



Surgical Considerations after Neoadjuvant Chemotherapy

Kelly K. Hunt, MD

Professor

Department of Surgical Oncology

THE UNIVERSITY OF TEXAS

**MD Anderson
Cancer Center**

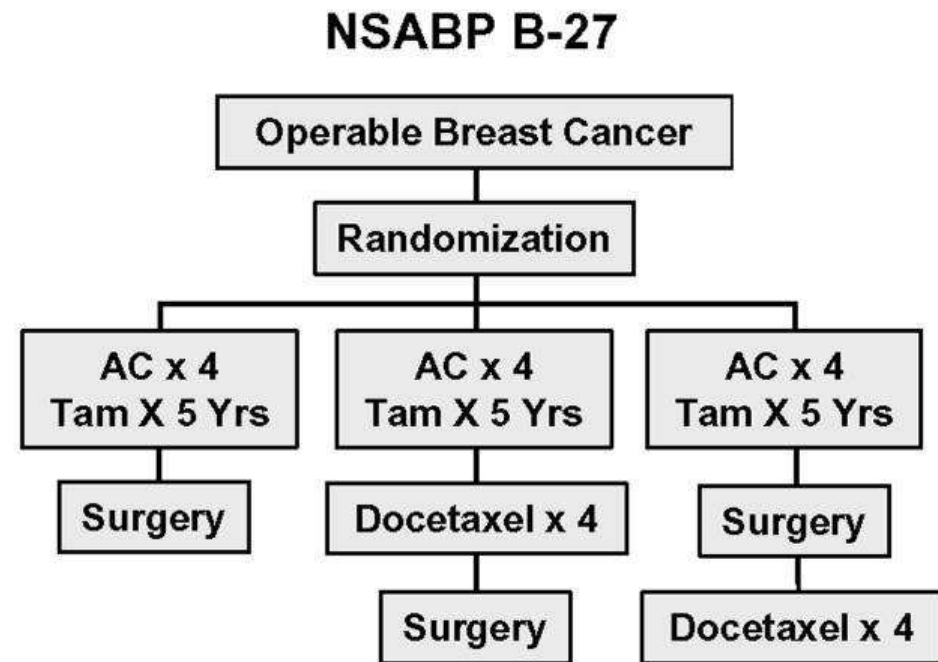
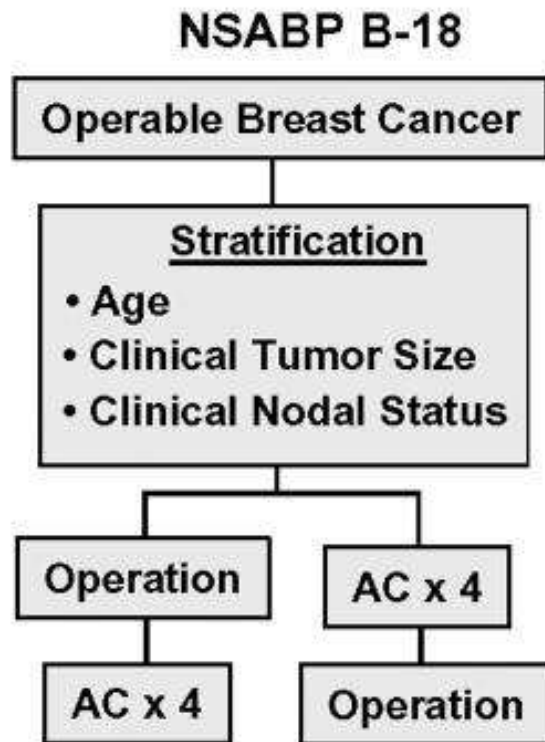
Overview

- Review of data supporting use of neoadjuvant chemotherapy
- Surgical management of:
 - Breast
 - Axilla

Neoadjuvant Chemotherapy

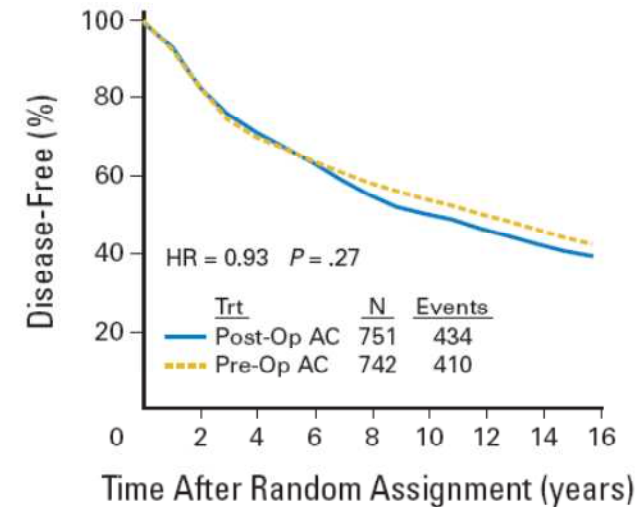
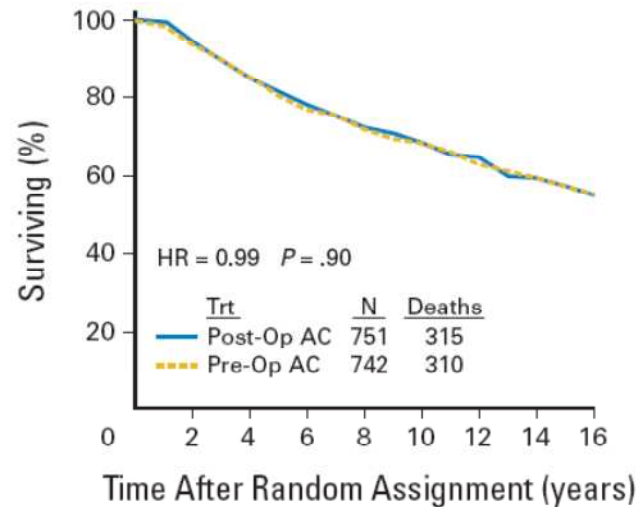
- Increasingly used in operable breast cancer
 - Facilitates breast conserving surgery
 - Response to therapy
 - Long-term outcome correlates with pathologic tumor response rates

