

# Indications and Technical Considerations for Adjuvant Radiation after Neoadjuvant Chemotherapy in Breast Cancer

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Nothing to Disclose

# Neoadjuvant Chemotherapy

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## History

- once reserved for inoperable disease
  - excellent response rates
- now increasingly more common
- its increased use raises new questions

# Neoadjuvant Chemotherapy

## Advantages

- excellent research tool
  - compare agents
  - study biology
- in vivo assessment of response
- increase breast conservation

# Neoadjuvant Chemotherapy

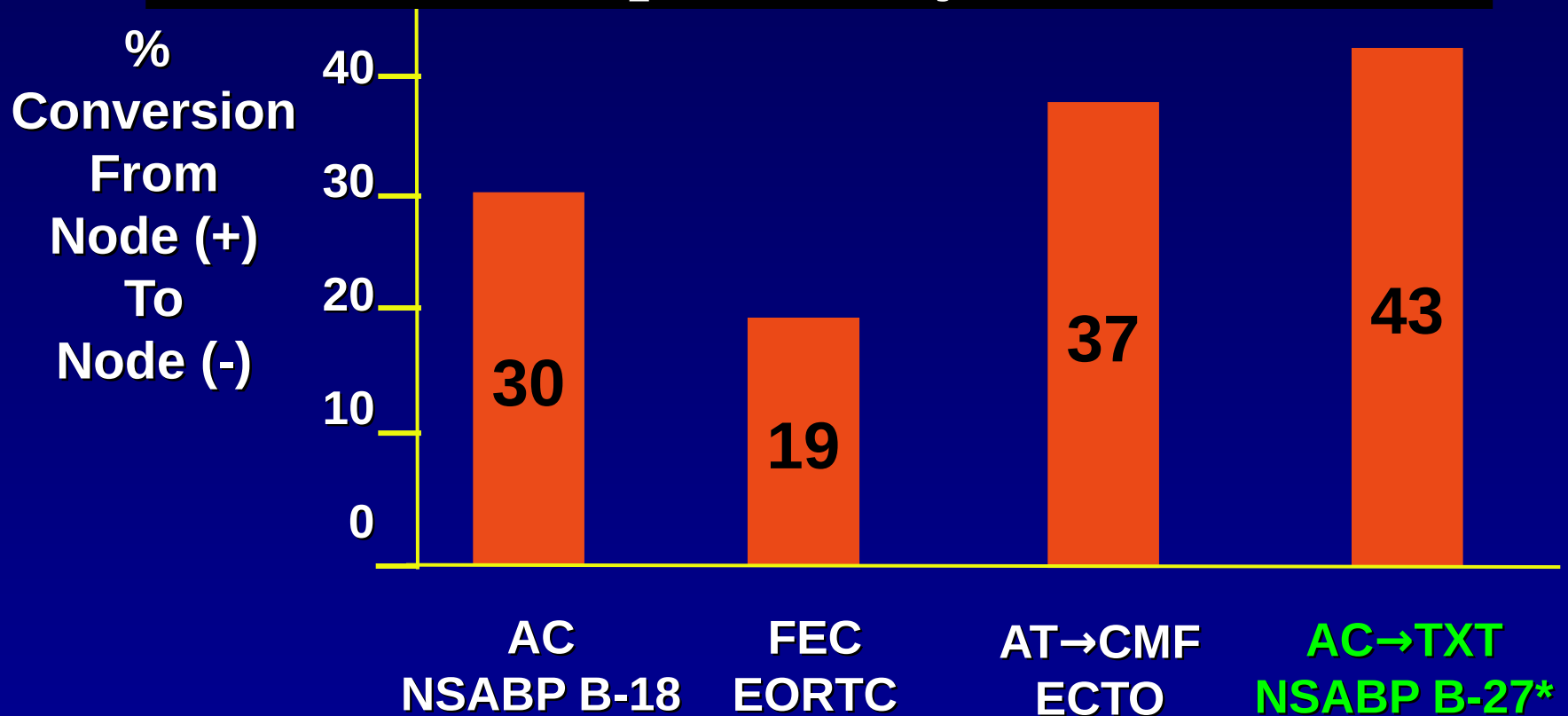
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## Possible Disadvantages

- sentinel lymph node surgery
- recurrence rates after breast conservation
- indications for postmastectomy XRT

# Axillary Node Down-Staging with NCT

More than 40% of initially node-positive women could potentially avoid ALND!



\*Assuming 30% nodal down-staging with neoadjuvant AC

# 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)
<u>NSABP B-32 Randomized Trial</u>	<u>10%</u>	<u>(75/766)</u>
NSABP B-27 (After NC)	11%	(15/140)
Meta-Analysis (Xing, 2006)	12%	(65/540)
Meta-Analysis (Kelly, 2009)	8%	(~64/758)

