The Role of Sentinel Lymph Node Biopsy and Axillary Dissection

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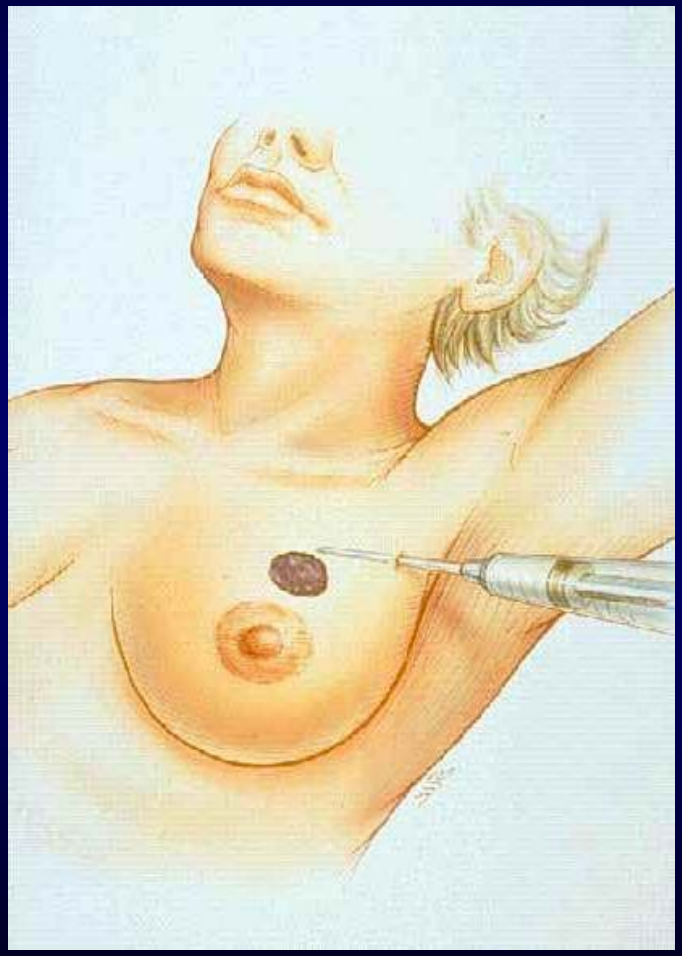
SLN Biopsy

- Revolutionized surgical practice
- Marked decreased need for axillary dissection
- Major decrease in lymphedema, shoulder dysfunction, pain/parasthesia rates

Lymphatic Mapping Technique



Radioactive colloid, blue dye

2010 AJCC Staging Changes: Definitions

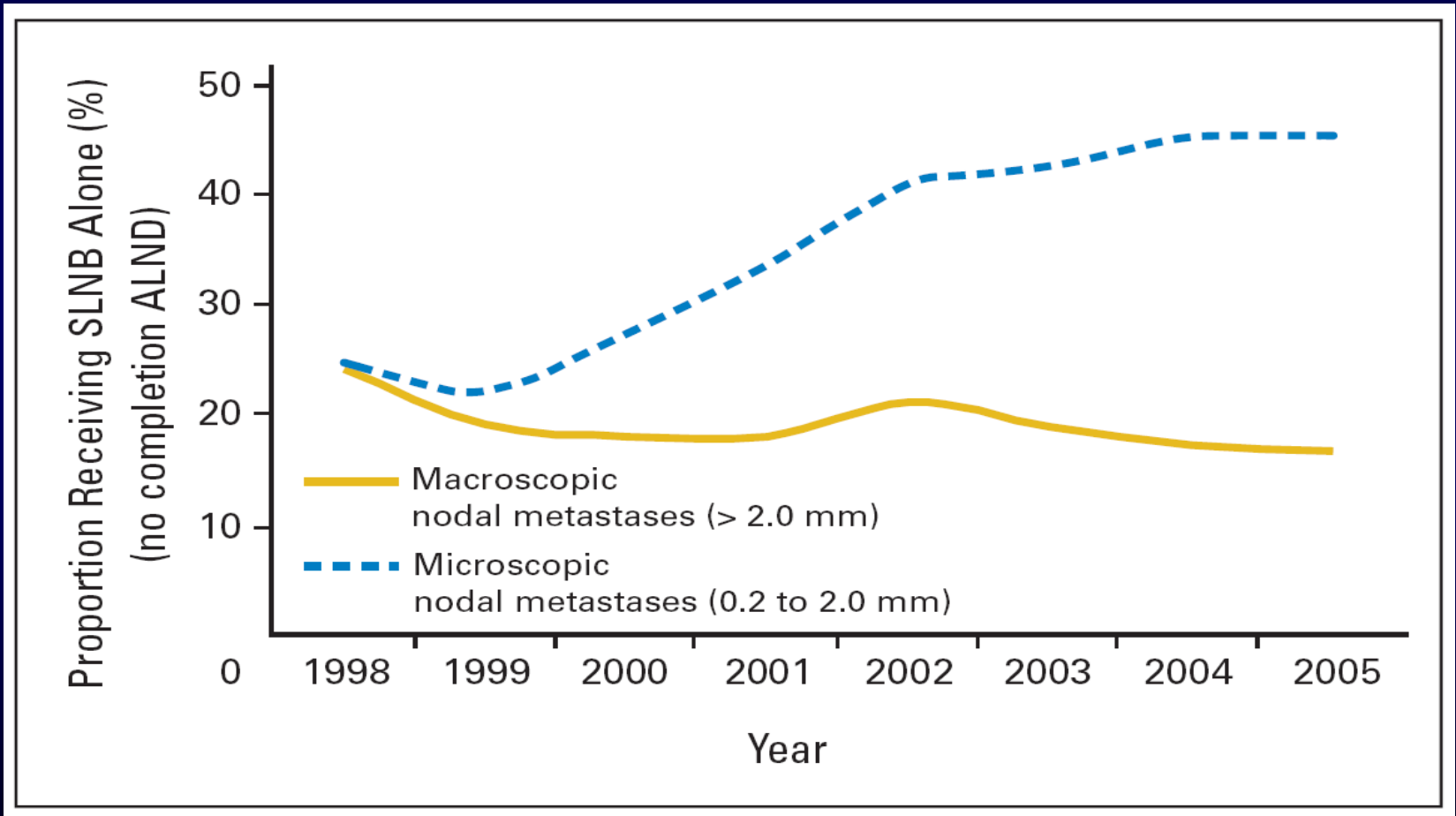
- pN0(i+): Cluster < 0.2 mm
- Classification of ITC < 200 cells on histologic section
- Micrometastases: 0.2 to 2 mm
- Stage I now TWO GROUPS
  - IA: T1 NO MO
  - IB: T0 N1mi M0
    T1 N1mi M0