NSABP B-18 and B-27

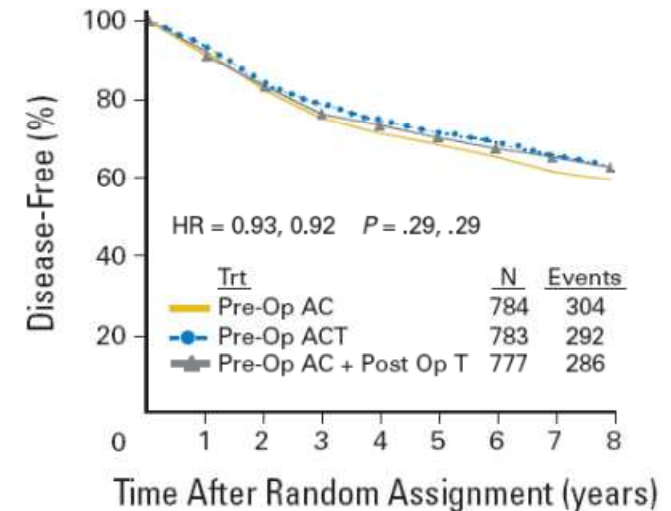
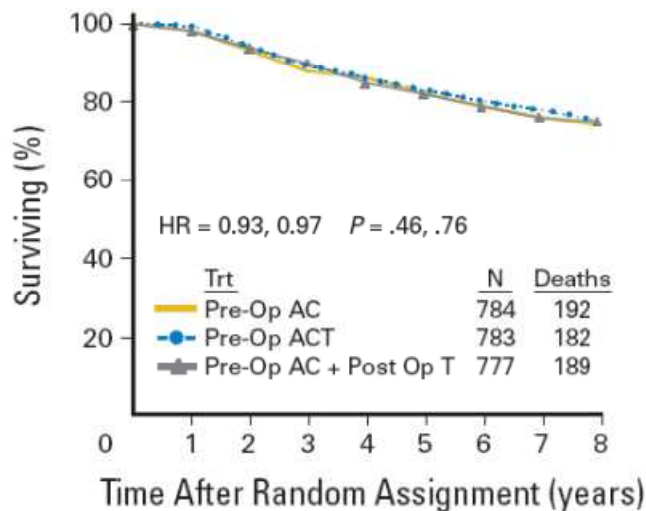


