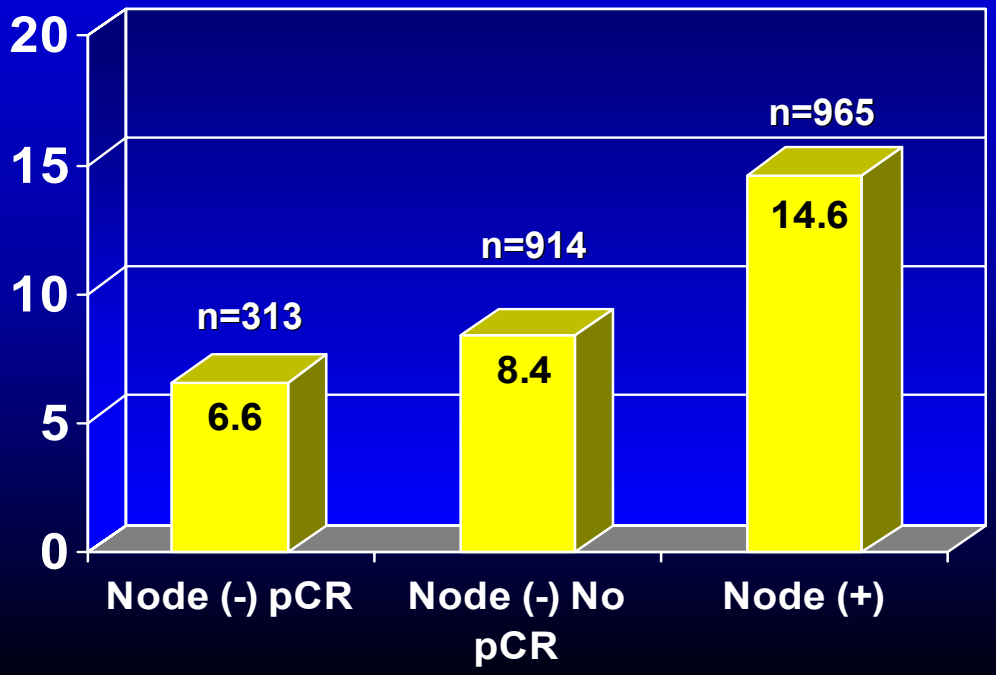
LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by Clinical Tumor Size



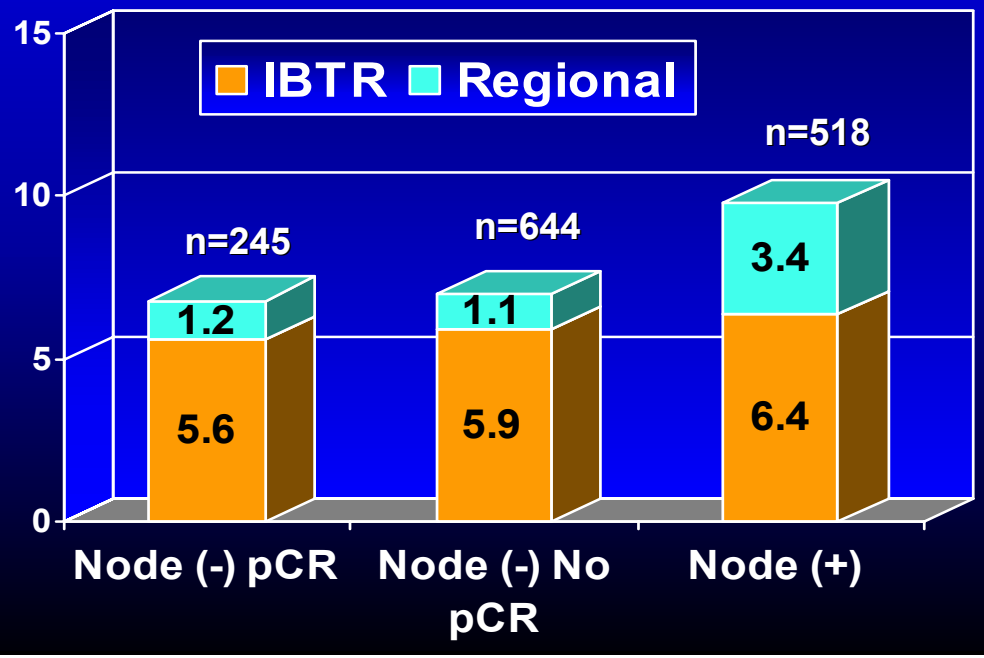
LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by Clinical Nodal Status