Edge et al, 2009

SLN Trials

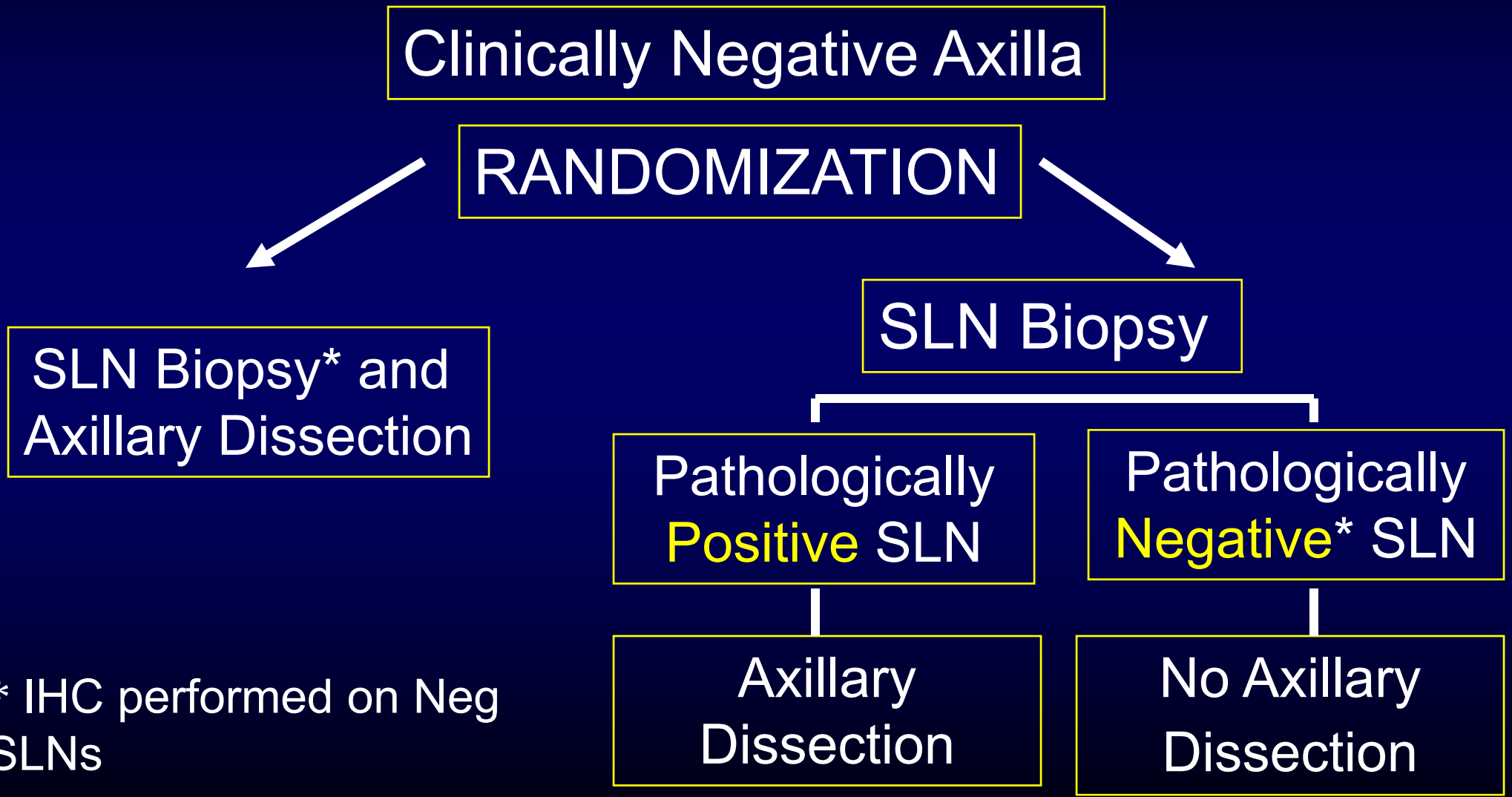
Recent Results from US Trials 1998-2004

Practice Patterns: US National Cancer Database 1998 - 2005



Bilimoria K, et al. *J Clin Oncol* 2009

NSABP Protocol B-32 N=5,611



* IHC performed on Neg SLNs

NSABP B-32 False Negative Rate

9.7%

(7.6 - 11.9)*

*95% CI

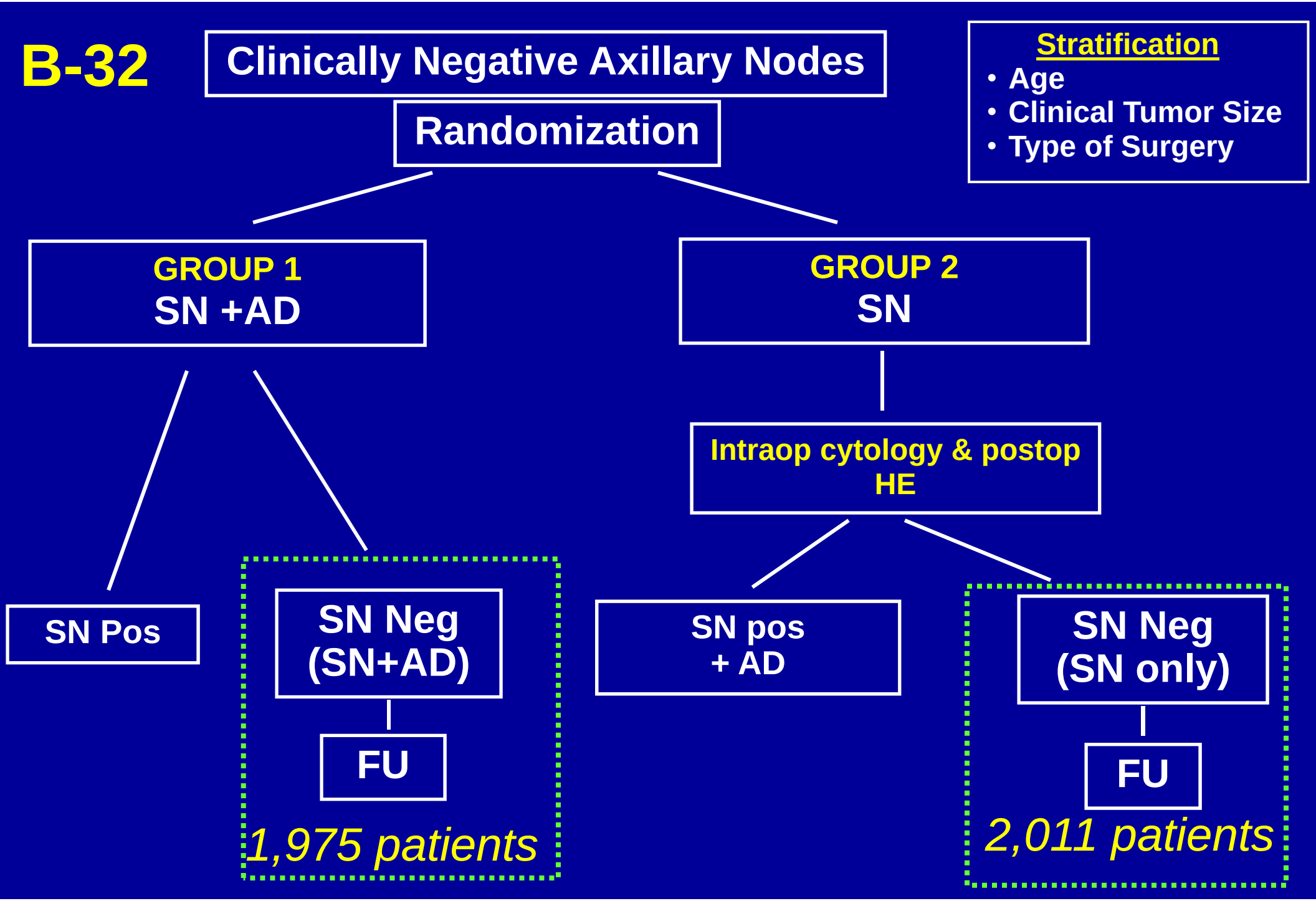
Julian et al, SABC, 2004

NSABP B-32

Sentinel Node by Biopsy Type

Type	Technical Success %	False Negative Rate %
Overall	**97.1**	**9.7**
FNA/Core	**97.0**	**8.0**
Incisional	**97.6**	**14.3**
Excisional	**97.3**	**15.2**
	P=0.83	P=0.02

B-32


Clinically Negative Axillary Nodes
Randomization
Stratification
• Age
• Clinical Tumor Size
• Type of Surgery
GROUP 1
SN +AD
GROUP 2
SN
Intraop cytology & postop HE
SN Pos
SN Neg (SN+AD)
FU
1,975 patients
SN pos + AD
SN Neg (SN only)
FU
2,011 patients

B-32 Analysis Plan

- 3,989 - SN neg (71% of 5611)
- 99.9% - follow-up information
- 7.92 years - average time on study