NSABP B-18 and B-27

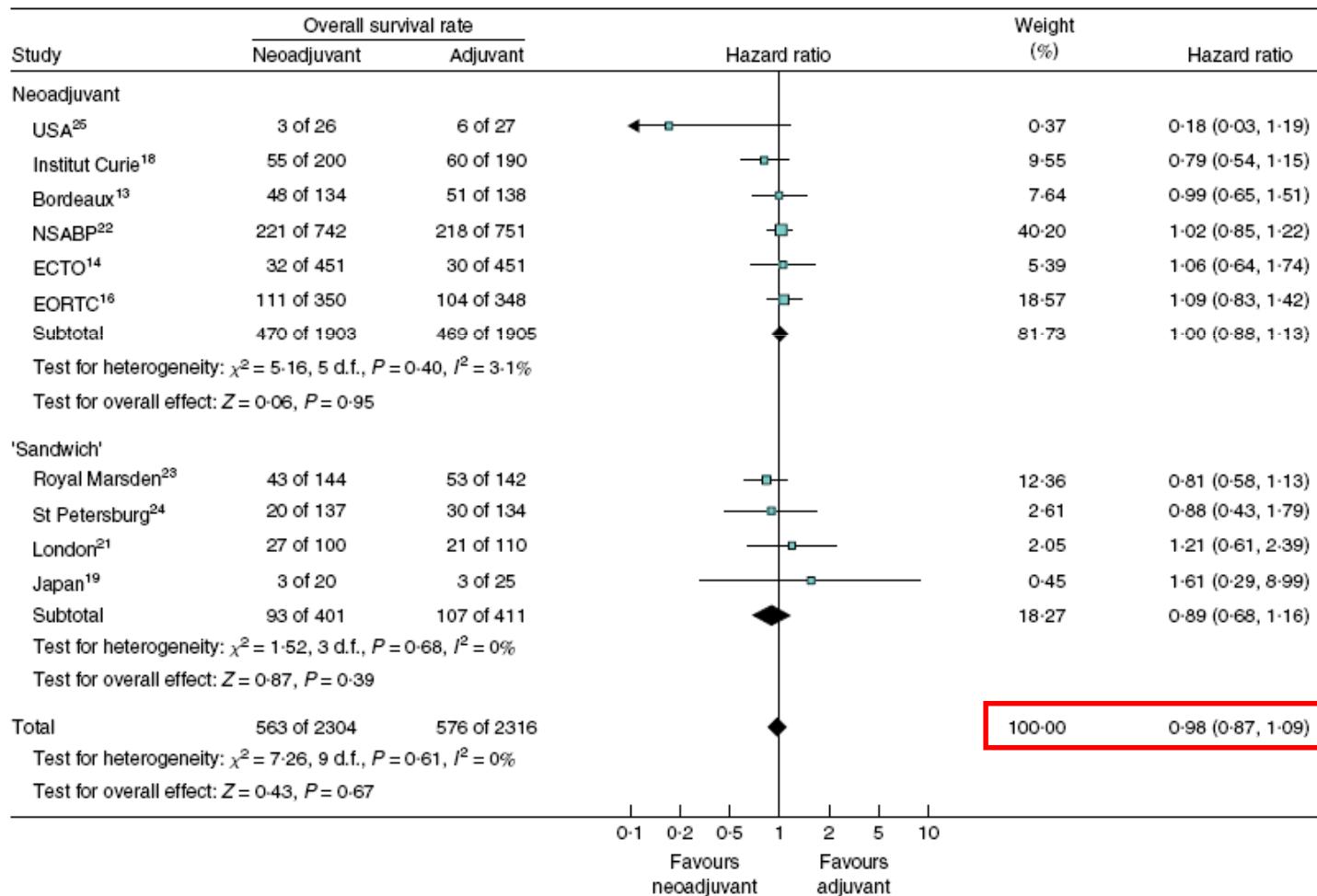
NSABP B-18
16 yrs f/u



NSABP B-27
8.5 yrs f/u



Neoadjuvant Chemotherapy



Locoregional Treatment After Neoadjuvant Chemotherapy

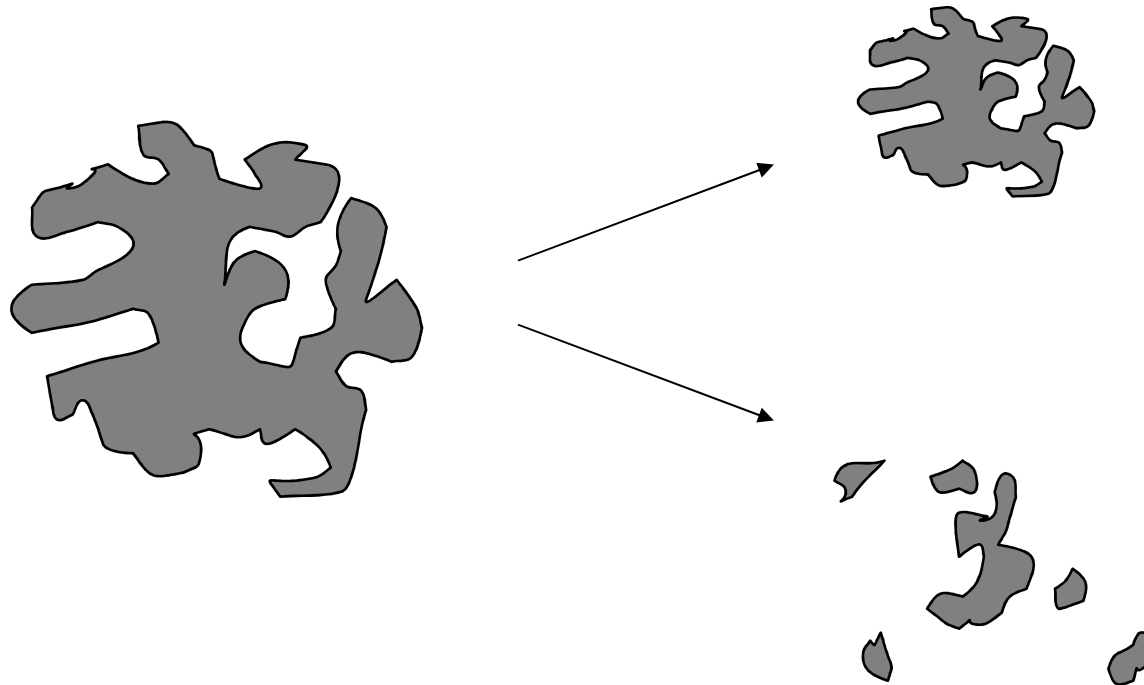
- Mastectomy rate ↓ by 17%
- NSABP B-18

Clinical Tumor Size (cm)	Lumpectomy Proposed (%)	Lumpectomy Performed (%)
All patients	65	67
≤ 2.0	89	81
2.1 – 5.0	68	71
≥ 5.0	3	22

BCT After Neoadjuvant Chemotherapy

Pretreatment

Post-treatment



BCT After Neoadjuvant Chemotherapy

Determine effect of neoadjuvant chemotherapy on:

- Volume of tissue excised
- # of breast operations performed

BCT After Neoadjuvant Chemotherapy

Variable	Postoperative Chemotherapy (n=91)	Preoperative Chemotherapy (n=150)	P value
T1 tumors			
Vol resected tissue (cm ³)	98	111	0.5
Median tumor size (cm)	1.5	2.0	0.006
Re-excision rate (%)	16	8%	.5
T2 or T3 tumors			
Vol resected tissue (cm ³)	213	113	0.004
Median tumor size (cm)	3.0	3.45	0.13
Re-excision rate (%)	14%	14%	1

