

Neoadjuvant Treatment of Breast Cancer: Role of Radiotherapy

Neoadjuvant Chemotherapy

Many new questions for radiation oncology?

- lack of path stage to guide indications
- should treatment response affect indications
 - breast conservation
 - postmastectomy radiation
 - regional lymph node radiation
- do we need new strategies for poor responders

Case Illustration

45 yo with a T2 (4.5 cm) N1, G3, triple negative

- is BCT safe if she has a good response
- if LN- after chemo
 - should she have radiation to regional LN?
 - should she receive PMRT?
- if she has 10 +LN after chemo
 - is standard PMRT adequate?

Importance of Radiation Treatment Decisions

Eradication of Local-Regional Disease Save Lives

- lower BCT recurrences improves cure rates
 - Oxford meta-analysis
- PMRT improves cure rates
 - Oxford meta-analysis
- regional LN radiation decreases distant mets
 - MA20 trial

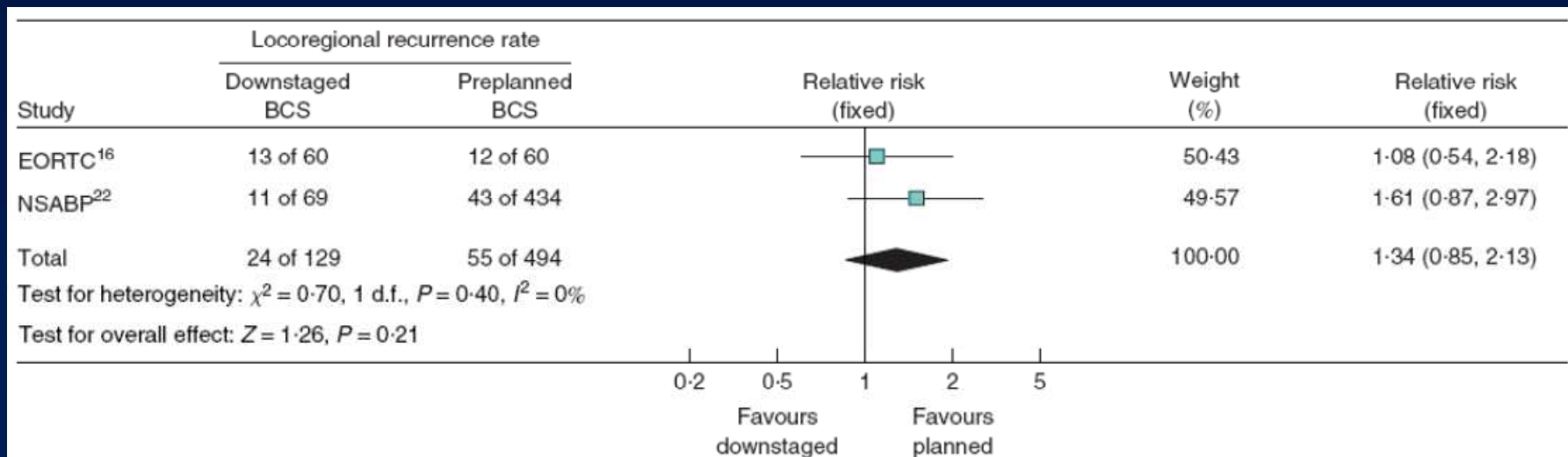
**None of These Trials
Included Patients Treated
With Neoadjuvant
Chemotherapy**

**Is BCT a Safe Option
If Patient Has a
Good Response?**

Yes

Metaanalysis: LRR With BCT After Neoadjuvant Chemotherapy

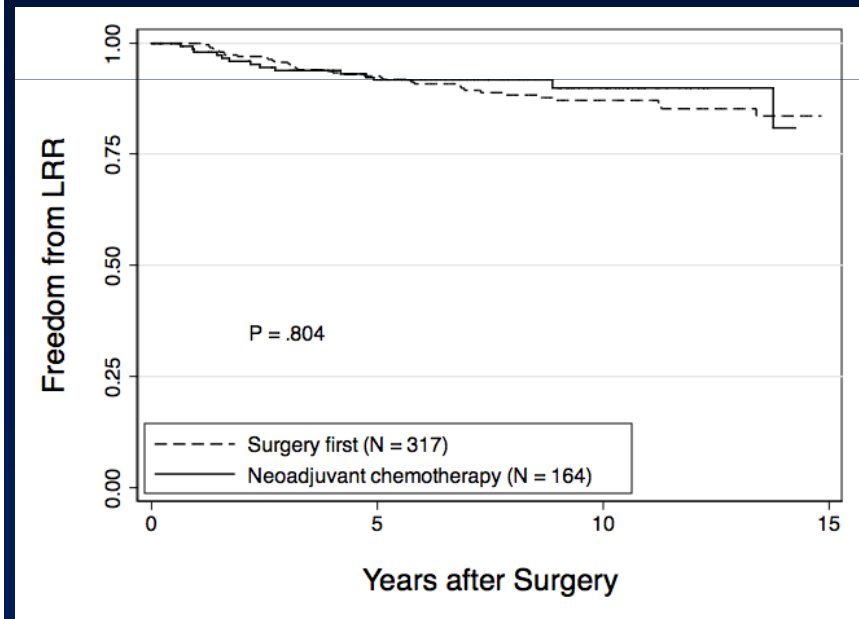
- LRR rates similar after BCT for neoadjuvant vs. adjuvant chemo
- LRR not different in neoadjuvant group downstaged to BCT