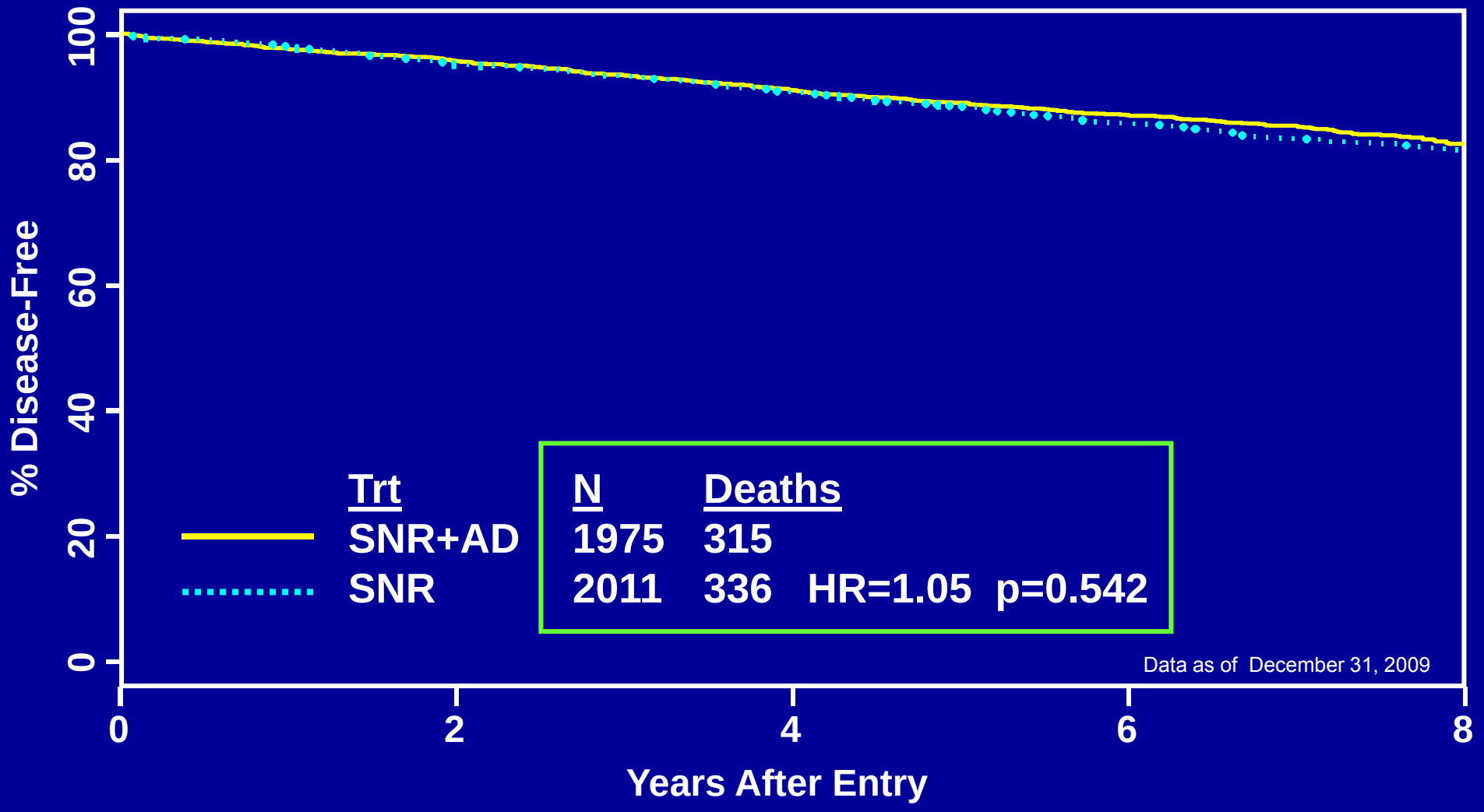
- Primary endpoints OS, DFS, Regional Control
- Study powered to detect 2% difference OS

Krag *et al* ASCO 2010

B-32 DFS

NSABP Protocol B-32

Disease-Free Survival for Sentinel Node Negative Patients



Krag *et al Lancet Oncol 2010*

Krag *et al* ASCO 2010

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%)

Krag *et al Lancet Oncol 2010*

Krag *et al* ASCO 2010

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%

Krag *et al Lancet Oncol 2010*
Ashikaga et al JSO, 2010

All differences p<0.001

Effect of Occult Metastases on Survival in "Node-Negative" Patients: NSABP B-32

- Occult metastases: 15.9%
- Independent predictor of prognosis
- Overall survival difference: 1.2%
  - 94.6% v. 95.8%
- Concluded no clinical benefit of serial sectioning and or IHC

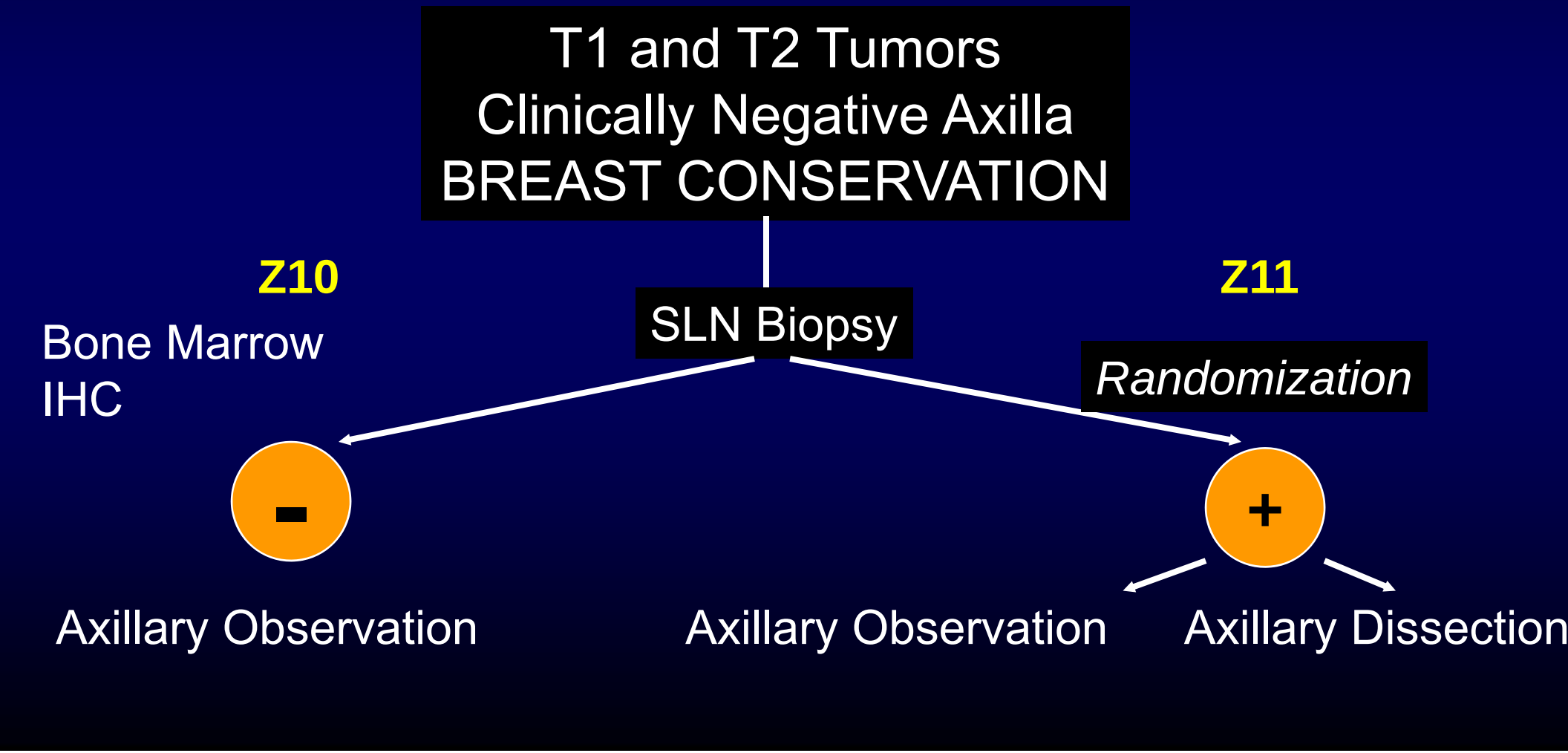
Weaver et al, *NEJM*, 2011

NSABP B-32
Overall Conclusions

- No significant differences were observed OS, DFS, or Regional Control SLN vs AD
- 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.