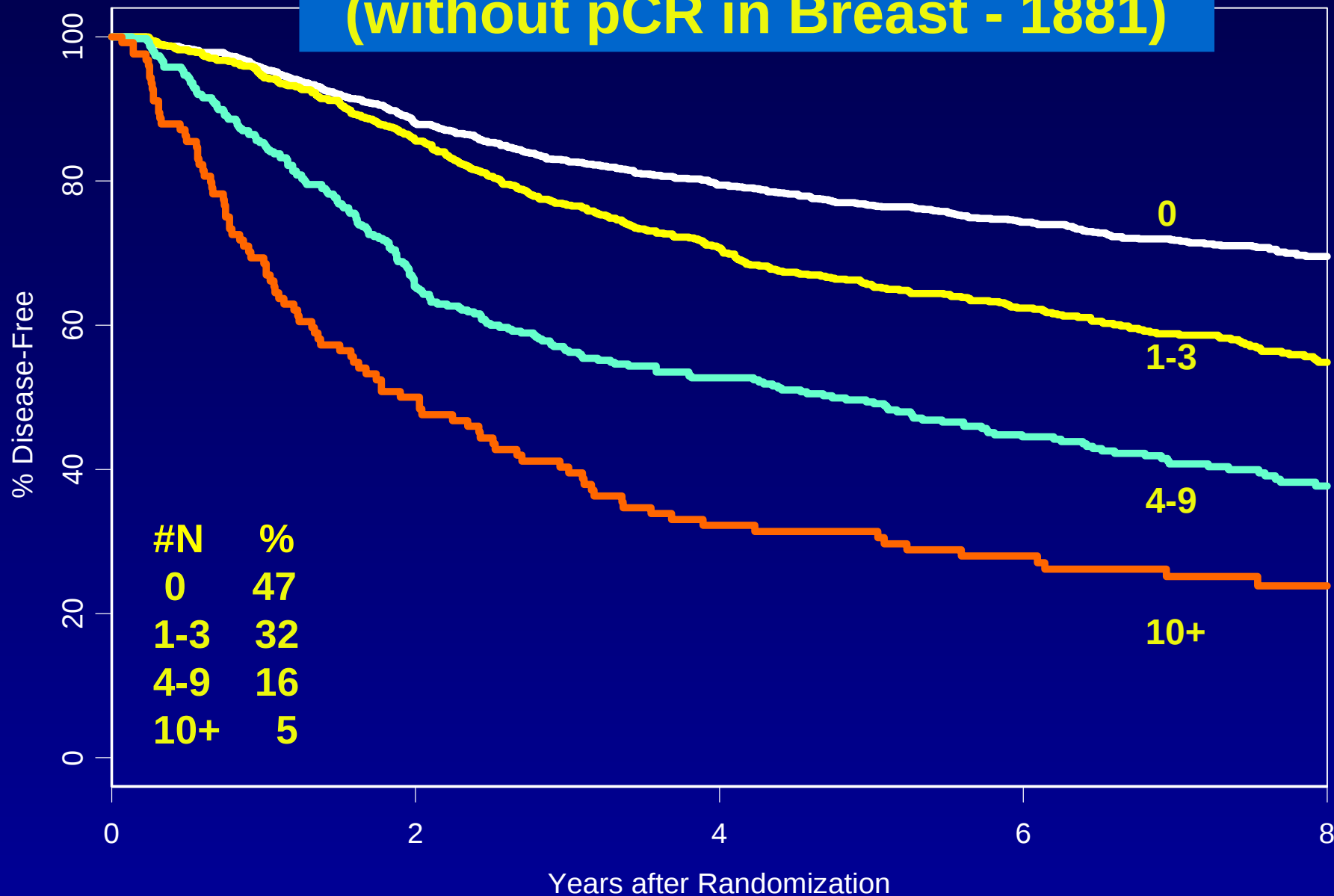
Krag DN: N Engl J Med 1998    Veronesi U: N Engl J Med 2003    McMasters KM: J Clin Oncol 2000  
 Mamounas EP: J Clin Oncol 2005    Tafra L: Am J Surg 2001    Xing Y: Br J Surg 2005    Julian JB: SABCS  
 2004. Kelly, AM: Acad Radiol, 2009

# Arguments Against SLN Biopsy After NCT

Loss of important prognostic information derived from pre-chemo nodal pathology

(Leads to recommendation to do SLN prior to treatment)

# B-27 DFS By Nodes (without pCR in Breast - 1881)





## SLN Biopsy After Neoadjuvant Chemotherapy – Do We Lose Prognostic Information?

- Post-treatment nodal status is at least as powerful as pre-treatment nodes
- In fact, by possibly removing the only positive nodes with SLNB prior to treatment, we lose even more important information

# **ACOSOG Z1071 Schema**

## **Accuracy of SLN After NCT in Node Positive Breast Cancer**

**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**

# ACOSOG Z1071

- N = 663
- T0-T4, N1, N2
- No node identified 7.1%
- PCR nodes 41%
- FNR 12.6%
- Negative for endpoint: < 10%

# Targeted Axillary Dissection

- **Clip the involved node upfront:**
- **FNR:**

<b>Clipped node</b>	<b>4.2%</b>
<b>SLN</b>	<b>10.1%</b>
<b>Both</b>	<b>1.4%</b>
- **Clip and SLN not the same 23%**

# LRR in ACOSOG Z1071

	Univariable	
Variable	HR (95% CI)	p-value
Clinical T stage		
T0-T2	1.00 (ref)	0.34
T3-T4	1.38 (0.72 – 2.65)	
Path CR breast		
No	1.00 (ref)	0.019
Yes	0.35 (0.15 – 0.84)	
Path CR axilla		
No	1.00 (ref)	0.064
Yes	0.51 (0.25 – 1.04)	
Path CR both		
No	1.00 (ref)	0.040
Yes	0.37 (0.15 – 0.96)	
RCB		
0	1.00 (ref)	0.035
1	1.38 (0.15 – 12.36)	
2	2.25 (0.66 – 7.69)	
3	4.65 (1.53 – 14.12)	

Hafty et al,  
ASTRO 2016

# LRR ACOSOG Z1071

	<b>Univariable</b>	
<b>Age</b>		
<50	1.00 (ref)	0.42
>50	1.30 (0.69 – 2.45)	
<b>Tumor Biology</b>		
HRpos/Her2-	1.00 (ref)	0.002
Her2 +	1.49 (0.65 – 3.45)	
Triple negative	3.59 (1.68 – 7.68)	
<b>Surgery Done</b>		
BCT	1.00 (ref)	0.067
Mastectomy	0.55 (0.29 – 1.04)	
<b>RT done</b>		
Yes	1.00 (ref)	0.033
No	2.18 (1.06 – 4.48)	

Hafty et al,  
ASTRO 2016

# LRR ACOSOG Z1071

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Hafty et al,  
ASTRO 2016



# Radiation Treatment Approach

	LRR (5 YR)	HR(p)
▶ <b>Mastectomy</b>		
◦ Residual Node Positive		
• PMRT	93.7%	2.24 (.17)
• No PMRT	59.8%	
◦ Residual Node Negative		
• PMRT	100%	
• No PMRT	95.4%	
▶ <b>Breast Conserving Surgery</b>		
◦ Residual Node Positive		
• Regional Nodal RT	88.5%	1.01 (.99)
• No Regional Nodal RT	90.5%	
◦ Residual Node Negative		
• Regional Nodal RT	90.3%	1.59 (.54)
• No Regional Nodal RT	93.8%	





# Outcomes by Radiation in patients Eligible for NRG B51

(Patients with Axillary pCR after NAC)

## ▶ Mastectomy patients with axillary pCR (Eligible for NRG B51)

	With PMRT	Without PMRT
◦ LRR	100%	95.4%
◦ DSS	90.7%	77.5%
◦ BCSS	96.2%	95.6%
◦ OS	95.3%	88.6%

## ▶ BCS patients with axillary pCR (Eligible for NRG B51)

	With Regional Nodal RT	Without Regional Nodal RT
◦ LRR	90.3%	93.8%
◦ DSS	91.1%	92.8%
◦ BCSS	100%	94.6%
◦ OS	100%	90.0%