BCT After Neoadjuvant Chemotherapy

- Median f/u = 33 months
- 2 IBTR
 - 1 neoadjuvant chemo
 - 1 adjuvant chemo

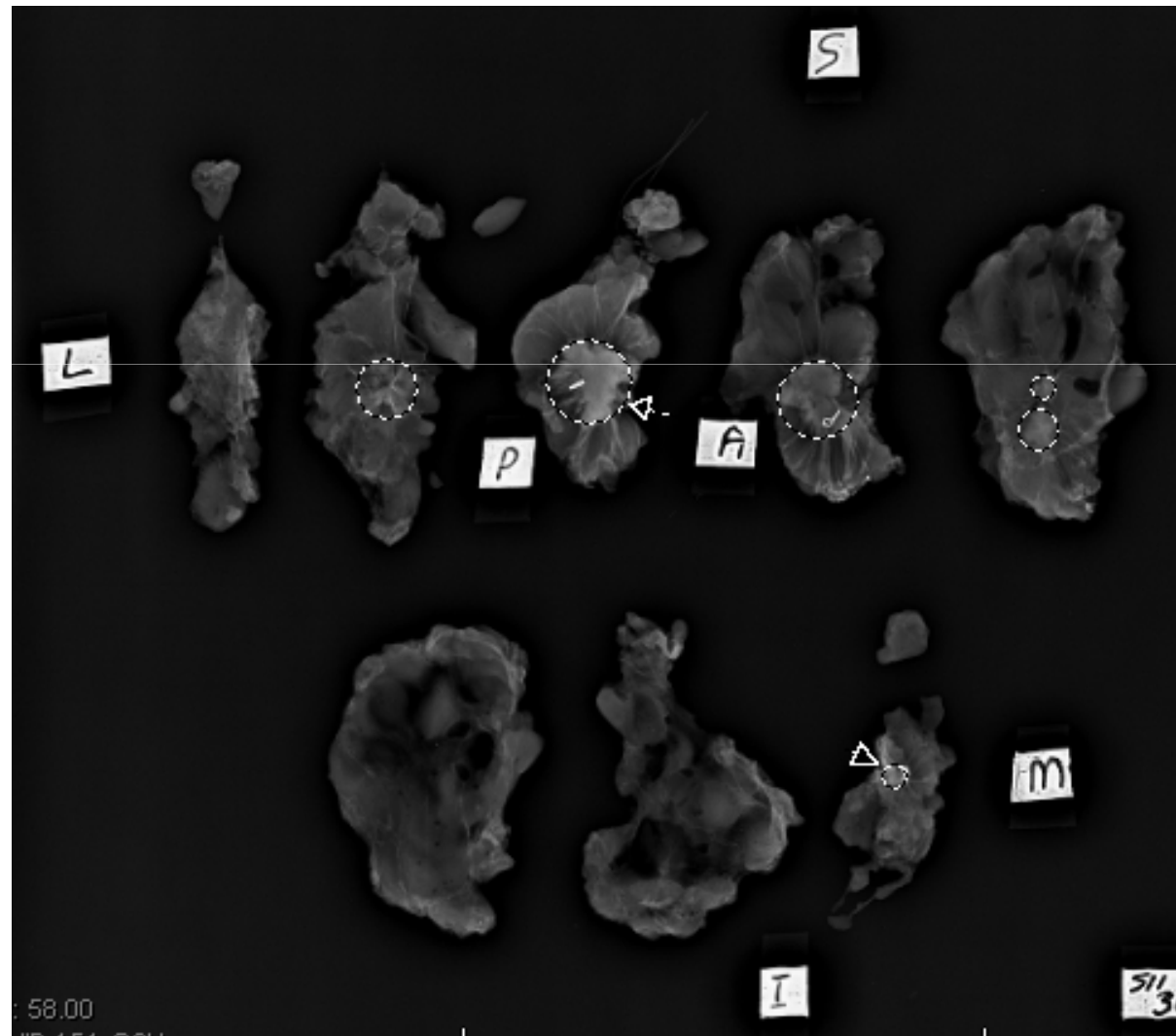
BCT After Neoadjuvant Chemotherapy

- For T2/T3 tumors, neoadjuvant chemo reduces volume of tissue excised
- No change in rates of re-excision or recurrence
- Do *not* need to excise pre-chemotherapy volume

MD Anderson Approach to BCT

- US of breast and regional nodal basins at diagnosis
- Segmental mastectomy
 - Any radiographic abnormality, calcifications and clip targeted for resection
 - Margin of normal tissue
 - No attempt to excise pre-chemotherapy volume
- Intraoperative margin assessment

Intraoperative Margin Assessment



MD Anderson BCT Experience

- Goal: evaluate long-term results of BCT for patients undergoing surgery first vs neoadjuvant chemotherapy
- 1987 – 2005
- N=2984 (segmental mastectomy + WBI)
 - 2331 (78%) surgery first
 - 652 (22%) chemotherapy first

MD Anderson BCT Experience

Factor	Surgery First (N=2331)	Neoadjuvant Chemotherapy (N=652)	P value
Clinical stage			<.001
I	80%	7%	
II	19%	69%	
III	1%	24%	
Grade			<.001
1	11%	2%	
2	53%	30%	
3	34%	66%	
NR	2%	1%	
ER			<.001
Positive	71%	51%	
Negative	24%	48%	
Unknown	5%	1%	

MD Anderson BCT Experience

Factor	Surgery First (N=2331)	Neoadjuvant Chemotherapy (N=652)	P value
LVI			0.584
Present	15%	16%	
Absent	85%	84%	
Multifocal Dz			0.006
Yes	7%	10%	
No	93%	90%	
Margin Status			0.144
Negative	96%	95%	
Close (< 2mm)	3%	4%	
Positive	1%	1%	

Response to Neoadjuvant Chemotherapy

- Neoadjuvant chemotherapy
 - pCR in 131 (20%)
 - Clinical stage II/III disease
 - 608 (93%)
 - Pathologic stage II/III disease
 - 305 (46%)
- } P<0.001

LRR-free Survival Rates

	5-yr	10-yr
Surgery First	97% (95% CI:96-98)	94% (95% CI:93-95)
Neoadjuvant Chemotherapy	93% (95% CI:91-95)	90% (95% CI:87-93)

Median f/u:

Surgery 7.9 yrs

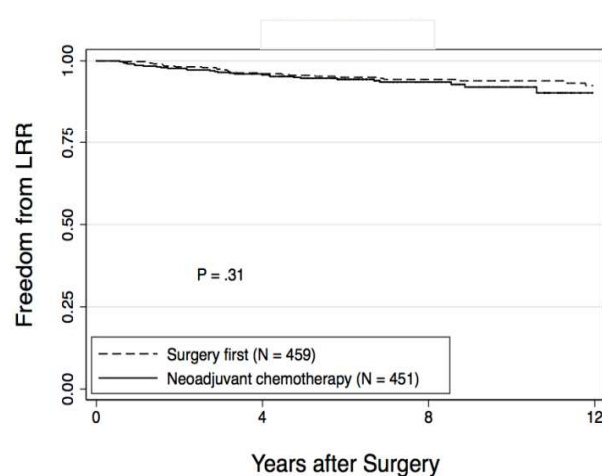
Neoadjuvant Chemo 7.2 yrs

LRR-free Survival Rates

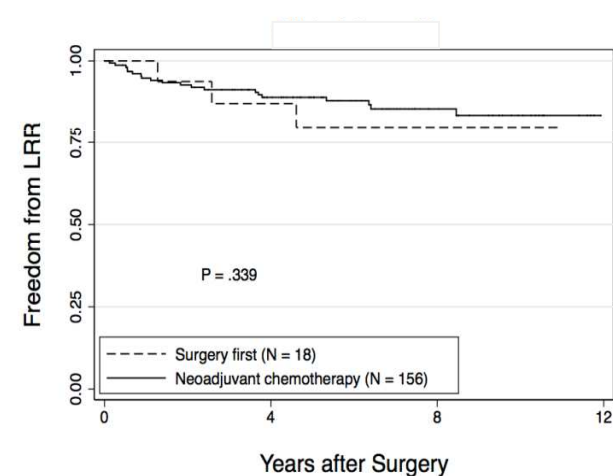
Clinical Stage I



Clinical Stage II



Clinical Stage III



Multivariate Analysis: Factors Associated with LRR

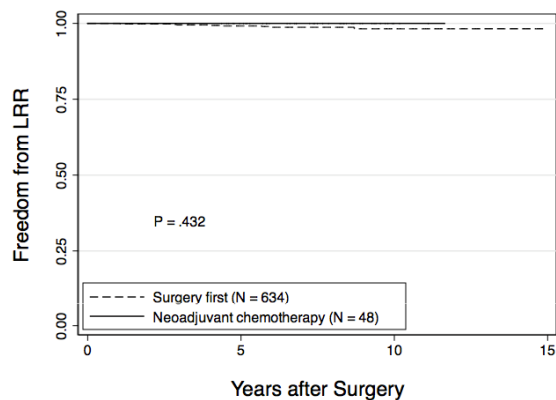
Factor	HR	P-value	95% CI
Age < 50	1.9	<.0001	1.4-2.7
Clinical stage III disease	2.5	<.0001	1.6-3.9
Grade 3	1.9	.001	1.3-2.7
ER negative	2.4	<.001	1.6-3.6
ER positive, no hormonal tx	2.8	<.001	1.8-4.4
Multifocal disease	1.9	.01	1.2-3.1
LVI positive	1.5	.04	1.0-2.2
Close/pos margins	2.5	.001	1.5-4.4
Neoadjuvant Chemotherapy	1.23	0.32	0.82-1.85

Distribution of Factors Identified on MV Analysis

Number of Factors	Surgery First	Neoadjuvant Chemotherapy
0	634	48
1	656	125
2	499	206
3	317	164
4	71	70
5	7	18
6	1	3

LRR-free Survival

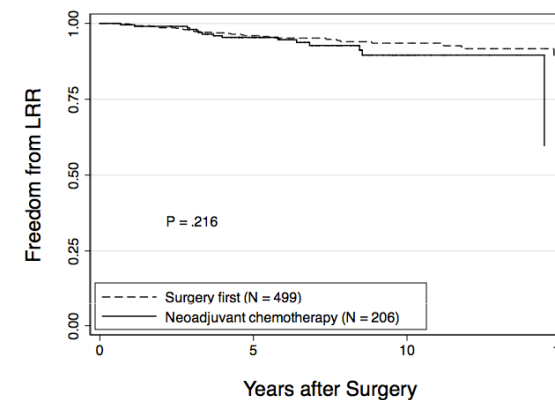
0 factors



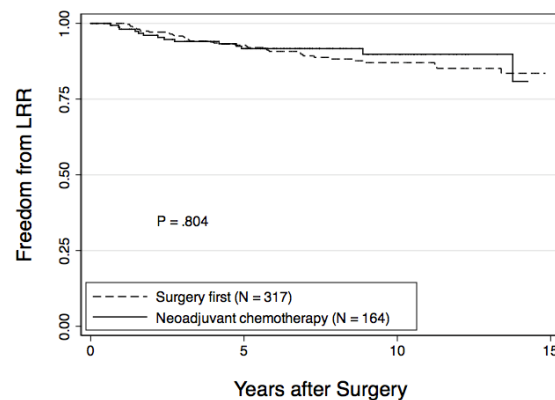
1 factor



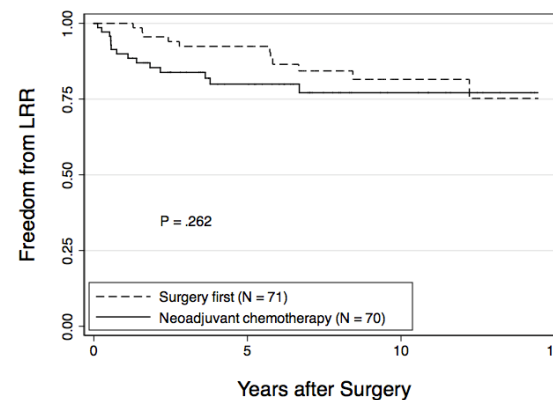
2 factors



3 factors



4 factors



Summary

- Neoadjuvant chemotherapy downstages significant number of patients with clinical stage II/III disease
- Appropriately selected patients achieve high rates of LR control with BCT
- LRR after BCT is driven by biologic factors, not the timing of chemotherapy

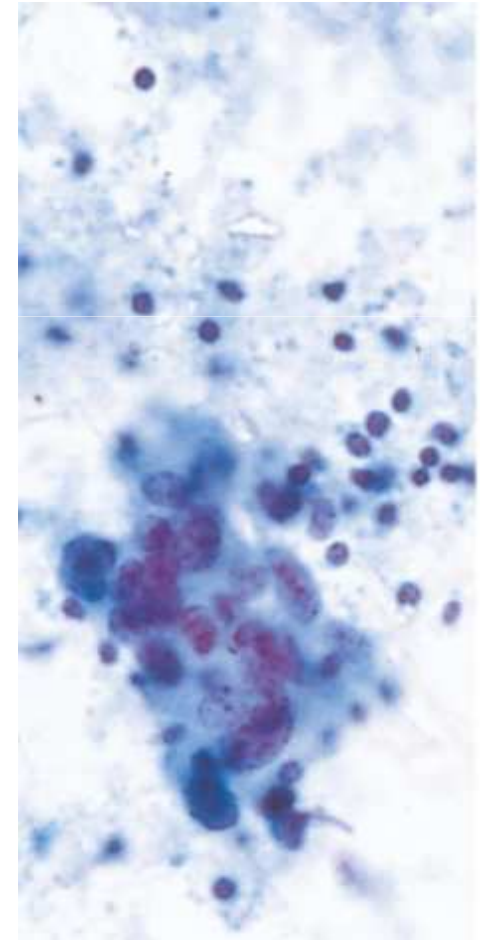
Axillary Management

- US of regional nodal basins performed at time of diagnosis
- FNA of suspicious LNs
- Value of identifying clinical NP disease
 - Consider neoadjuvant chemotherapy
 - Omit SLNB