American College of Surgeons Oncology Group SLN Trial



ACOSOG Z0010 - Methods

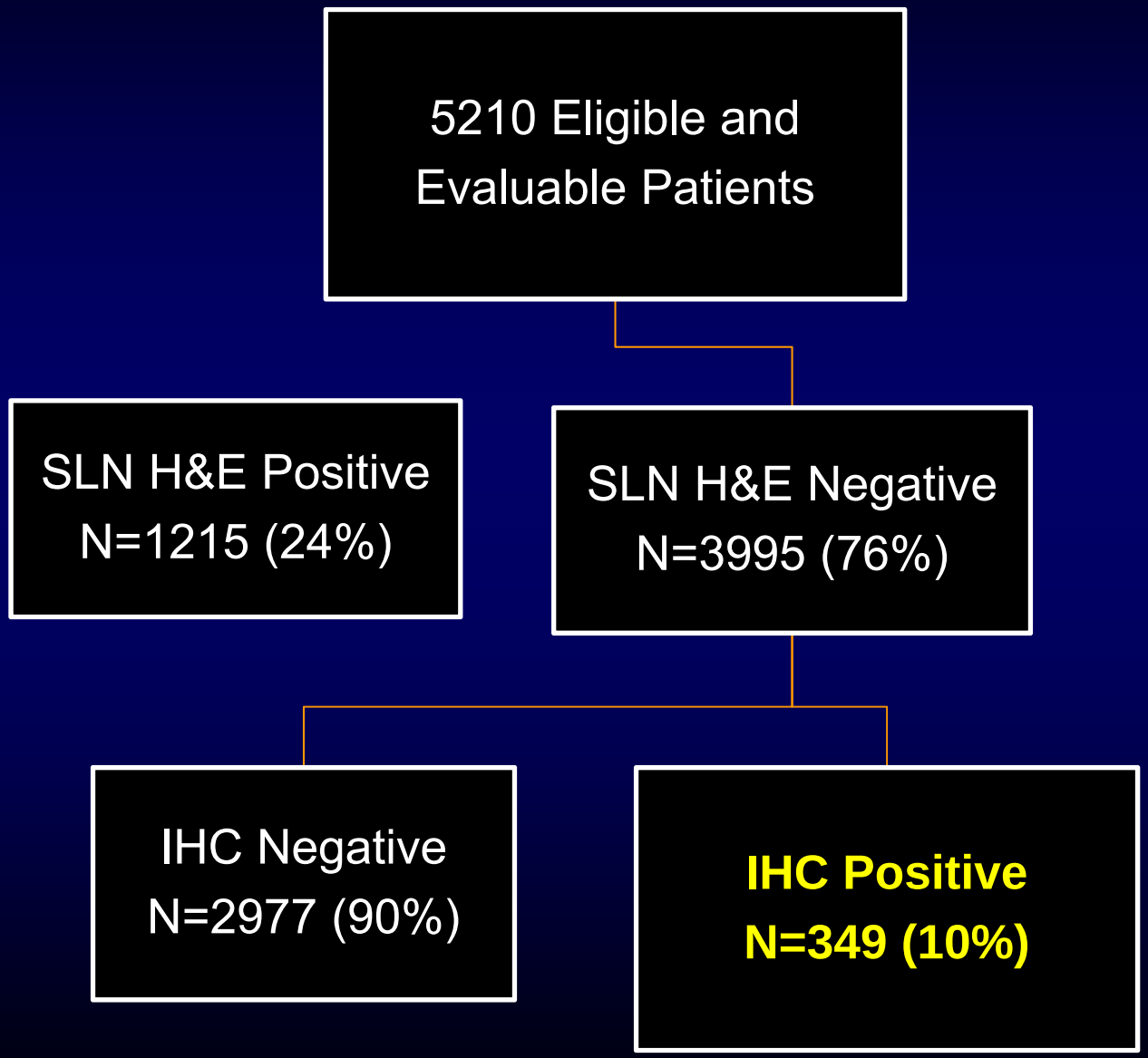
- **SLNs processed - standard pathology and H&E staining**
- **SLNs neg by H&E subjected to IHC for cytokeratin (investigators blinded to results)**

Z0010 Treatment Variables

Total SLNs Removed	
Median (Min, Max)	2 (0,32)
Missing	689
ALND Performed, N(%)	
Yes	925(18.0)
No	4203(82.0)
Missing	82
Chemotherapy, N(%)	
Yes	2297(53)
No	2035(47)
Missing	878

Hormonal Rx, N(%)	
Yes	2943(67.9)
No	1389(32.1)
Missing	878
Radiation Rx, N(%)	
Yes	3884(90.8)
No	394(9.2)
Missing	932
Any Adj Rx, N(%)	
Yes	4210(98.4)
No	68(1.6)
Missing	932

Overall Rate IHC Positive SLNs Z10



ACOSOG Z0010: Occult Micrometastases

- **5-year overall survival was significantly higher with a negative vs. positive result for:**
  - SLN H&E (≈ 96% vs. 93%; *P* = .0009)
  - BM IHC (95% vs. 90%; *P* = .01)
- **SLN IHC was NOT significantly associated with overall survival.**

Overall Survival	Multivariable Analysis (Positive vs. Negative)	
	HR (95% CI)	***P* Value**
All Patients		
SLN H&E	1.44 (1.11-1.88)	.007
BM IHC	1.88 (1.12-3.17)	.017
SLN H&E$^-$ Patients		
SLN IHC	0.98 (0.62-1.54	.93
BM IHC	2.22 (1.21-4.10)	.011

Giuliano et al *JAMA* 2011

ACOSOG Z10 Conclusions

- IHC detected SLN metastases do not appear to impact overall survival
- Routine examination of SLN by IHC is not supported in this patient population by this study

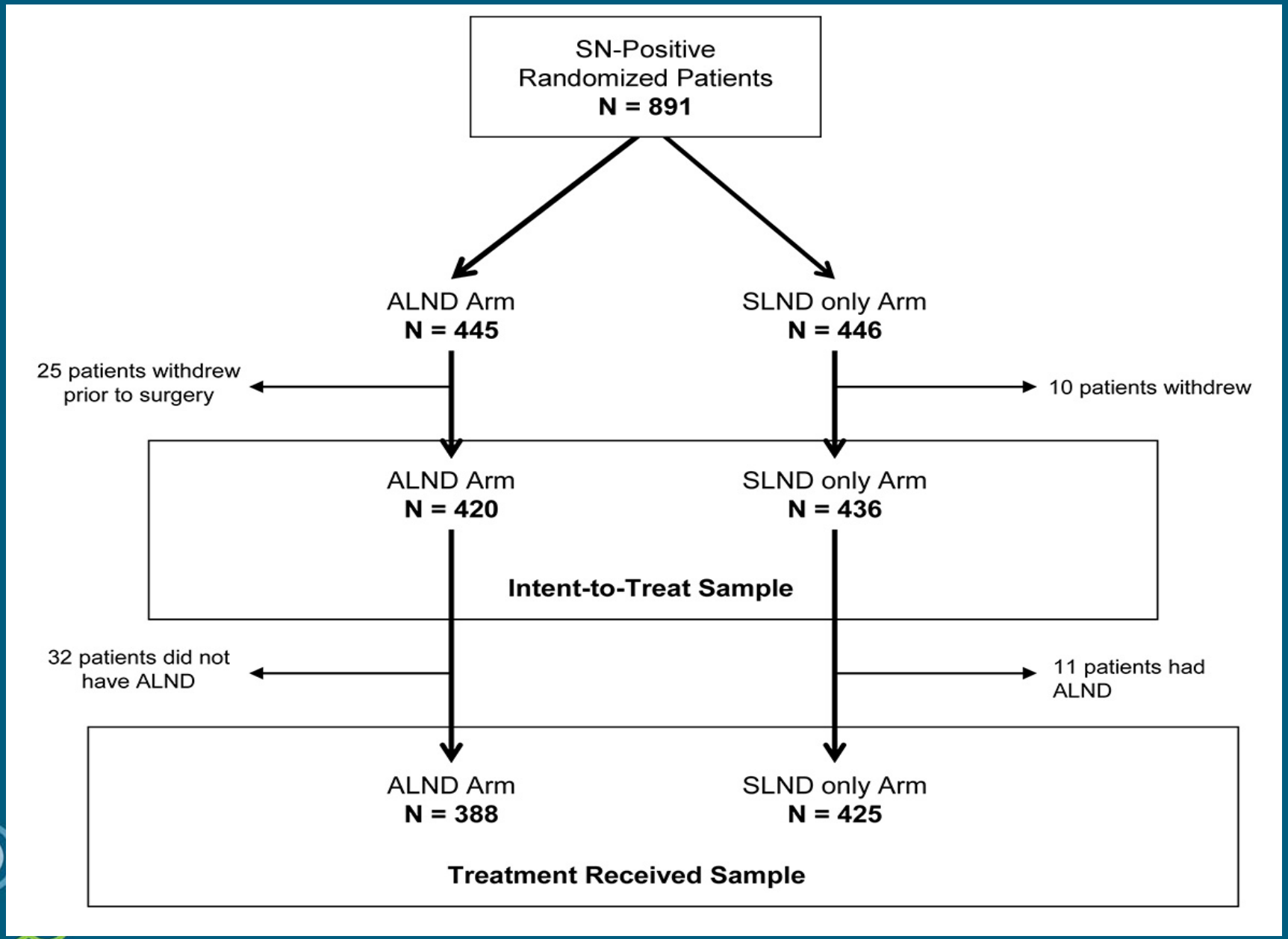
ACOSOG Z0011: A Randomized Trial of Axillary Node Dissection in Women with Clinical T1-2 N0 M0 Breast Cancer who have a Positive Sentinel Node