# Outcomes in Triple Negative Patients

	LRR (3 YR)	HR (p)
▶ <b>Mastectomy Patients</b>		
◦ PMRT	90%	2.85 (0.21)
◦ No PMRT	75.8%	
▶ <b>Breast Conservation Patients</b>		
◦ Regional Nodal RT	95.2%	.62 (.56)
◦ NoRegional Nodal RT	85.7%	

ALLIANCE

**RUTGERS**  
Cancer Institute  
of New Jersey

# Conclusions



- ▶ Risk of overall survival, disease free survival or distant metastasis free survival was no different in those receiving or not receiving post surgical radiation
- ▶ Although overall post surgical radiation had an impact on local–regional relapse, for those patients converting to node negative disease after NAC there is no evidence that omission of radiation had a significant impact on local–regional relapse, distant metastasis, disease specific or overall survival
- ▶ Tumor Biology had a significant impact on local–regional relapse rates with triple negative patients and Her2+ patients having a significantly higher LRR compared to Hormone Receptor Positive Patients

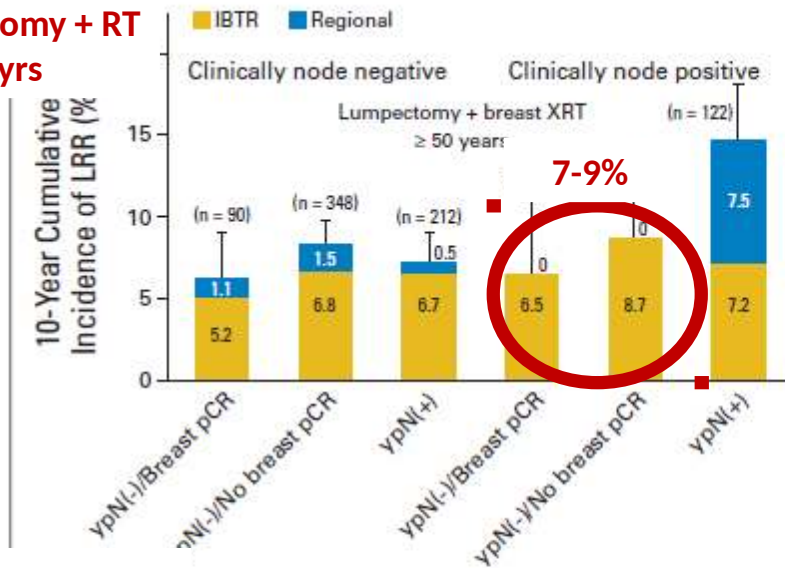


# Combined Analysis of B-18/B-27 Independent Predictors of LRF

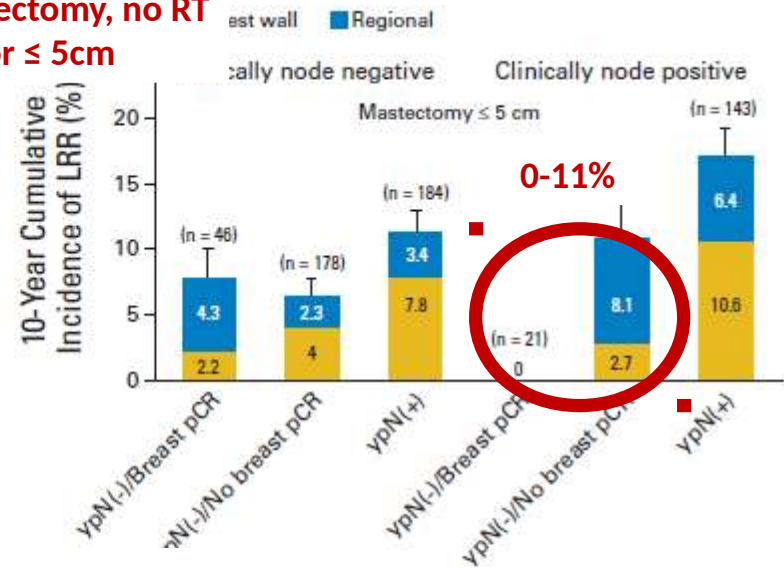
<b>Lumpectomy + XRT</b> <b>(1890 Pts, 190 Events)</b>	<b>Mastectomy</b> <b>(1070 Pts, 128 Events)</b>
<b>Age</b> ( $\geq 50$ years vs. $< 50$ years)	<b>Clinical Tumor Size</b> ( $> 5$ cm vs. $\leq 5$ cm)
<b>Clinical Nodal Status</b> (+) vs. (-)	<b>Clinical Nodal Status</b> (+) vs. (-)
<b>Breast/Nodal Path Status</b> Node(-)/No pCR vs. Node(-)/pCR Node(+) vs. Node(-) /pCR	<b>Breast/Nodal Path Status</b> Node(-)/No pCR vs. Node(-)/pCR Node(+) vs. Node(-) /pCR