Axillary Management



FNA



Axillary Management After Neoadjuvant Chemotherapy

- Node negative
 - SLN biopsy (after neoadjuvant chemo)
 - ALND if SLN +
- Node positive
 - ALND

SLNB After Neoadjuvant Chemotherapy

- Meta-analysis
 - N=27 studies; 2148 patients
 - 2000 - 2009

Success Rate	False Negative Rate
90.5% (88% - 92%)	10.5% (8.1% - 31.6%)

SLNB After Neoadjuvant Chemotherapy for cN0 Patients

- 1997-2007
- 3,746 clinically node negative patients with invasive breast cancer
 - 3,171 (85%) underwent surgery as first intervention
 - 575 (15%) underwent SLNB after chemotherapy

SLN Identification Rates

- Overall 98.5%
 - Surgery first 98.7%
 - Chemotherapy first 97.4%
- } P=0.017
- No impact of age, T size, histology, tumor location, biopsy type, surgery type

False Negative Rates

- Surgery first
 - 542 planned SLNB + ALND
 - 22 FN events = 4.1%
 - Chemotherapy first
 - 84 planned SLNB + ALND
 - 5 FN events = 5.9%
- } P=0.39

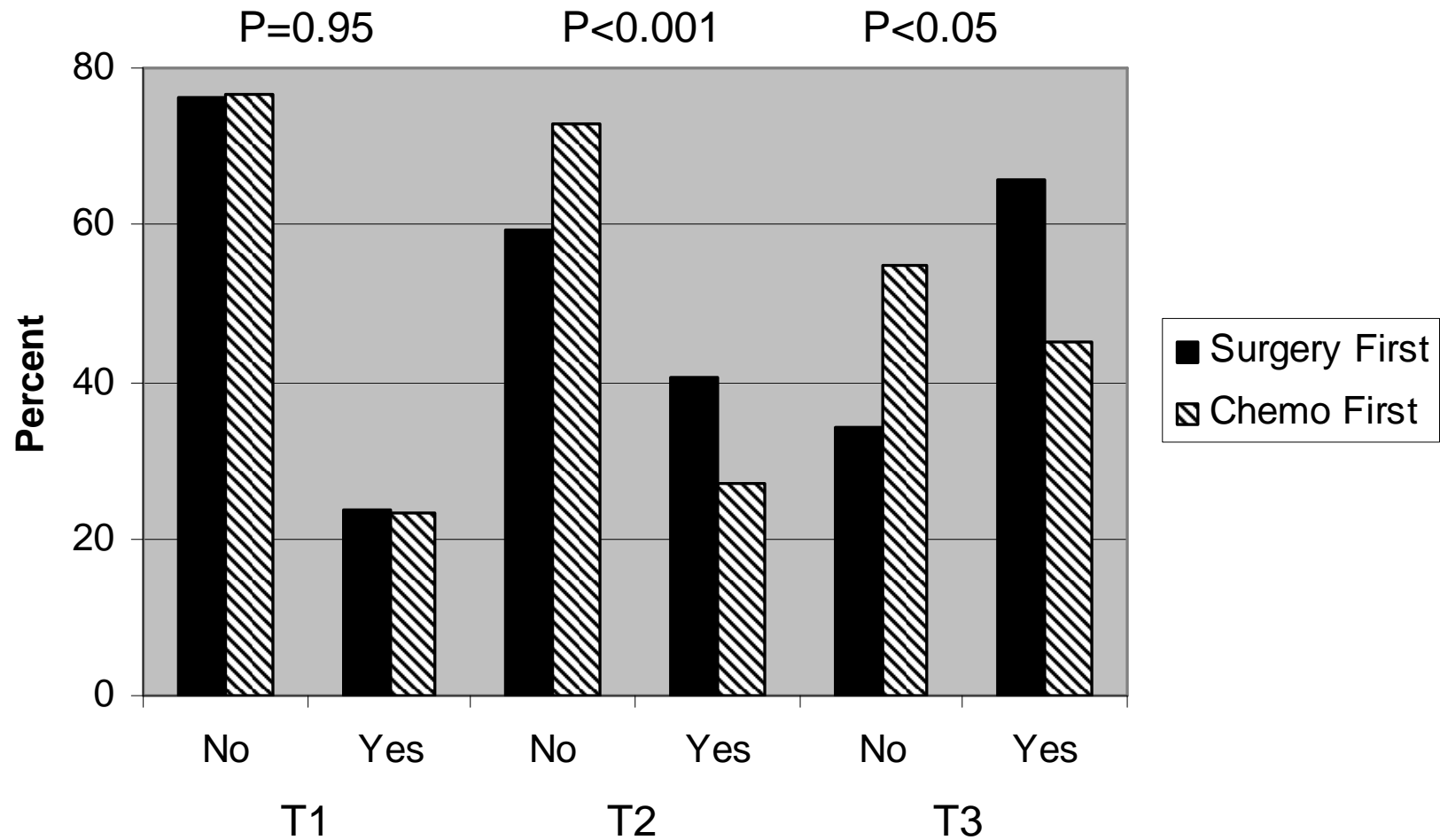
False Negative Rates

- Factors associated with a FN event:
 - Fewer than 2 SLN removed ($p=0.001$)
 - Blue dye alone used ($p<0.001$)