Giuliano AE, McCall L, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, Hunt K, Morrow M, Ballman KV

ASCO Annual '10 Meeting

Giuliano et al *JAMA* 2011

Study Population Schema 5/99–12/04



106 (27.4%) patients treated with ALND had additional positive nodes removed beyond SLN

72.6% patients treated with SLND had all positive nodes removed with the technique

Patient Characteristics Z11

- Median age: 55 years
- 70% T1 tumors
- 82% ER-positive disease
- All patients had node positive breast cancer (overall low burden)
  - 58% had only one node positive
  - Only 21% had ≥ 3 positive nodes

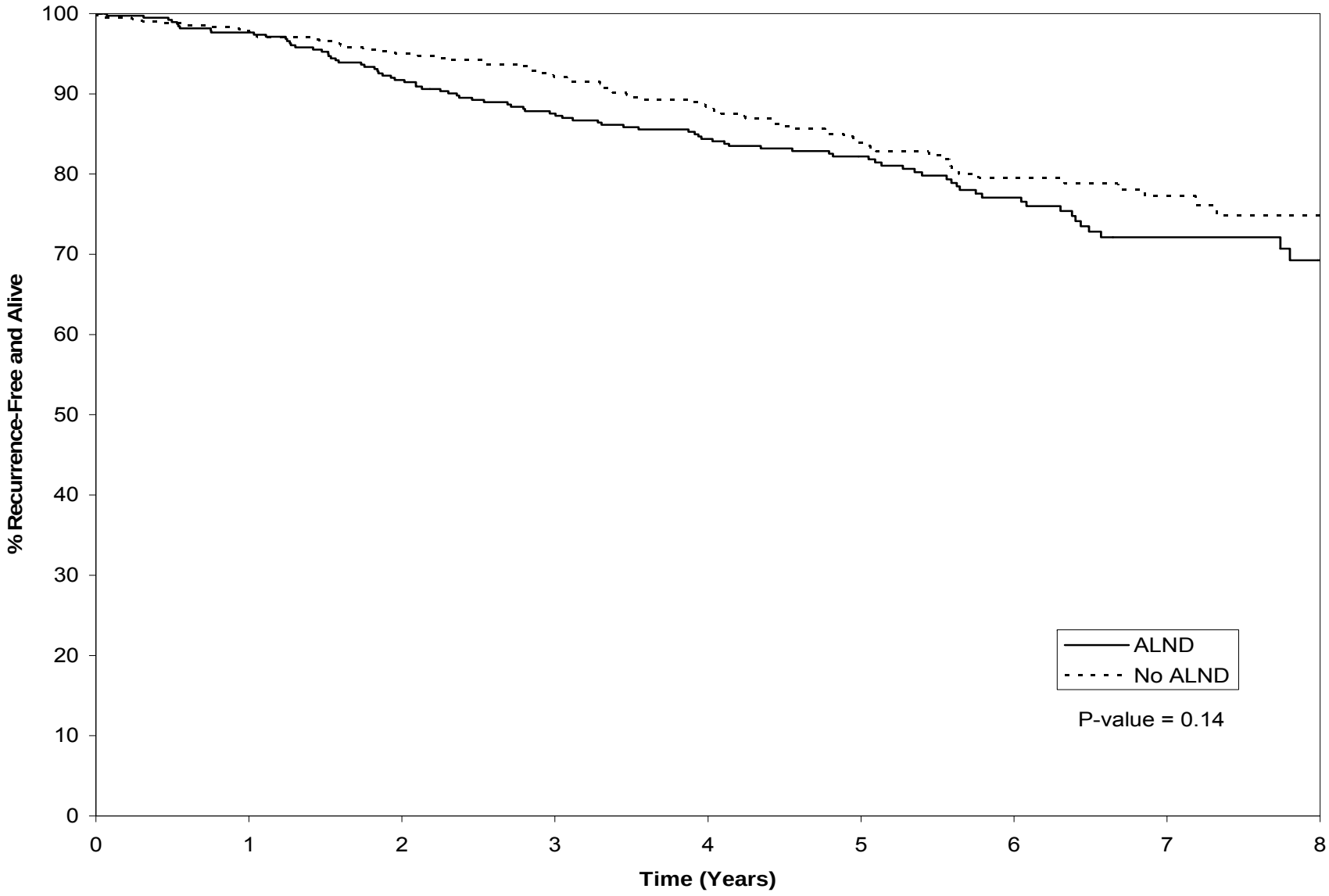
Locoregional Recurrences

Recurrence	ALND (420 pts)	SLND (436 pts)
Local (Breast)	15 (3.6%)	8 (1.8%)
Regional (Axilla, Supraclavicular)	2 (0.5%)	4 (0.9%)
Total Locoregional	17 (4.1%)	12 (2.8%)
	P = 0.11	

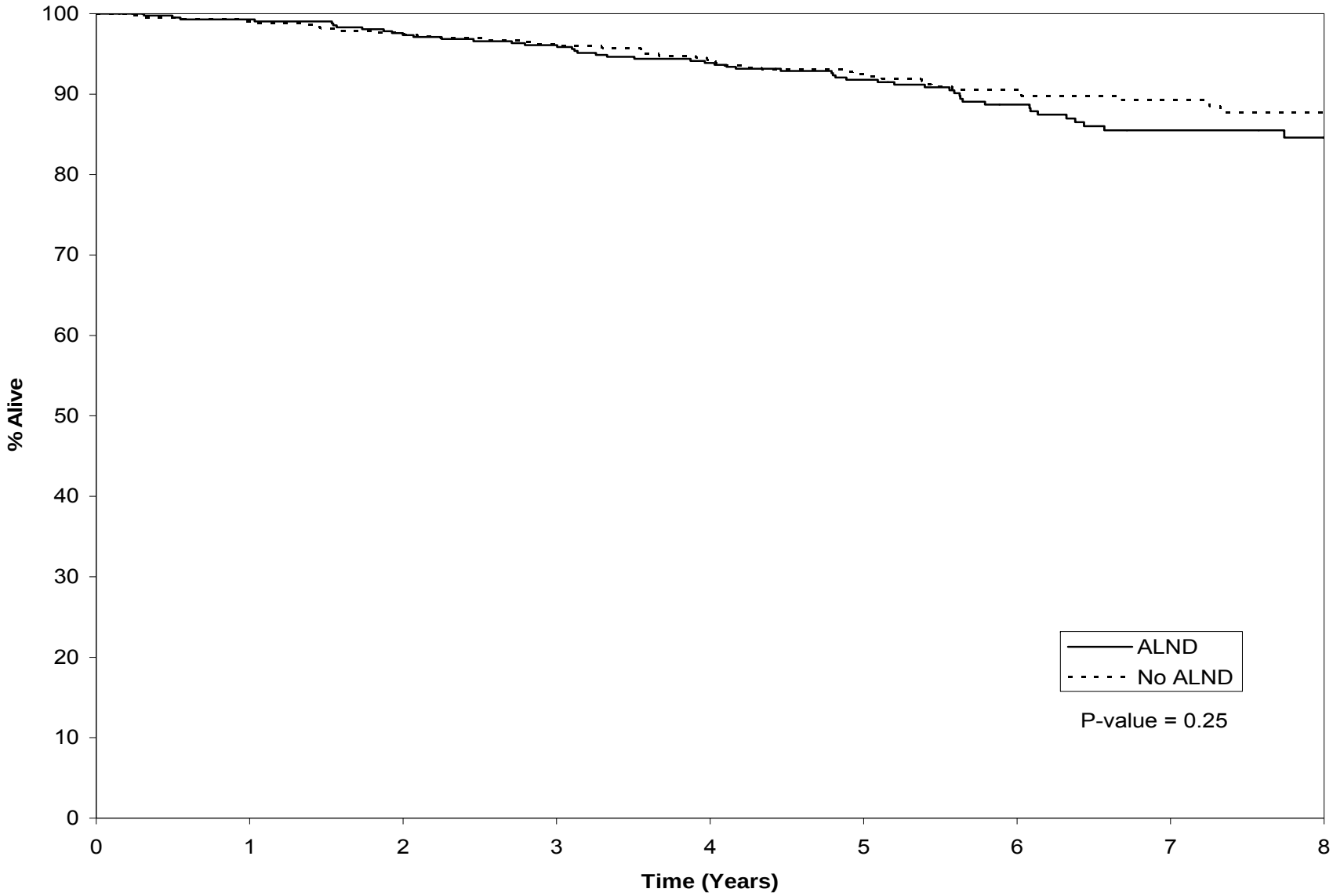
Median follow-up = 6.3 years

Regional recurrence seen in only 0.7% of the entire population

Disease-Free Survival



Overall Survival



IMPORTANT Caveats

- WHOLE BREAST RADIATION
  - Breast conserving therapy
- Adjuvant Systemic Therapy

Adjuvant Systemic Therapy

	ALND	SLND
Chemotherapy	57.9%	58.0%
Hormonal therapy	46.4%	46.6%
Either/Both	96.0%	97.0%

P = N.S.