# Moving to Biology-Based Loco-regional Treatment Decisions

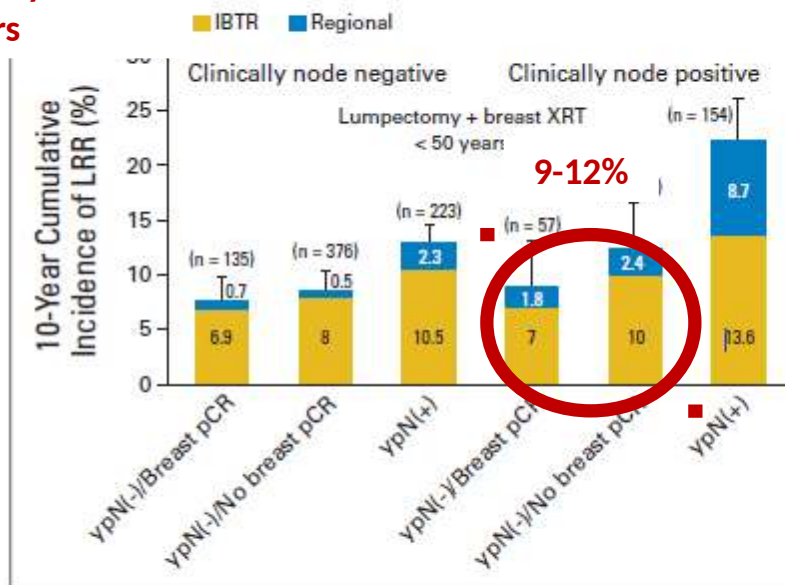
## Lumpectomy + RT Age ≥ 50yrs



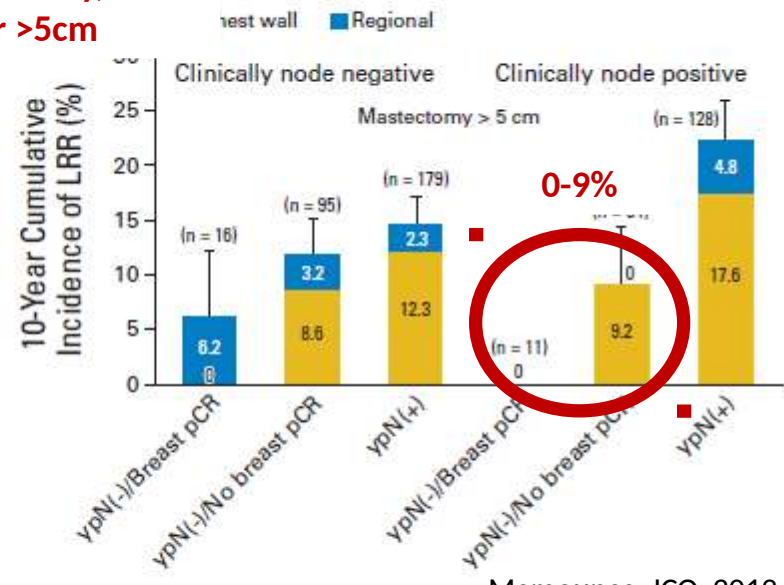
## Mastectomy, no RT Tumor ≤ 5cm



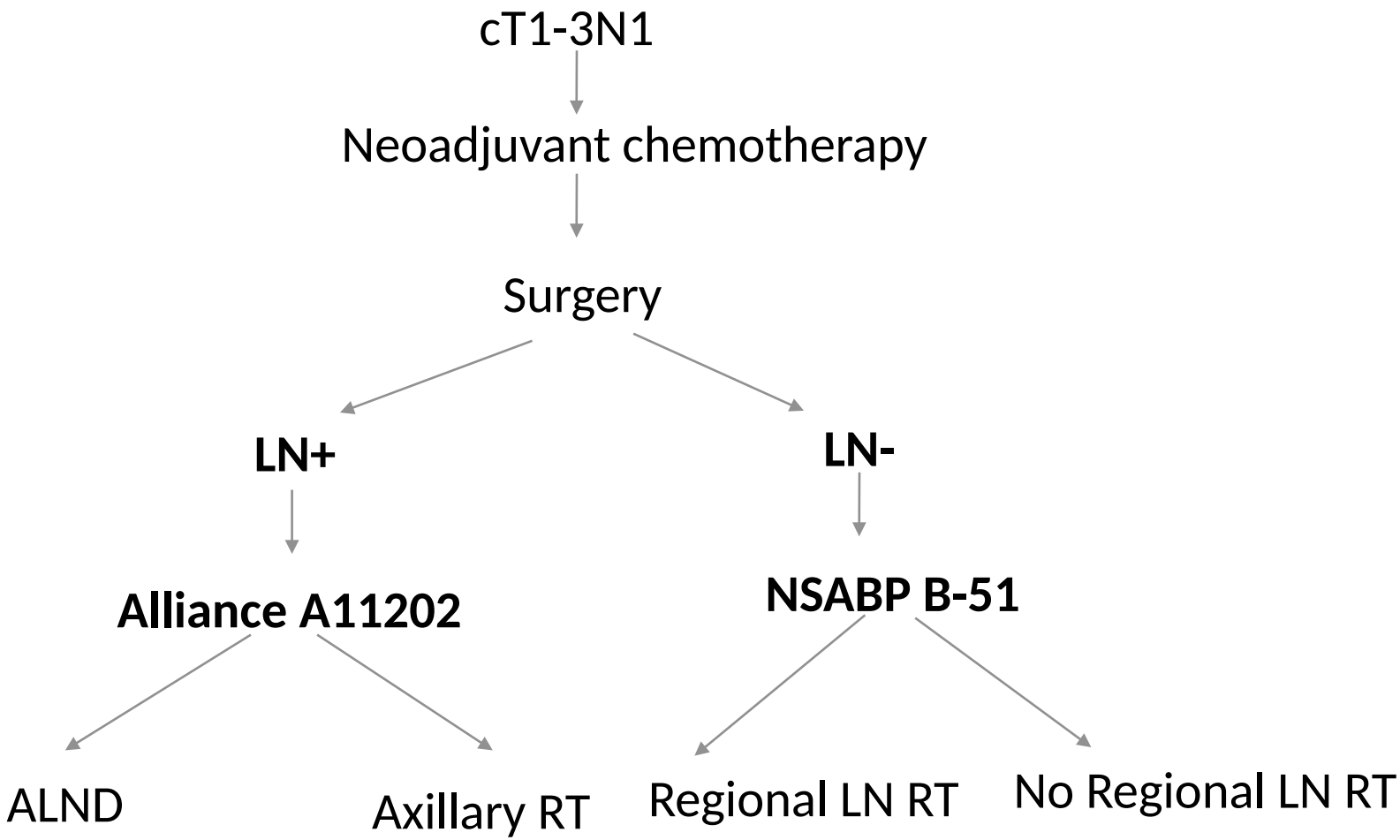
## Lumpectomy + RT Age < 50yrs



## Mastectomy, no RT Tumor >5cm



# Ongoing Trials: Moving to Biology-Based Loco-regional Treatment Decisions



# Summary I

- In patients with operable breast cancer, the **10-year cum. incidence of LRF** after neoadjuvant chemotherapy was **10-12%**
- Despite **worse** patient characteristics in B-27, **LRF with AC in B-27 was lower than in B-18** and there was an **effect of docetaxel (about 25% reduction)**
- Overall, the ratio of local vs. regional failure is about **3:1** but this ratio is influenced by type of surgery and other independent predictors of LRF

# Summary II

- Independent predictors of LRF in lumpectomy + breast XRT patients include: **age, clinical nodal status (before NC) and pathologic breast/nodal response**
- Independent predictors of LRF in mastectomy patients include: **clinical tumor size (before NC), clinical nodal status (before NC) and pathologic breast/nodal response**
- The effect of age (in lumpectomy patients), clinical tumor size (in mastectomy patients) and clinical nodal status on LRF appears to diminish with increasing pathologic response in the breast and axillary nodes