MD Anderson BCT Experience

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

LRR with 3 factors



**Which Patients Need PMRT
And/or Regional LN Radiation?**

Indications for PMRT and Regional LN radiation

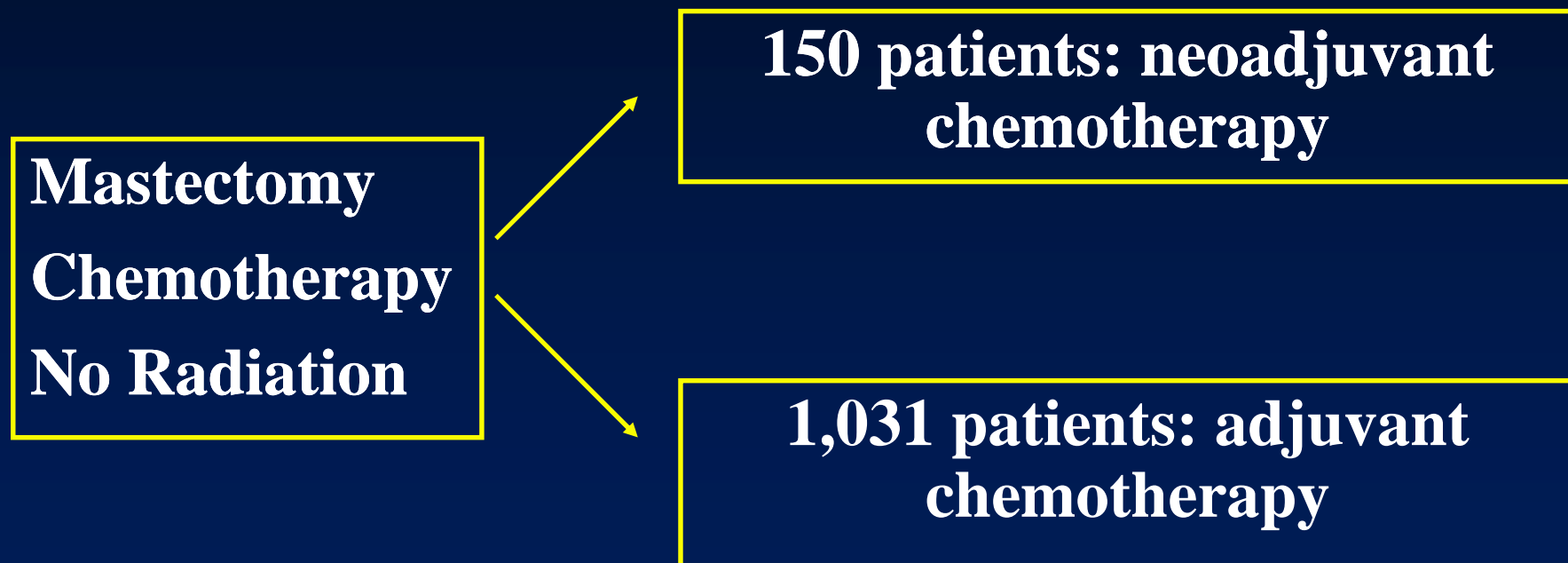
Historically indications based on pathology

- treatment decisions based on
 - pathological size of primary
 - involvement and number of +LN
- NCT: don't know the path extent of disease
- clinical staging of LN is imprecise