Recommendations at MD Anderson for + SLN?

- *Must be individualized*
- **No dissection:**
  - T1/T2
  - One or two positive SLNs
  - If Whole-breast radiotherapy
  - Receiving systemic therapy

Caudle, Hunt, Kuerer et al *Ann Surg Oncol*, 2011

Recommendations for Axillary Node Dissection at MD Anderson

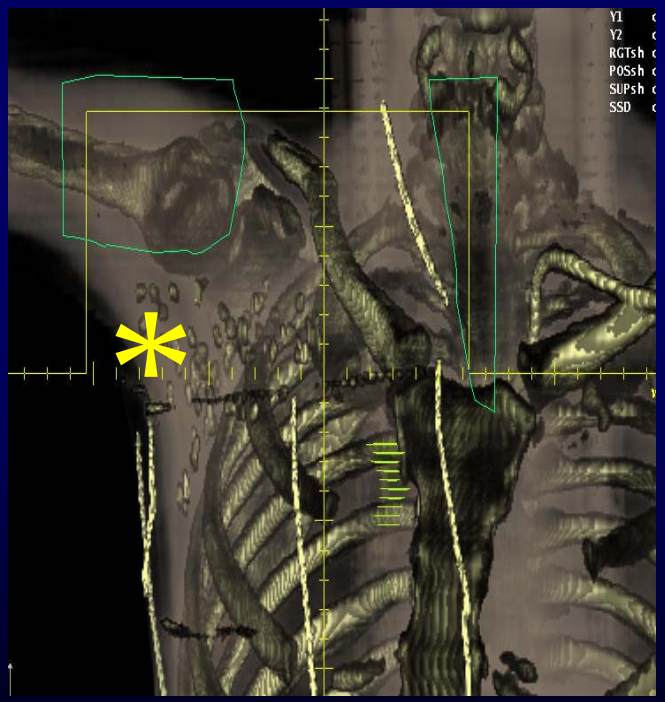
- Positive SLN
  - Mastectomy
  - Partial breast radiotherapy
  - Neoadjuvant chemotherapy

Caudle, Hunt, Kuerer et al *Ann Surg Oncol*, 2011

Sentinel Node Evolving Controversies

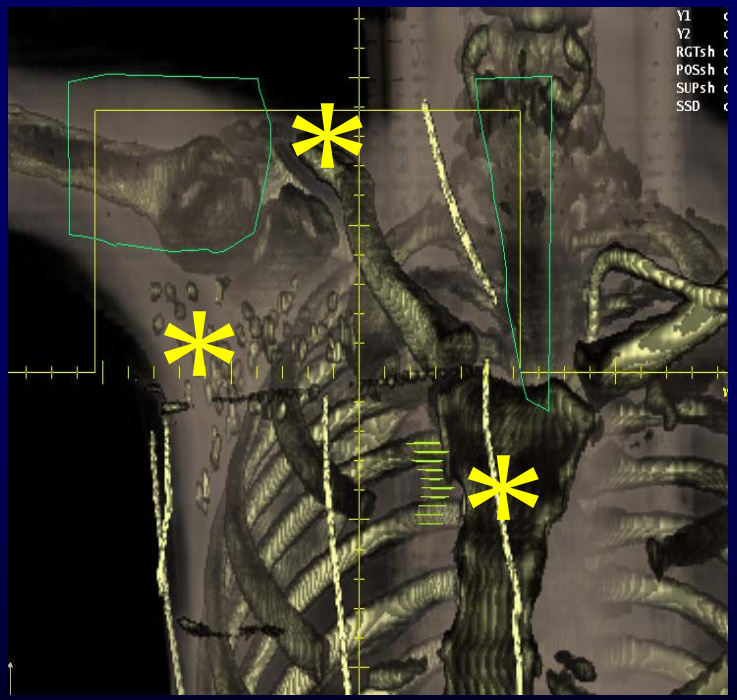
Complicated

Does the axilla need to be treated when positive SLN?



Many radiation oncologists will treat the axilla when a positive SLN is obtained and no dissection is performed

Extended Field Radiotherapy?



- Which patients?
- Recent presented MA.20 results
- Concern for over treatment/risk

Toxicity?

- Overall Survival for early Stage II breast cancer very high (>90%)
- What will be the long term effects on healthy:
  - Lymphatics?

Can Axillary *Radiation* Be Substituted for Completion Axillary Lymph Node Dissection

When a Sentinel Lymph Node Contains Metastases ?

AMAROS EORTC 10981

- Tumor ≤ 5 cm
- 4827 Total Patients
- SLN-Positive
- Randomized Component of Trial
  - ALND vs. Axillary Radiotherapy

Straver et al *Ann Surg Onc* & *J Clin Onc* 2010

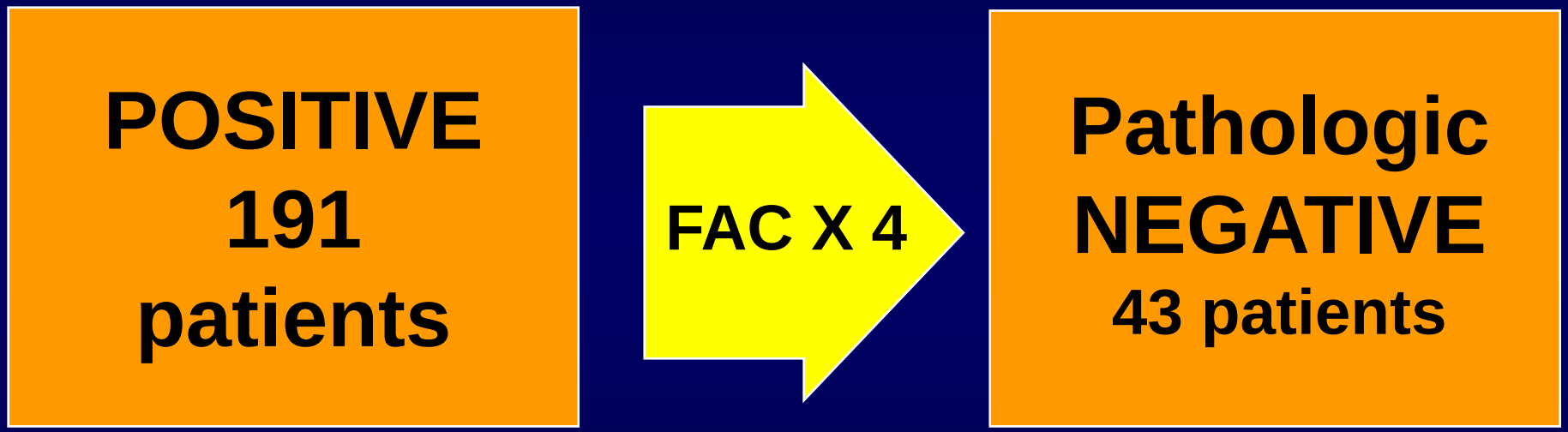
Sentinel Node Biopsy Before or After Neoadjuvant Chemotherapy ?