# MDA Practice

- RNI after breast conservation
  - For all ypN+
  - All cT3N+ ypN0, pending trial
  - Selected Stage II ypN0
- After Mastectomy Radiation is indicated for:
  - » All ypN+
  - » All T3N+ pending trial
  - » Selected Stage II ypN0

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**Breast Conservative  
Therapy After  
Neoadjuvant Chemotherapy**

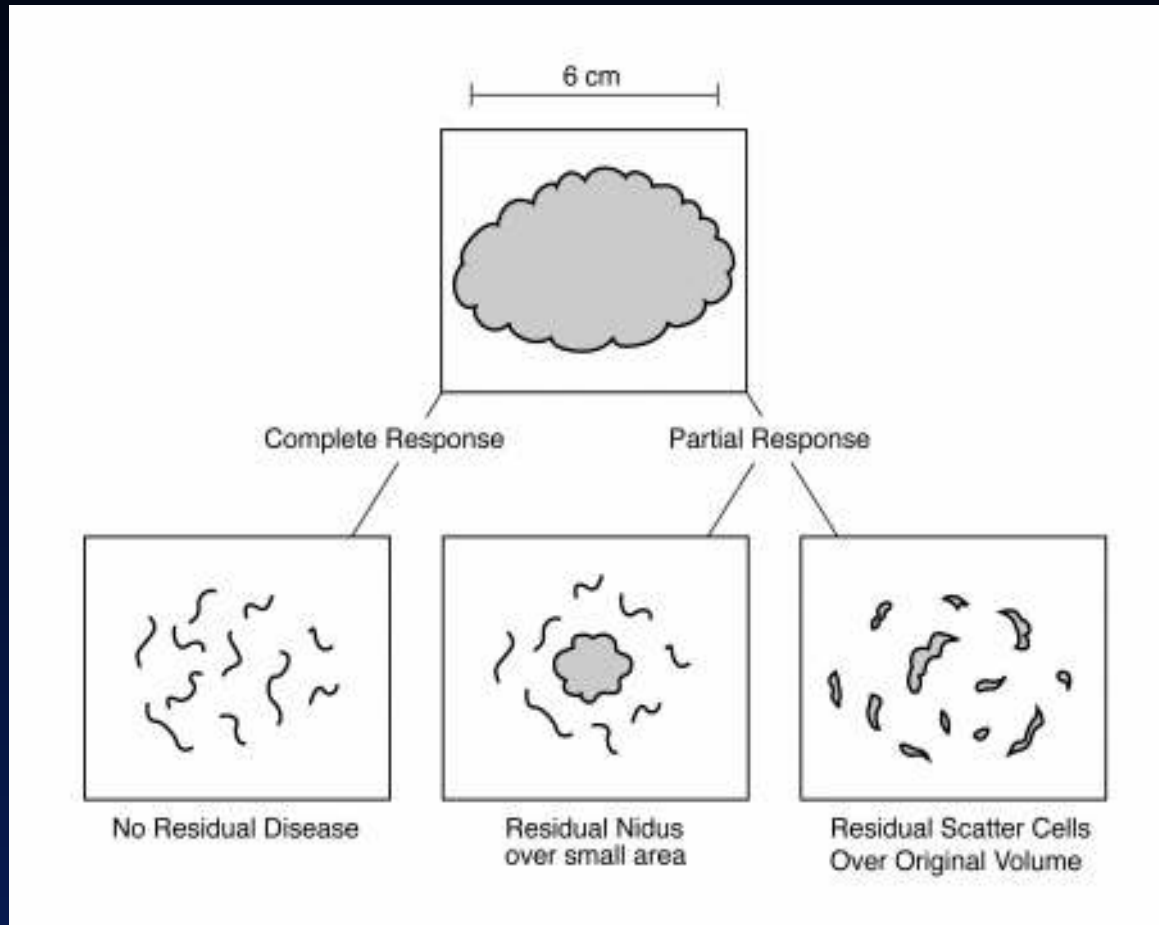
# Rationale for This Approach

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## Neoadjuvant Chemotherapy

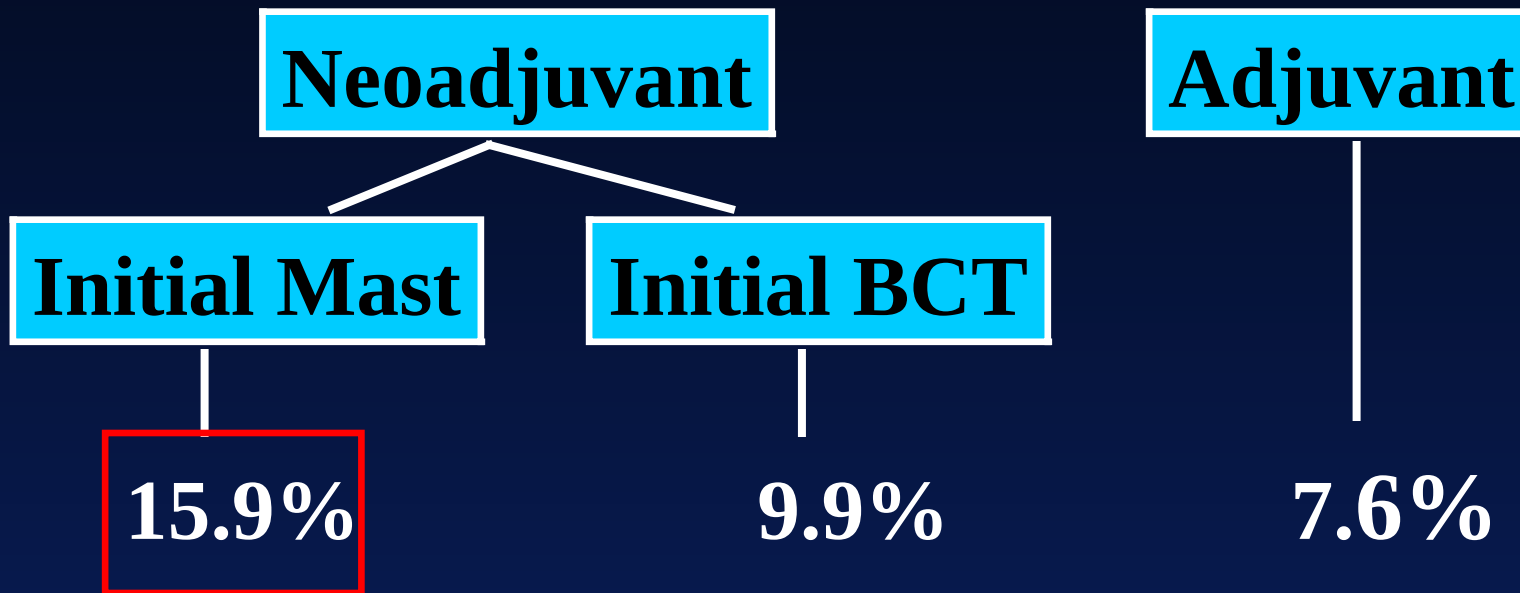
- 80% - 90% have significant response
- lumpectomy directed at post-chemo nidus
- allows for acceptable breast aesthetics