**Neoadjuvant Chemotherapy
Changes Pathological Extent
Of Disease In Most Patients**

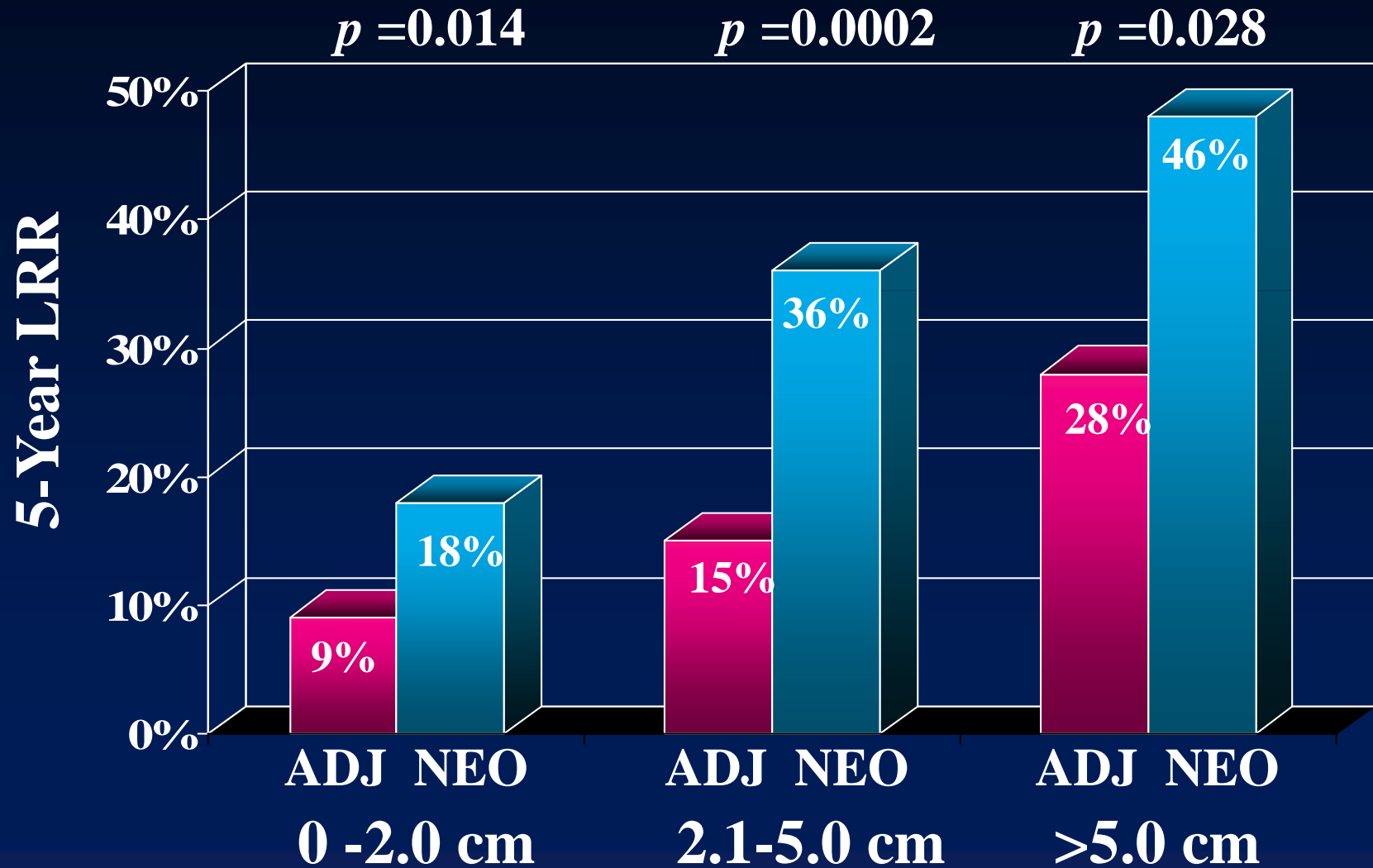
LRR and Pathological Extent of Disease

Correlated pathology and LRR

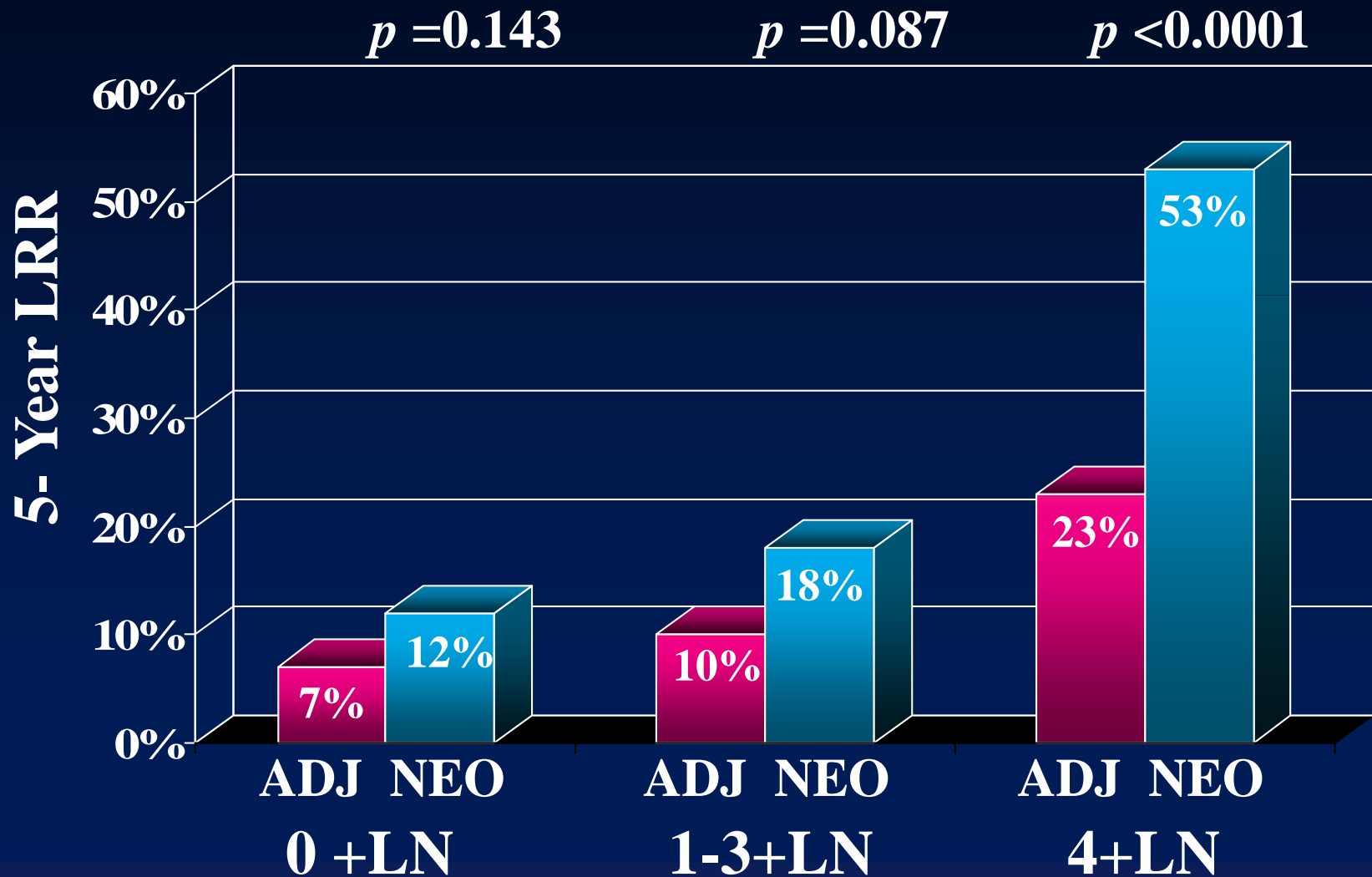


Buchholz et al., Int J Radiat Oncol Biol Phys, 2003