SLN Biopsy Before Neoadjuvant Therapy

- Commits patients to an extra axillary operation
- SLN Negative: Two operations
- SLN Positive: Commits patients to axillary lymph node dissection with a positive SLN before therapy

Conversion of Axillary Metastases:

FNA Positive to Pathologic Negative



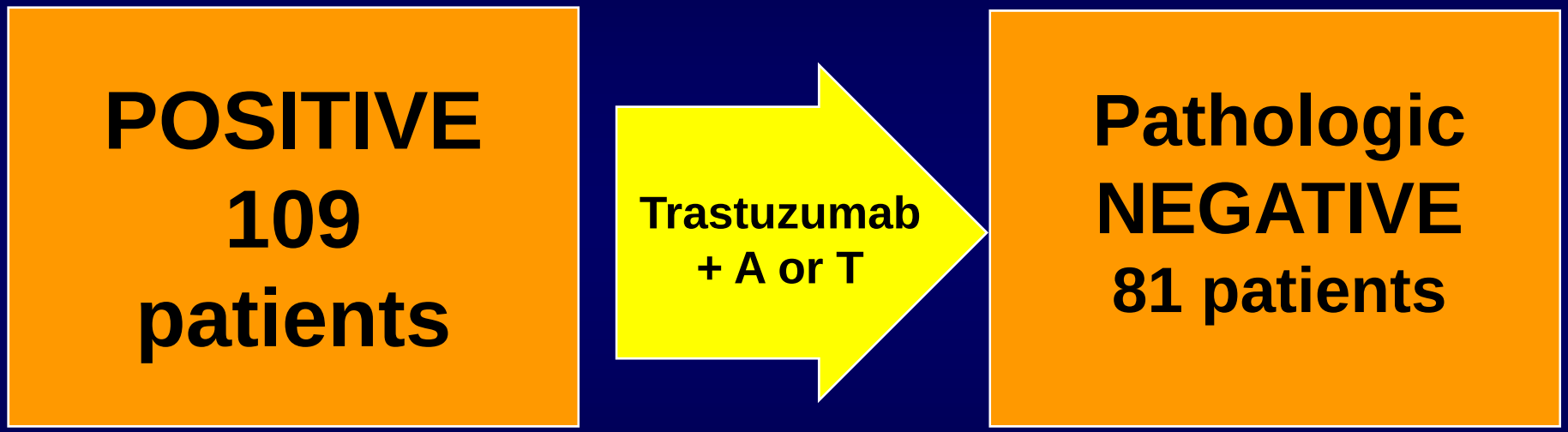
23%

Median # LNs Removed = 16

Kuerer *et al*, *Ann Surg*, 1999

Conversion of Axillary Metastases:

FNA Positive to Pathologic Negative



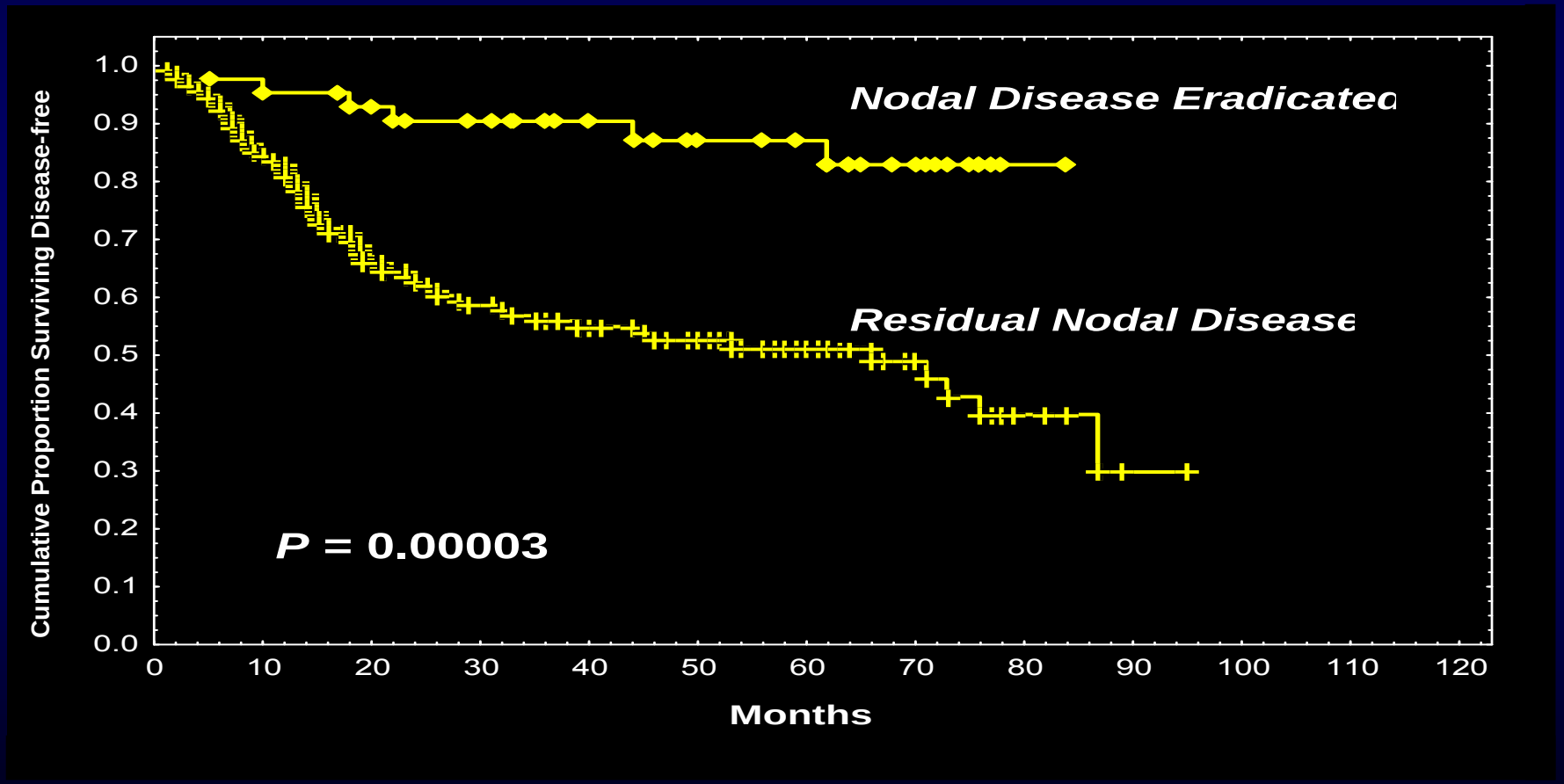
HER2+

74%

Median # LNs Removed = 19

Dominici et al. CANCER, 2010

Impact of Nodal Disease Eradication on DFS
Independent Prognostic Factor



Annals of Surgery, 1999

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

- Xing et al M D Anderson
- 21 studies
- 1273 patients
- Identification Rates: 72-100%
  - –Pooled estimate: 90%
- False Negative Rates: 0-33%
  - –Pooled estimate: 12%

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

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

ACOSOG Z1071

SLN surgery after neoadjuvant chemotherapy for node positive breast cancer

PI - Judy C. Boughey MD

Z1071 schema

T1-4 N1-2 invasive breast cancer

(Pretreatment axillary ultrasound with FNA or core biopsy documenting axillary metastases)

REGISTER*

↓

Patients receive chemotherapy

(stratify patients by age, stage and number of cycles and type of chemotherapy)

↓

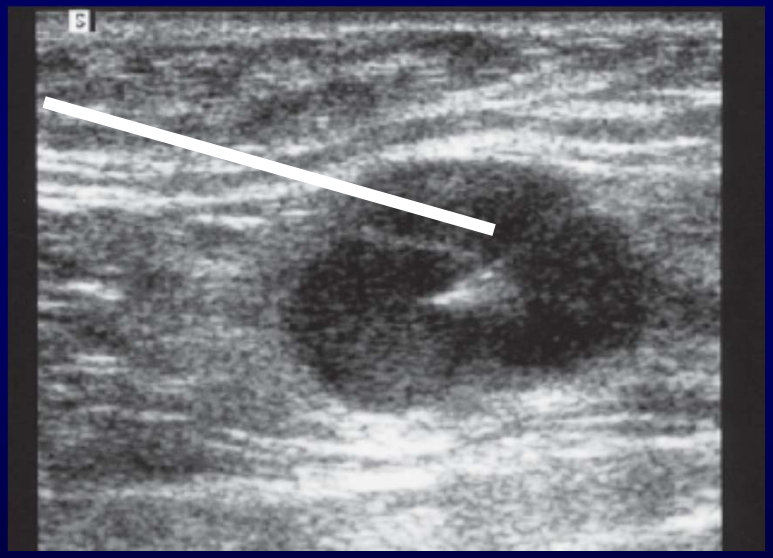
REGISTER*

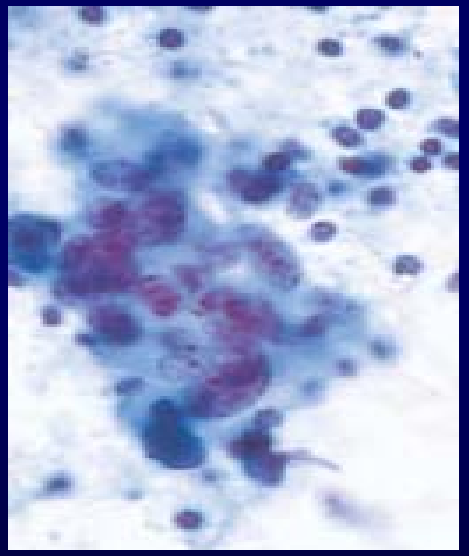
↓

SLN and ALND

Alternatives to SLN Biopsy BEFORE Neoadjuvant Chemotherapy?