# Concern Over This Approach: Responses Are Not Uniform



# IBTR May Be Higher in Advanced Tumors

## NSABP B-18: 9-yr IBTR Rates



# High Recurrence Risk

Mauriac et al

*(Ann Oncol, 1999)*

- T2 or T3 disease > 3 cm
- median f/u: 10 yrs
- 40 pts treated with NCT + surg + XRT
- no data provided on margins
- IBTR: 9 pts (23%)

# High Recurrence Risk

Rouzier et al

*(J Clin Oncol, 2001)*

- 257 women, 90% T1, T2
- 28% close or positive margins
- IBTR: 16% (5yr), 21% (10yr)
  - age < 40, (40% vs 15%)
  - margin  $\leq$  2mm (32% vs 17%)
  - residual  $\geq$  2cm (30% vs 19%)

# M. D. Anderson Experience

## BCT after neoadjuvant chemotherapy

- treatment years: 1987-2000
- doxorubicin-based, median 4 cycles
- all patients received XRT
- careful selection criteria
- multidisciplinary team approach

**340 eligible patients**

*Chen et al., JCO, 2004*



# Selection Criteria

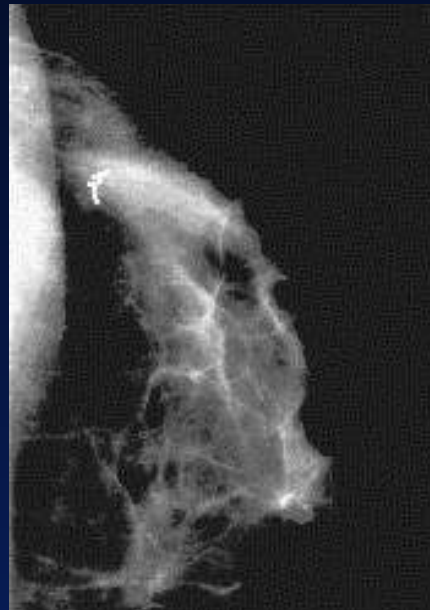
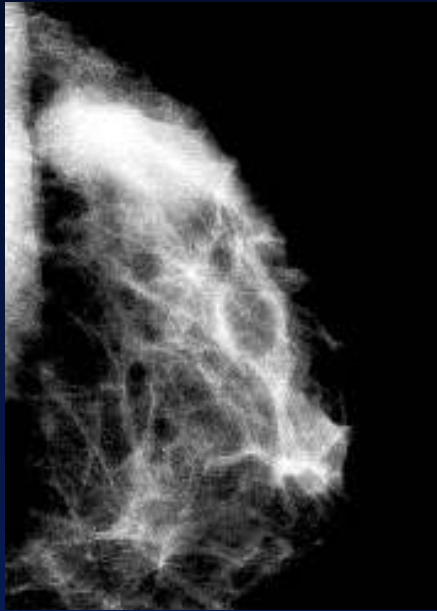
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## Exclusions

- diffuse calcifications
- inability to clear margins
- multicentric disease
- residual skin changes
- significant residual disease post-chemo

# Follow-up During Chemotherapy

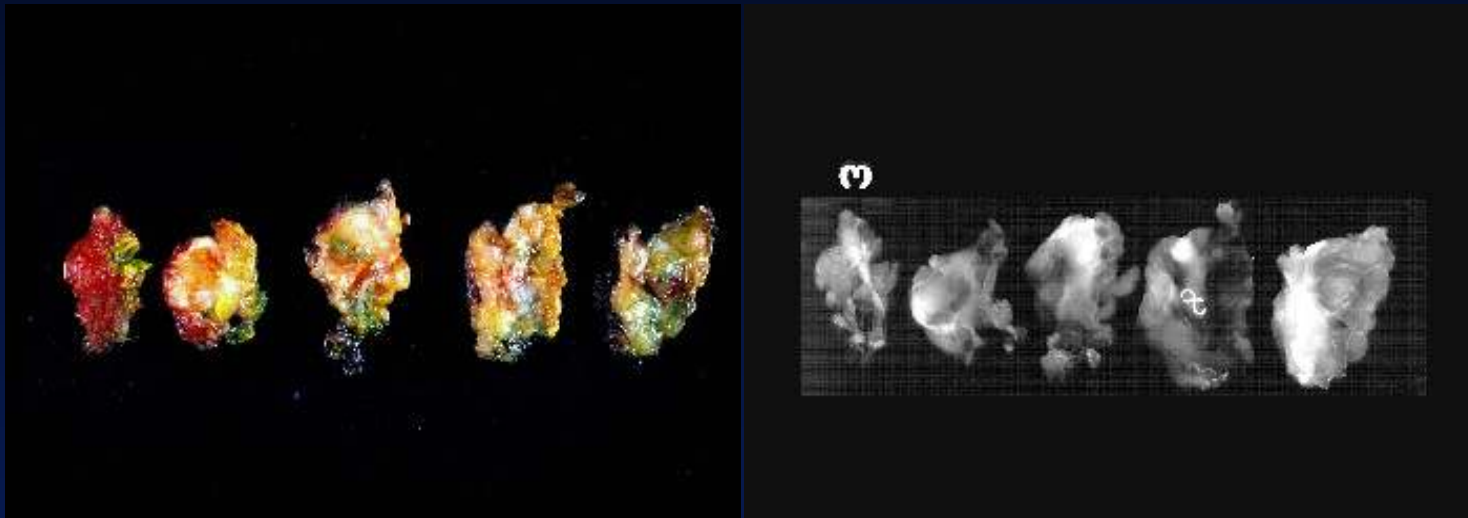
- careful multidisciplinary eval
- metallic clip placement