Primary Tumor Size



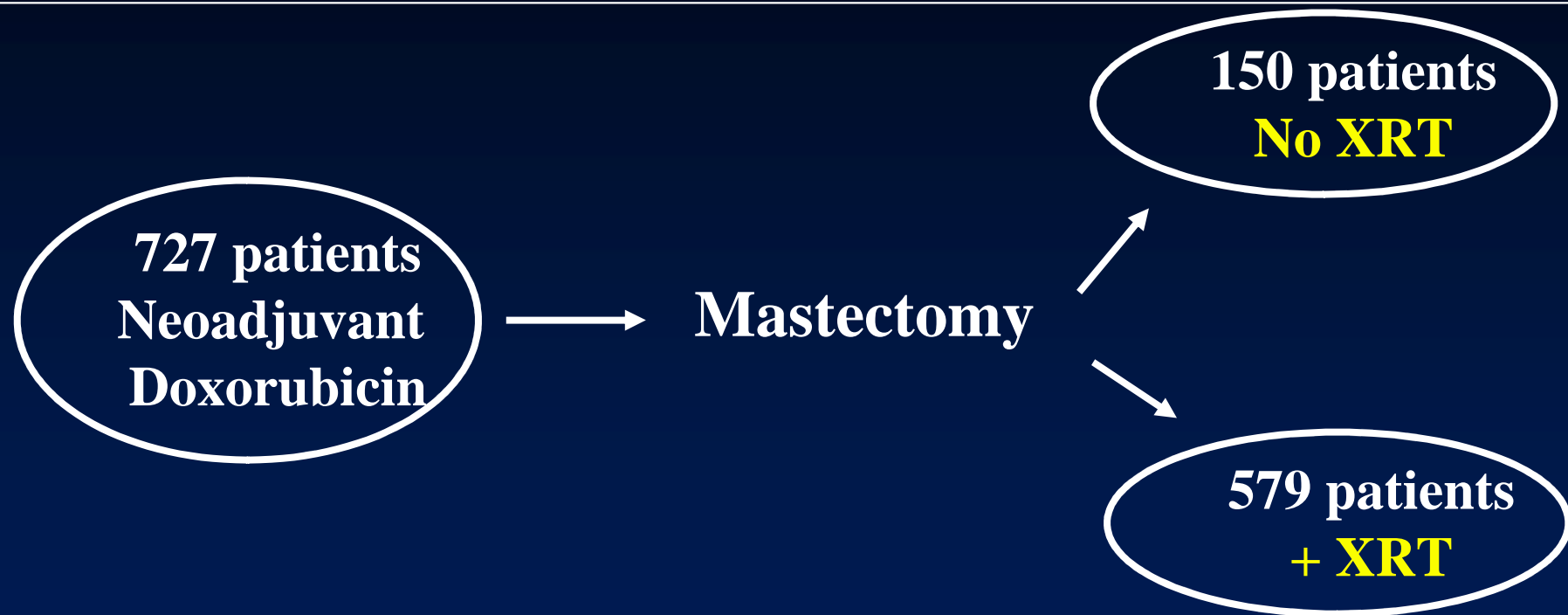
Pathological Nodal Status



**The Risk of LRR According To
Pathological Extent of Disease
After Neoadjuvant Chemotherapy
Is Different than the Risk In
Patients Treated
With Initial Surgery**