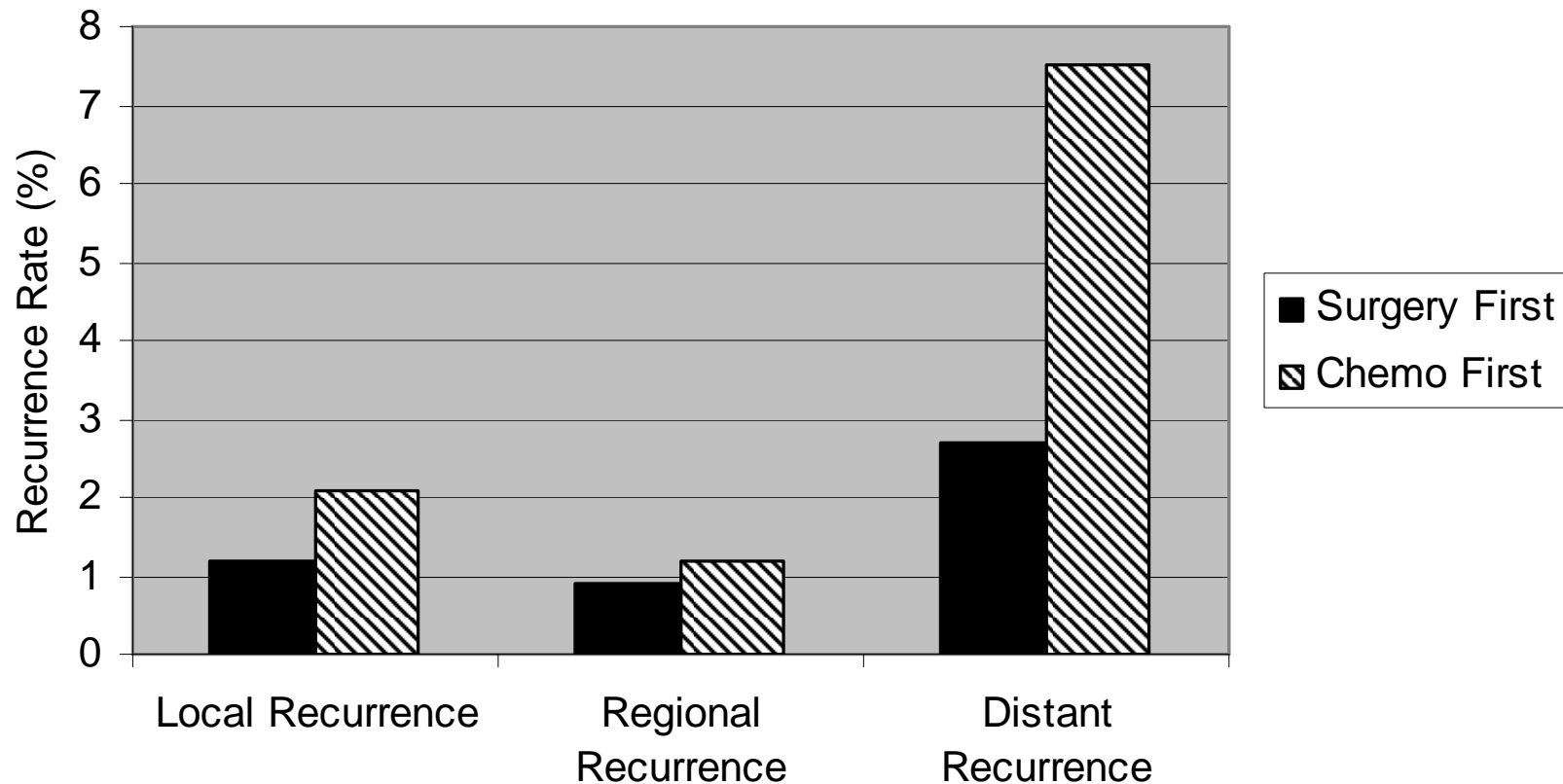
SLN Positive Incidence by Presenting T Stage

T stage	Surgery First	Neoadjuvant Chemo	P value
T1	19%	13%	0.20
T2	37%	21%	<0.0001
T3	51%	30%	0.04

ALND Rates by Presenting T Stage



Follow-Up and Recurrence Rates



Median follow-up

- Surgery first 47 mo (0-169)
- Chemotherapy first 55 mo (2-168)

Follow-Up and Recurrence Rates

	Surgery First (n=3171)	Neoadjuvant Chemotherapy (n=575)	P value
Clinical Stage			<0.0001
I	2560 (80.7%)	72 (12.4%)	
II	608 (19.2%)	502 (87.4%)	
III	3 (0.09%)	1 (0.2%)	

SLNB After Neoadjuvant Chemotherapy for cN0 Patients

- SLNB after chemotherapy is associated with similar ID and FN rates as in upfront surgery
- Use of neoadjuvant chemotherapy results in lower nodal positivity rates and fewer ALNDs for patients with T2 and T3 tumors
- SLNB after neoadjuvant chemotherapy does not lead to higher LR failure rates

Axillary Management After Neoadjuvant Chemotherapy

- Node negative
 - SLN biopsy
 - ALND if SLN +
- Node positive
 - ALND

SLNB After Neoadjuvant Chemotherapy

Institution (Trial)	Number of Patients	FN rate for SLNB in patients with clinically node positive disease
MD Anderson 2007	40	25%
MD Anderson 2012	111	21%
University of Michigan	40	11%
French Multi-Institutional	24	13%

Shen J et al. *Cancer* 2007;109:11255-1263

Alvarado R et al. *Ann Surg Oncol* 2012;19:3177-3184

Newman L et al. *Ann Surg Oncol* 2007;14:2946-2952

Classe J et al. *J Clin Oncol* 2009;27:726-732

ACOSOG Z1071

- SLNB after neoadjuvant chemotherapy for node positive breast cancer
- Hypotheses:
 - SLNB is an accurate method of axillary staging after neoadjuvant chemotherapy
 - Axillary US provides accurate reflection of axillary disease