*Buchholz et al.,  
Cancer, 2003*

# Careful Margin Assessment

- serial section radiographs
- re-resection of margins



# Patients and Methods

## Study Population

- median age: 46, 58% premenopausal
- Stage
  - I 4%
  - IIA 24%
  - IIB 33%
  - III 39%

# Patients and Methods

## Surgical margin status

- negative 79%
- < 2 mm 15%
- positive 4%
- unknown 2%

# IBTR Results

## IBTR-free Rates

5-yr

10-yr

94%

90%

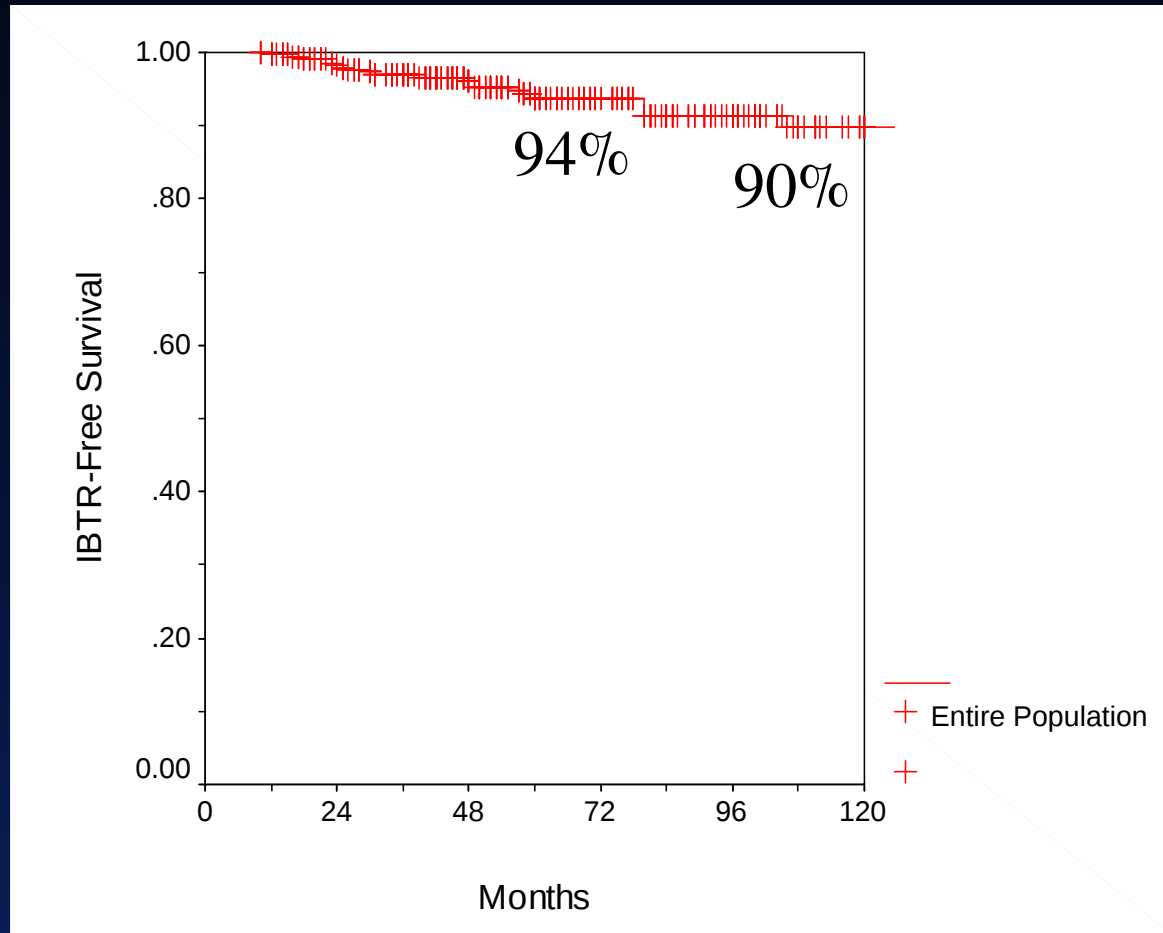
## LRR-free Rates

5-yr

10-yr

90%

85%



# M. D. Anderson Prognostic Index

<u>Factor</u>	<u>Score</u>	<u>value</u>
N2 or N3	yes/no	0 or 1
LVSI	yes/no	0 or 1
> 2 cm residual	yes/no	0 or 1
Multifocality	yes/no	0 or 1