**So What Should Be The
Indications for PMRT and/or
Regional LN Radiation?**

MDACC Retrospective Data



XRT: Non-randomized

6 consecutive prospective trials, 1974-1998

Buchholz et al., JCO, 2002

Huang et al., JCO, 2005

Predictors of LRR in Patients Who Did Not Receive Radiation

<u>Factors</u>	<u><i>p</i> value</u>	<u>hazard ratio</u>
• clinical T4 or N2/3	<0.001	4.5
• 4 or more + LN	0.008	2.7
• no tamoxifen use	0.027	3.9

Local-Regional Recurrence By Clinical Stage

Factor	10-year LRR Rate		<i>P</i>
	No Radiation (%)	Radiation (%)	
Clinical T-stage			
T1	0	8	.535
T2	10	7	.408
T3	22	8	.002
T4	46	15	< .0001
Clinical N-stage			
N0	23	10	.014
N1	14	9	.062
N2-3	40	12	< .0001

Local-Regional Recurrence By Pathological Stage

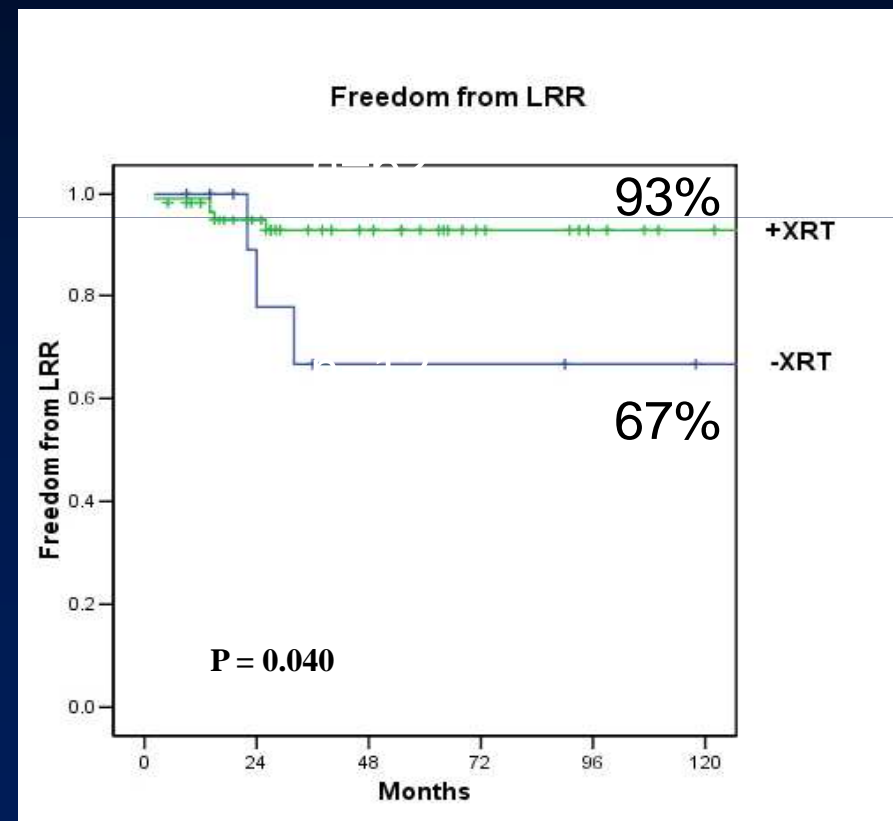
Factor	10-year LRR Rate		<i>P</i>
	No Radiation (%)	Radiation (%)	
Pathological tumor size, cm			
0-2	13	8	.051
2.1-5.0	31	14	.002
≥ 5.1	52	13	.001
No. of positive nodes			
0	11	4	.010
1-3	13	11	.636
≥ 4	59	16	< .0001

Importance of Clinical Stage: Patients with a pCR

Clinical Stage II Disease

- no radiation: 0/20
- radiation: 0/10
- no LRR events

Clinical Stage III Disease



McGuire et al., Int J Radiat Oncol Biol Phys, 2007

NSABP B-18/B-27

(Mamounas, ASCO breast 2010, abstract #90)