ACOSOG Z1071

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



REGISTER*



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



REGISTER*

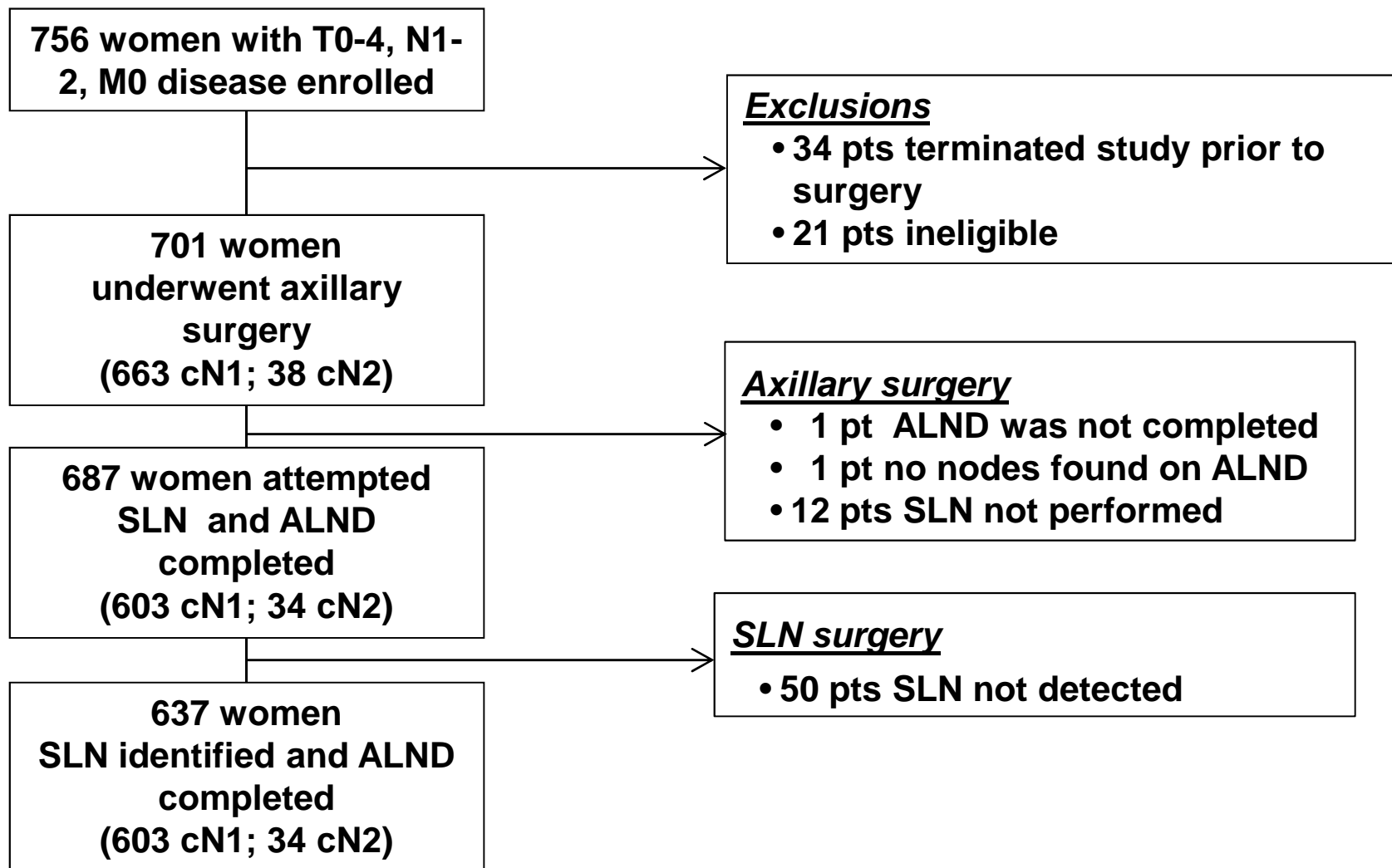


SLN and ALND

ACOSOG Z1071

- Primary endpoint
 - Determine FN rate
- Secondary endpoints
 - US correlation with residual disease
 - Correlation between FN rate and extent of residual disease
 - Path node status after neoadjuvant chemo
 - pCR and DFS rates in node positive patients receiving neoadjuvant chemo

ACOSOG Z1071



Z1071: SLN Identification Rate

SLN(s) detected in 637 (93%) of 689 women

Patients	N	SLN identified	SLN identification rate (%)	CI
All patients	689	639	92.7	90.5 - 94.6
cN1	651	605	92.9	90.7 - 94.8
cN2	38	34	89.5	75.2 - 97.1

Z1071: False Negative Rate

FNR among patients with cN1 disease and at least 2 SLNs examined

$$\text{FNR} = \frac{\# \text{ pts SLN - / ALND +}}{\# \text{ pts SLN + or ALND +}}$$

310 patients had residual nodal disease

39 of these patients had negative SLNs

$$\text{FNR} = 12.6\%$$

95% probability that the false negative rate lies in the range
of 9.35 to 16.74%.

FNRs in cN1 Patients with 2+ SLNs examined

310 patients		p Value
Mapping Agent		
Blue dye only	2/9 (22.2%)	p=0.045
Radiolabeled colloid only	10/50 (20.0%)	
Both blue dye and radiolabeled colloid	27/251 (10.8%)	
Number of SLN Examined		
2	19/90 (21.1%)	p=NS
3	7/78 (9.0%)	
4	4/60 (6.7%)	
5+	9/82 (11.0%)	
Clinical T Stage		
T0/T1	6/39 (15.4%)	p=NS
T2	26/186 (14.0%)	
T3	6/74 (8.1%)	
T4	1/11 (9.1%)	

Z1071 Summary

- Nodal pCR rate = 40%
- SLN ID rate = 93%
- SLN correctly identified nodal status = 91%
- FNR in cN1 disease with 2+ SLN examined = 12.6%
- FNR with use of dual tracer = 10.8%

Conclusions

- Neoadjuvant chemo ↓ size of most tumors and ↓ incidence of + nodes
- BCT can be performed safely in appropriately selected patients following neoadjuvant chemotherapy
- SLNB following neoadjuvant chemotherapy in cN0 patients decreases LN + rates and need for cALND in patients with cT2/T3 tumors

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