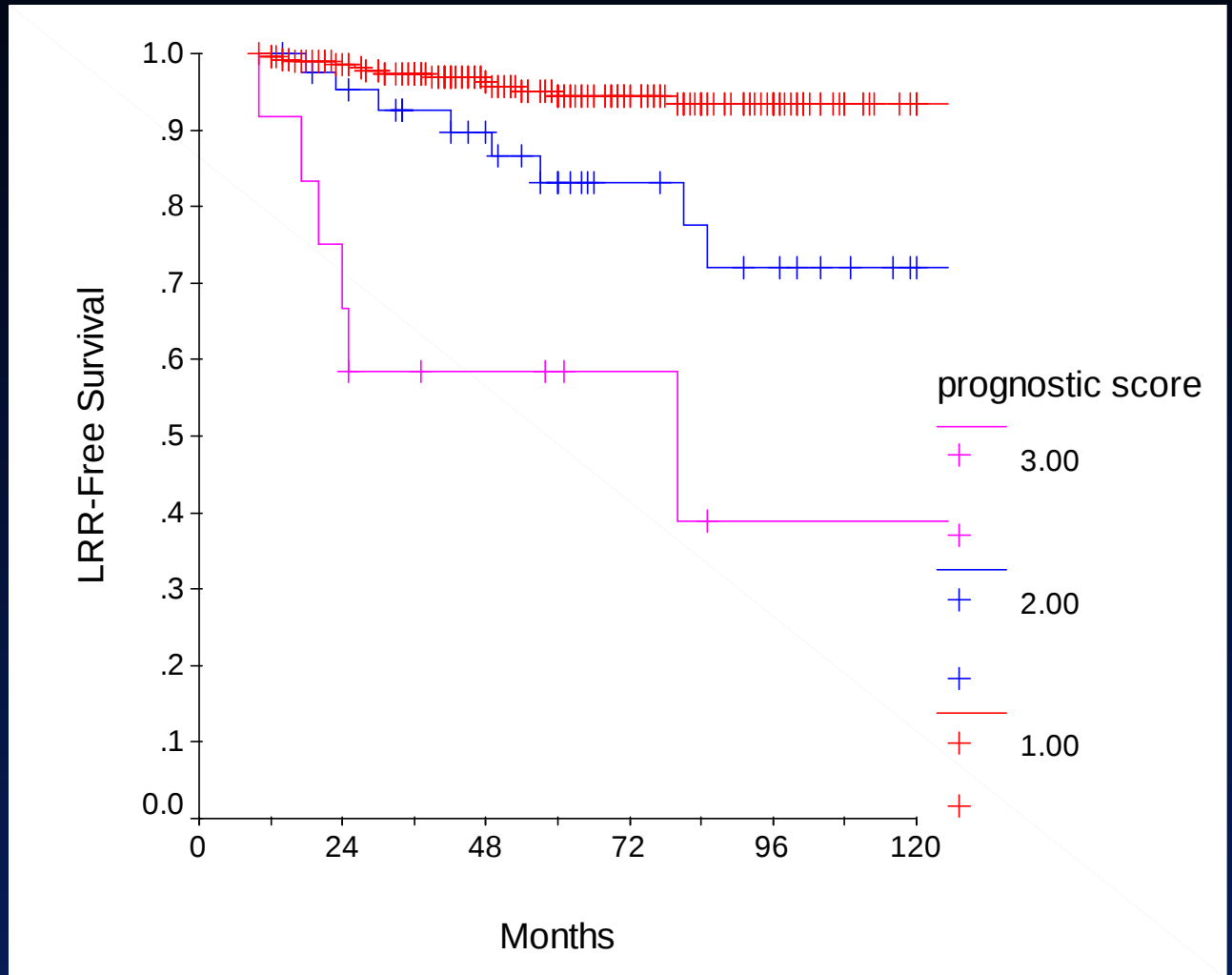
**Total Score Ranges From 0 -> 4**

*Chen et al., Cancer*

# LRR: Prognostic Class

## LRR-free Rates

<u>5-yr</u>	<u>10-yr</u>
94%	93%
83%	78%
58%	39%





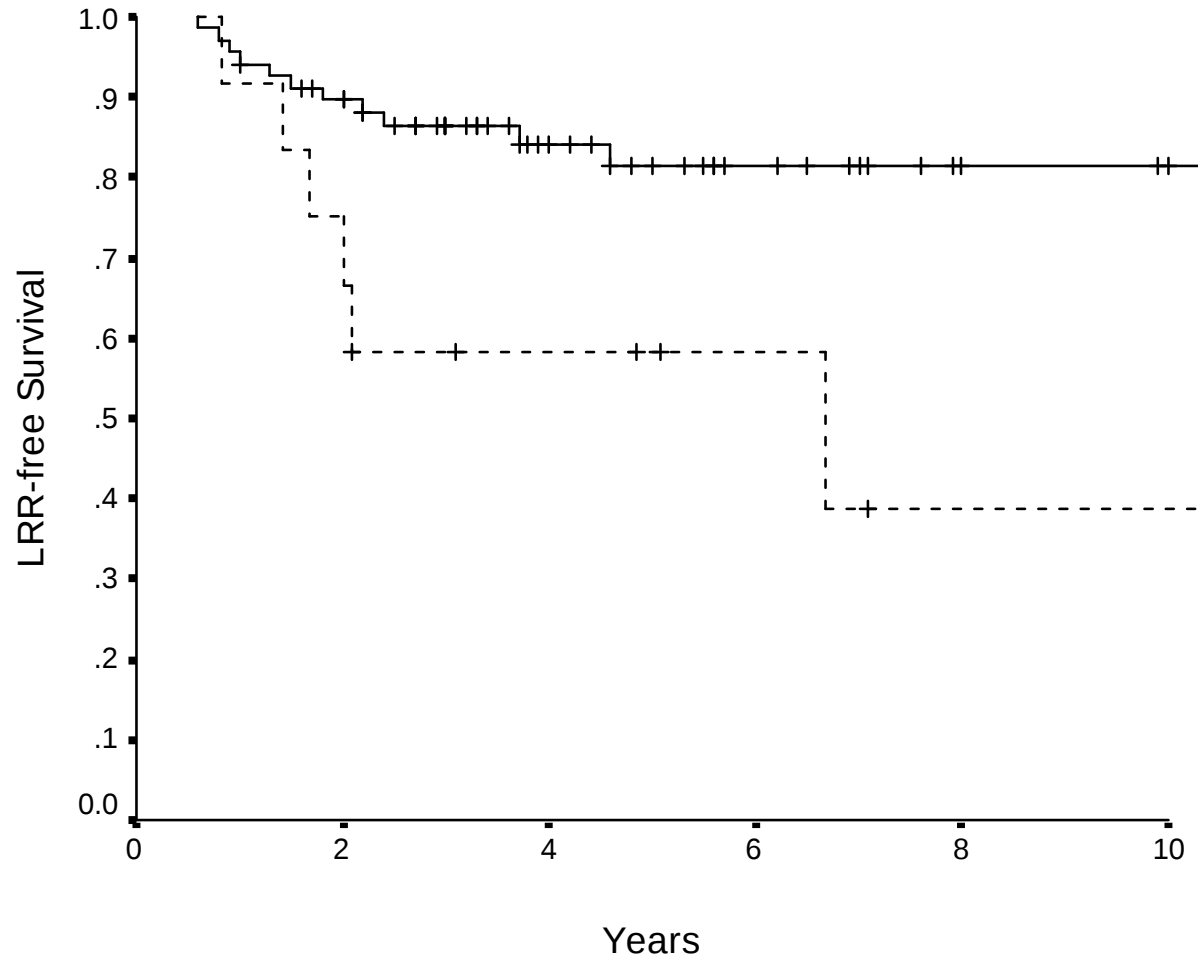
# Prognostic Score of 3/4

**LRR-free  
Rates**

10-yr

**MRM 81%**

**BCT 39%**



# Conclusion

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## BCT after neoadjuvant chemotherapy

- effective and safe treatment
- affords many option of BCT
- careful selection of patients is important

# Conclusion

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## Multidisciplinary Coordination Important

- careful serial imaging
- careful pathology
- margin assessment

# Acknowledgement/Contributors

## S

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