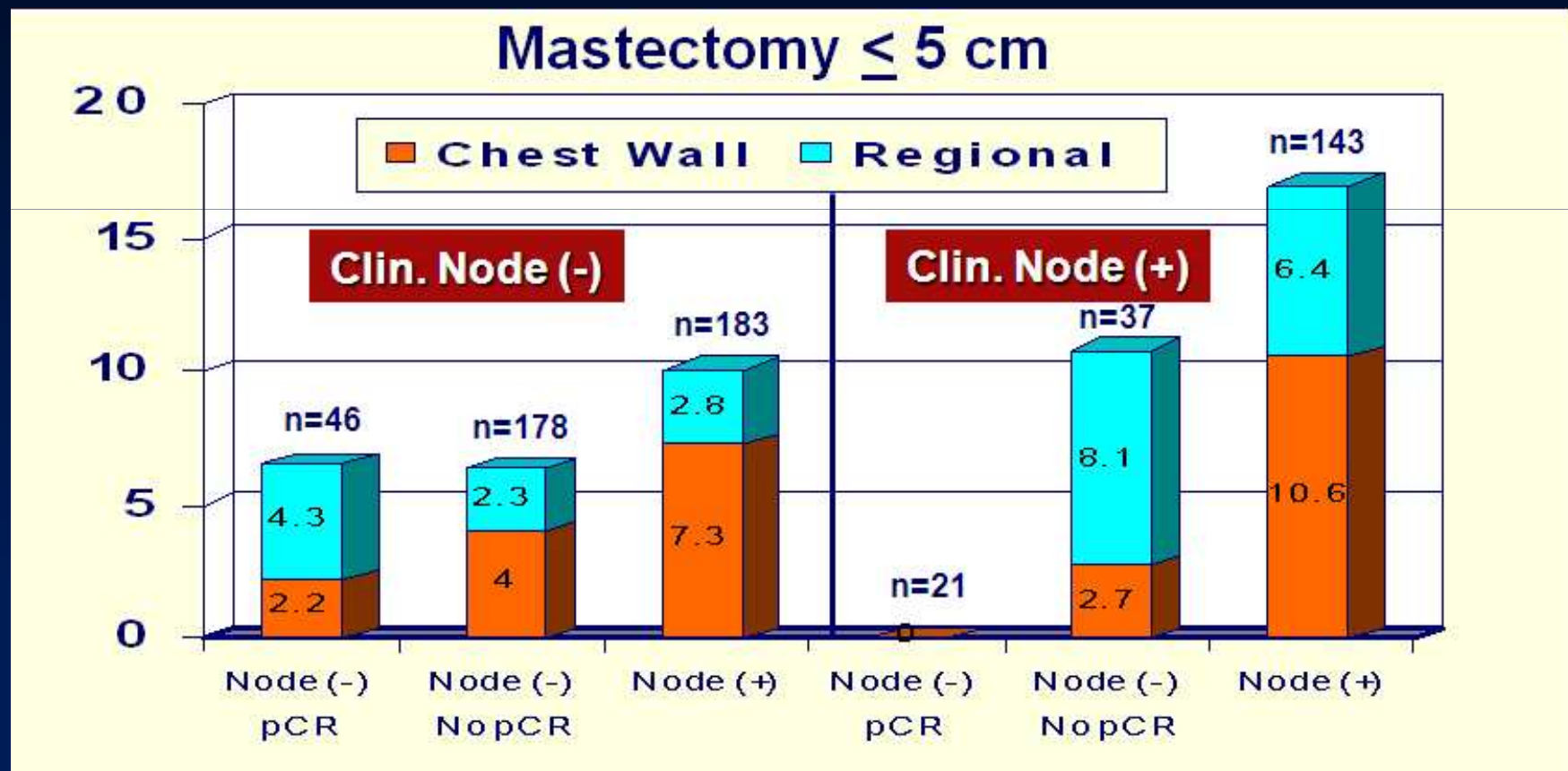
10-Year LRF: Mastectomy, Chemo, no XRT

Mastectomy (1027 Patients, 128 Events)		
Variable	HR (95% CI)	P-value
Clin. Tumor Size: (>5 cm vs. ≤5 cm*)	1.60 (1.13-2.27)	0.008
Clinical Nodal Status (+) vs. (-)*	1.61 (1.13-2.30)	0.008
Breast/Nodal Path Status: Node(-)/No pCR vs. Node(-)/pCR*	2.21 (0.78-6.33)	0.0004
Node(+) vs. Node(-) /pCR*	4.30 (1.58-11.72)	

NSABP B-18/B-27 T1,2

(Mamounas, ASCO breast 2010, abstract #90)