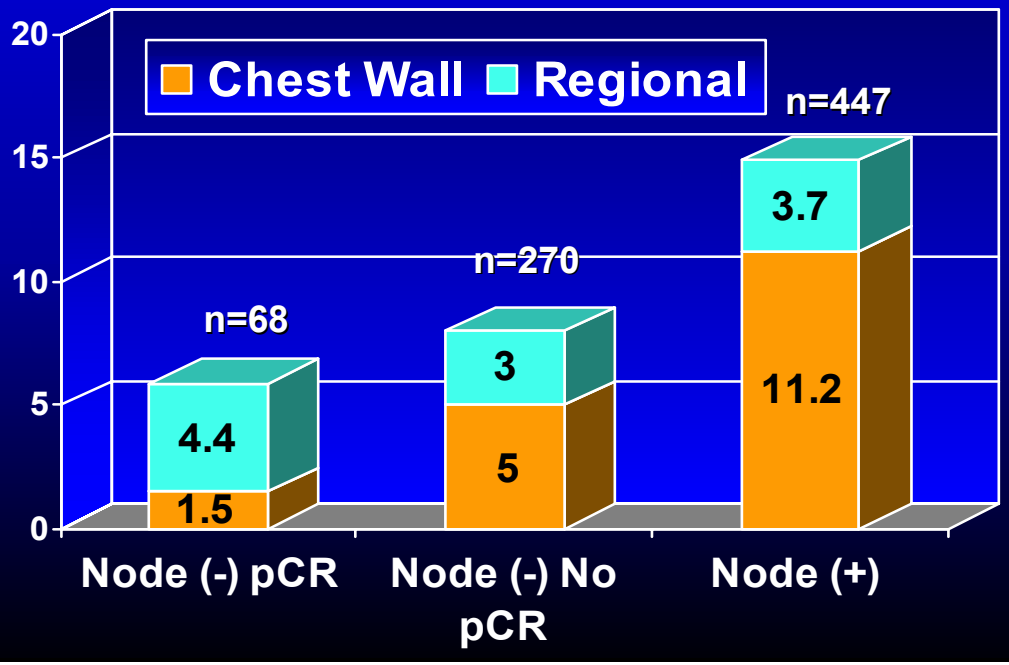
LRF Update: NSABP B-18/B-27
8-Year Cum. Incidence of LRF by Path Nodal Status and pCR



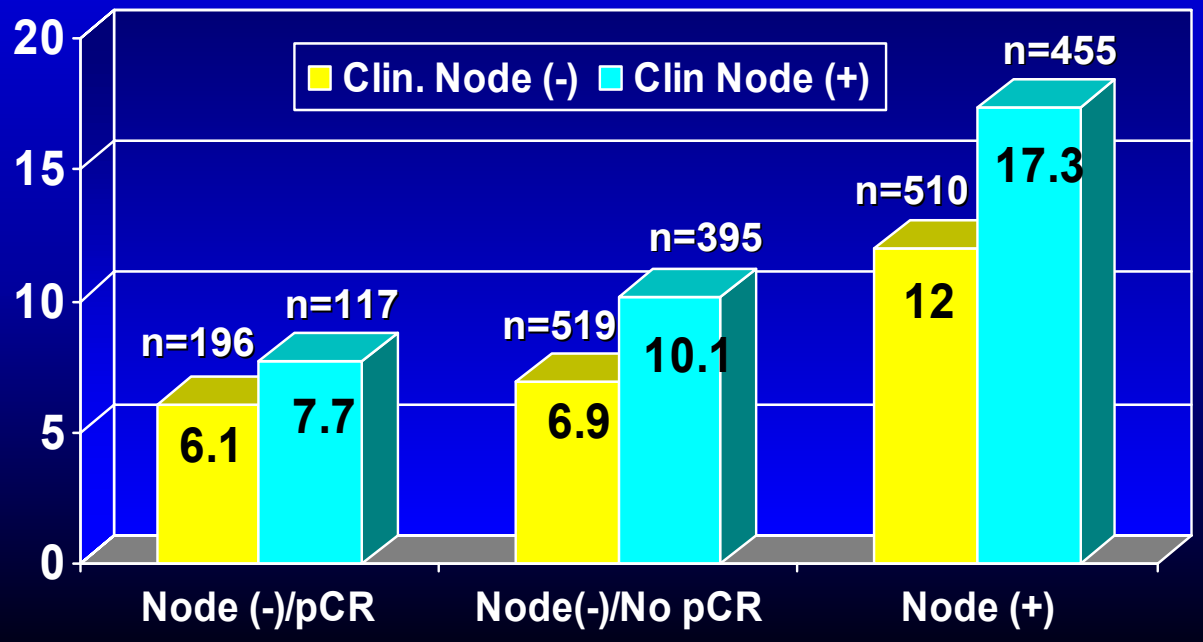
8-Year Cum. Incidence of LRF by Path Nodal Status and pCR (Lumpectomy Pts)



8-Year Cum. Incidence of LRF by Path Nodal Status and pCR (Mastectomy Pts)



8-Year Cum. Incidence of LRF by According to Path Nodal Status/pCR and Clinical Nodal Status



Conclusions

- SNB after NC is feasible and accurate with performance characteristics similar to those for SNB before systemic therapy
- 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