Initial Nodal Ultrasound and FNA Biopsy
Avoiding Surgical SLN Biopsy



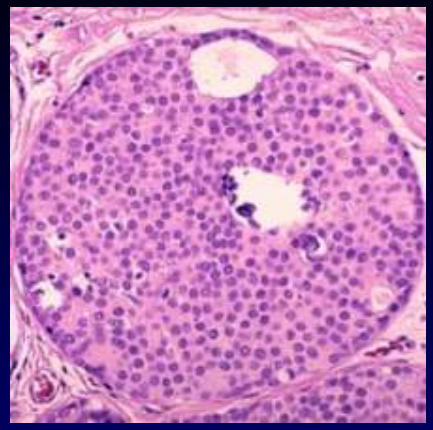


Krishnamurthy et al, *Cancer* 2002

Pros and Cons in Timing of SLN Biopsy with Neoadjuvant Therapy

- Presence of axillary metastases can be identified with either SLN biopsy or FNA before neoadjuvant therapy
- Chemotherapy can eradicate lymph node metastases in 30 to 40%
  - Axillary dissection may be avoided if SLN biopsy performed after pre-op therapy

DCIS



Should Patients with DCIS be Offered SLN Biopsy ?

Sentinel Lymph Node Biopsy
Patients With 'Pure' DCIS

- European Institute of Oncology
- 223 unselected patients with DCIS
- Metastases in 3.1%, most micromets
- Completion dissection no additional mets
- Select patients – palpable mass ? Diffuse disease ?

Intra et al, *Arch Surg* 2003

SLN Biopsy for 'High Risk' DCIS

- DCIS with microinvasion (N=31)
  - 10% Positive SLN
- 'High-Risk' DCIS (N=76)
  - Palpable or mass on MMG
  - Extensive high-grade lesions
    - 12% Positive SLN
- Mastectomy = Lose chance for later SLN

Klauber-DeMore, *Ann Surg Onc*, 2000

MD Anderson Cancer Center
Selective Use of SLN Biopsy in DCIS

- 399 patients with INITIAL diagnosis of DCIS
- 20% of patients will have invasive carcinoma on final pathology
  - Predictors: CORE Biopsy diagnosis, age < 55, HG tumors, > 4 cm on MMG
- 10% positive SLN (H and E in 93%, n = 141)
  - Highly selected group of patients

Yen et al, *Journal American College of Surgeons*, 2005

Is Any Axillary Surgery in Elderly Women With ER+ Breast Cancer Needed?

Axillary Surgery in the Elderly

- Info gained may not influence adjuvant therapy selection or outcome
- Three prospective trials:
  - Evidence suggests that selected patients > 70 years, clinical normal axilla, ER+, < 2 cm, receiving endocrine therapy can safely avoid

Hughes et al *NEJM,* 2004; Martelli et al, *CANCER* 2008

IBCSG *J Clin Onc*, 2006

New Trials and Next Steps

- **S**entinel node vs. **O**bservation after axillary **U**ltrasou**ND** (SOUND)
- N=1,560
- European Institute of Oncology, Milan
- Eligibility: <2 cm, any age, negative preop axillary US, breast conservation

Gentilini & Veronesi, *Breast* 2012

Current Indications and Standards for Sentinel Node Biopsy

Clinically *NEGATIVE* axilla

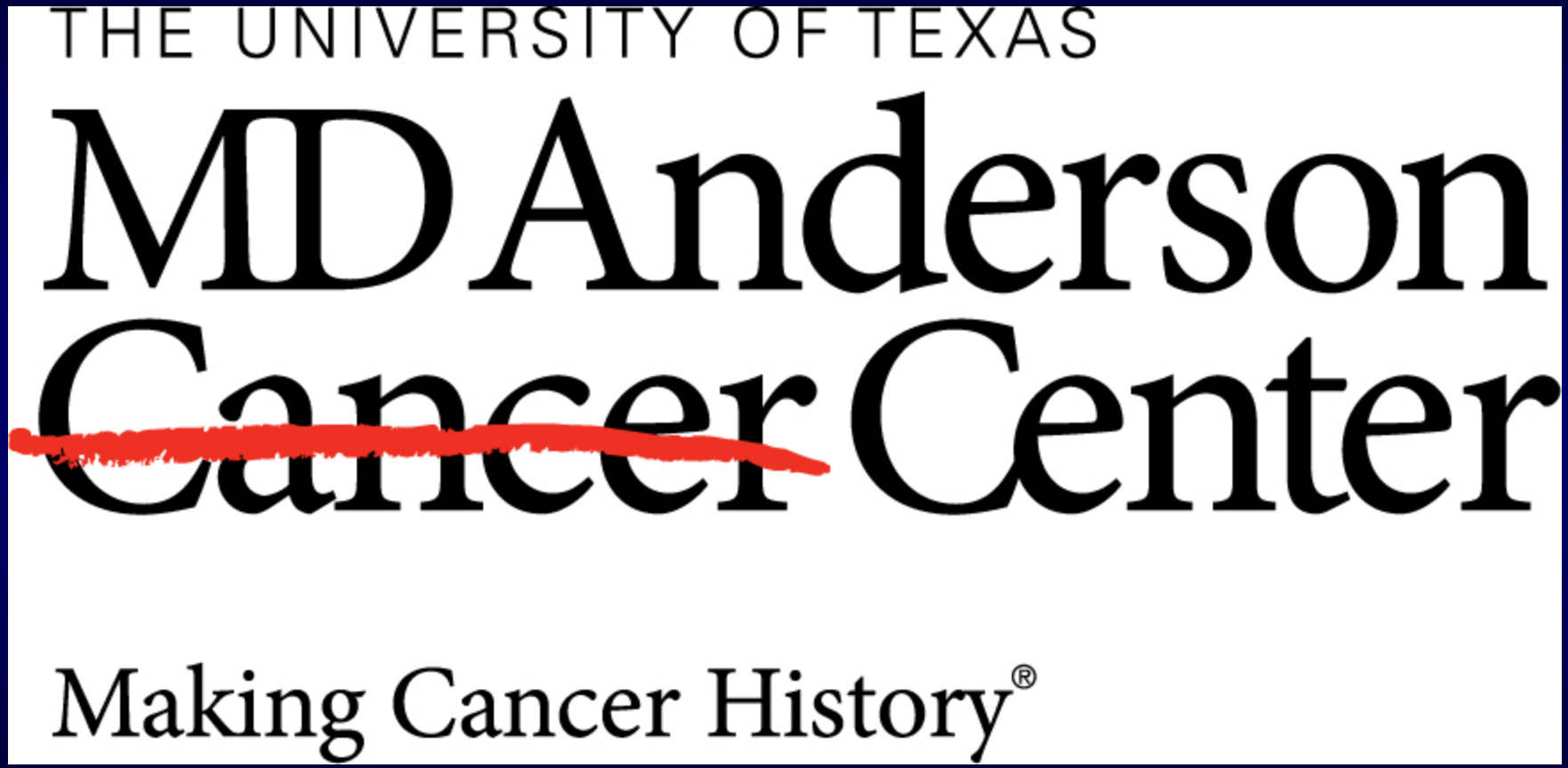
- T1, T2, T3 tumors

- If a SLN is found to be positive:
  - Mastectomy: Completion dissection
  - Breast Conserving w WBT: Individualize

- DCIS: High-risk for Invasive and receiving mastectomy

Current Indications and Standards for Sentinel Node Biopsy

- Neoadjuvant therapy
  - Before or after chemo; prefer nodal ultrasound with FNA biopsy
  - Risks and benefits should be discussed in detail with patient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