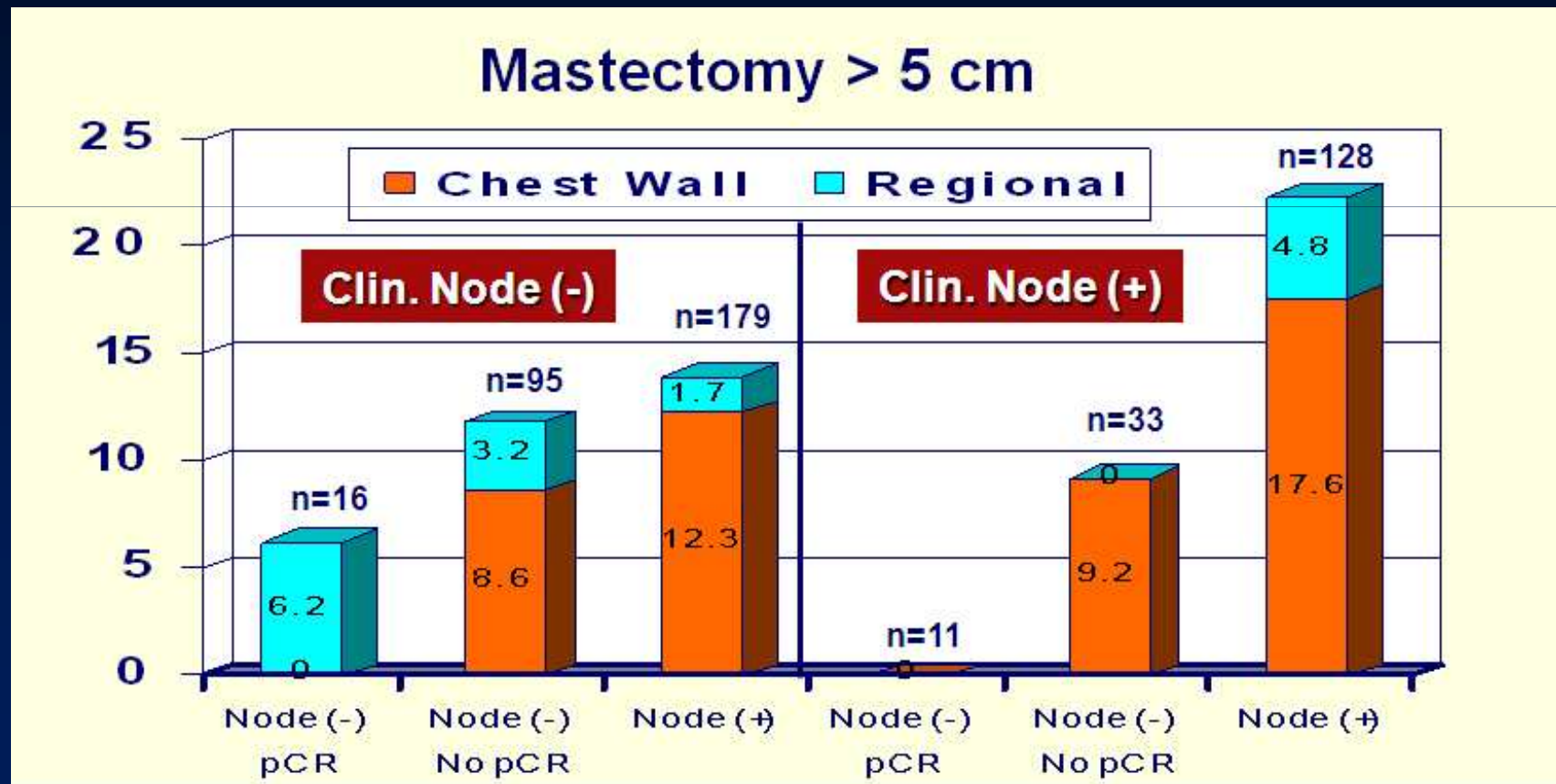
10-Year LRF: Mastectomy, Chemo, no XRT



NSABP B-18/B-27 T3

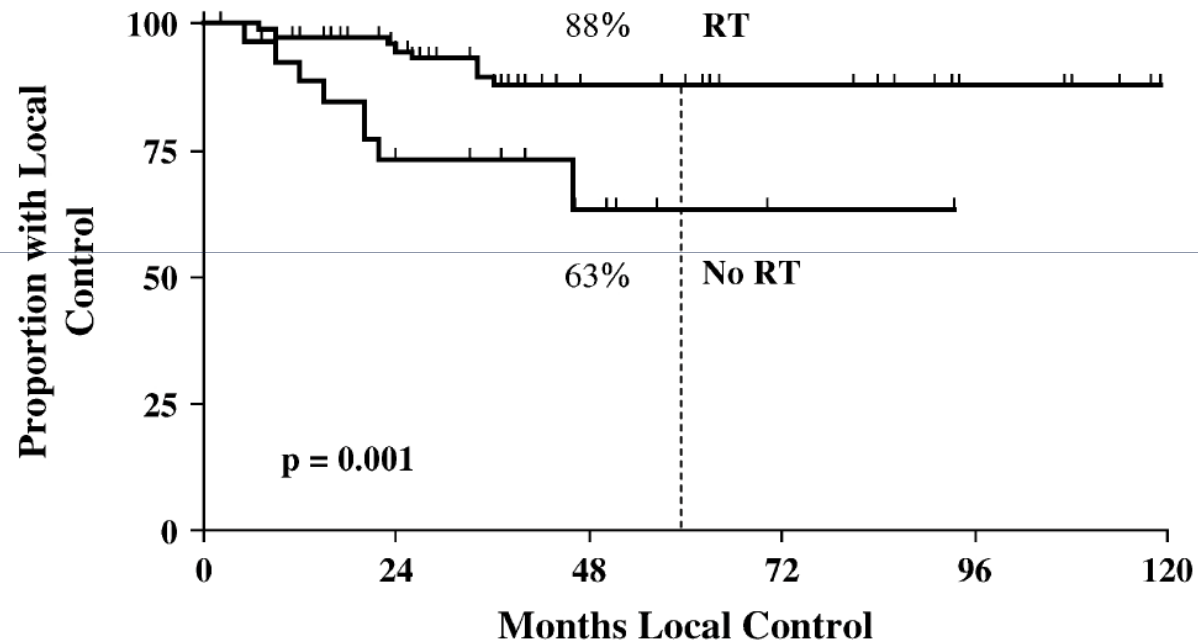
(Mamounas, ASCO breast 2010, abstract #90)

10-Year LRF: Mastectomy, Chemo, no XRT



Importance of Young Age

Importance of Young Age Patients ≤ 35 years Old



	No. patients	No. Events
No RT	27	10
RT	80	8

Take Home Message

Risk for LRR depends on

- High risk features
 - clinical stage III: cT4, cN2/3
 - residual pathological involvement of LN
 - age 35 or under
- What about stage II?

**Can We Tailor
Postmastectomy Radiation
Indications According
To Response To Neoadjuvant
Chemotherapy?**

Postmastectomy Radiation Use Will Be Increasing in the U.S.

Patients with Stage II disease, 1-3+LN

- **Oxford meta-analysis suggests survival advantage with PMRT**
- **Canadian MA.20 trial**
- **Can radiation decisions be tailored according to response?**

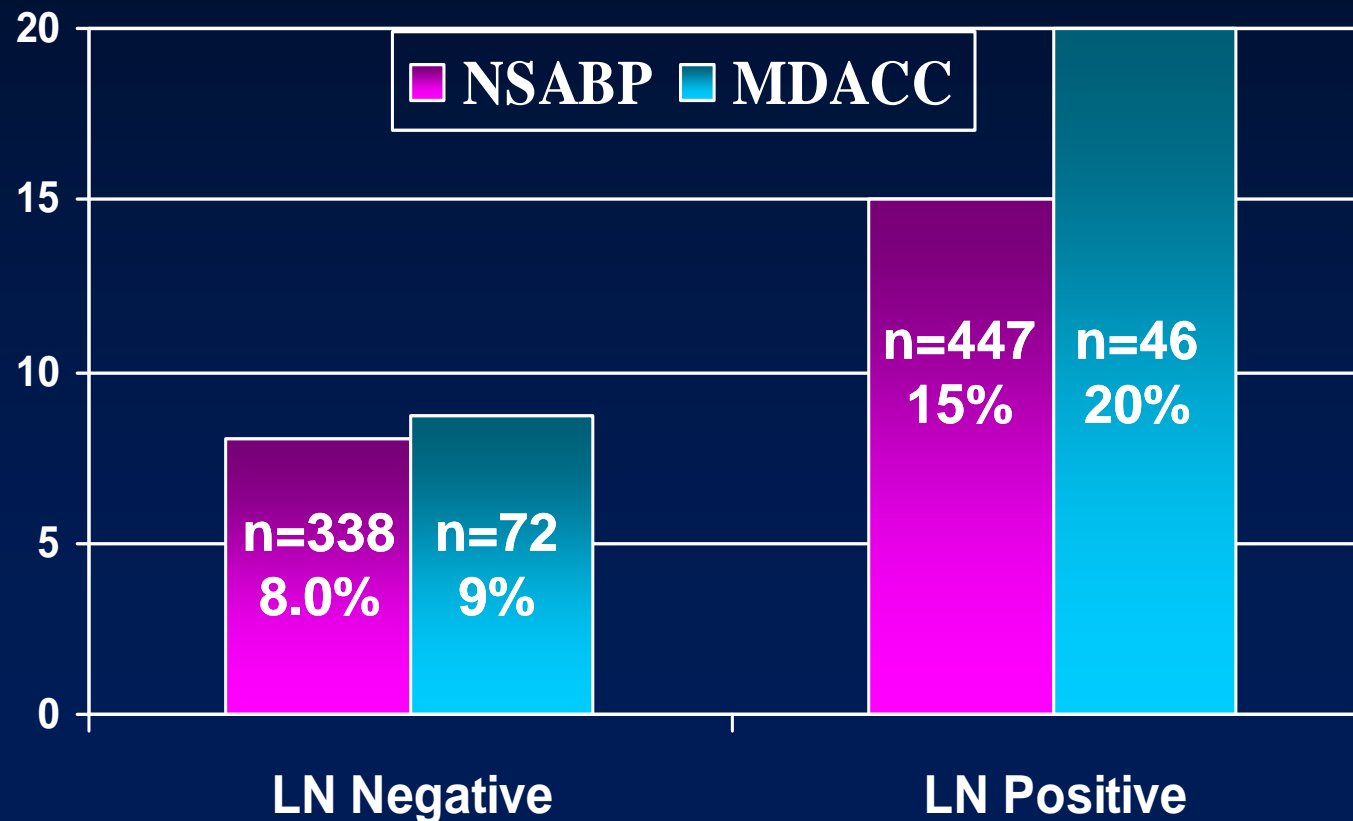
U. S. Postmastectomy LRR Data

Patients with Stage II disease, 1-3+LN

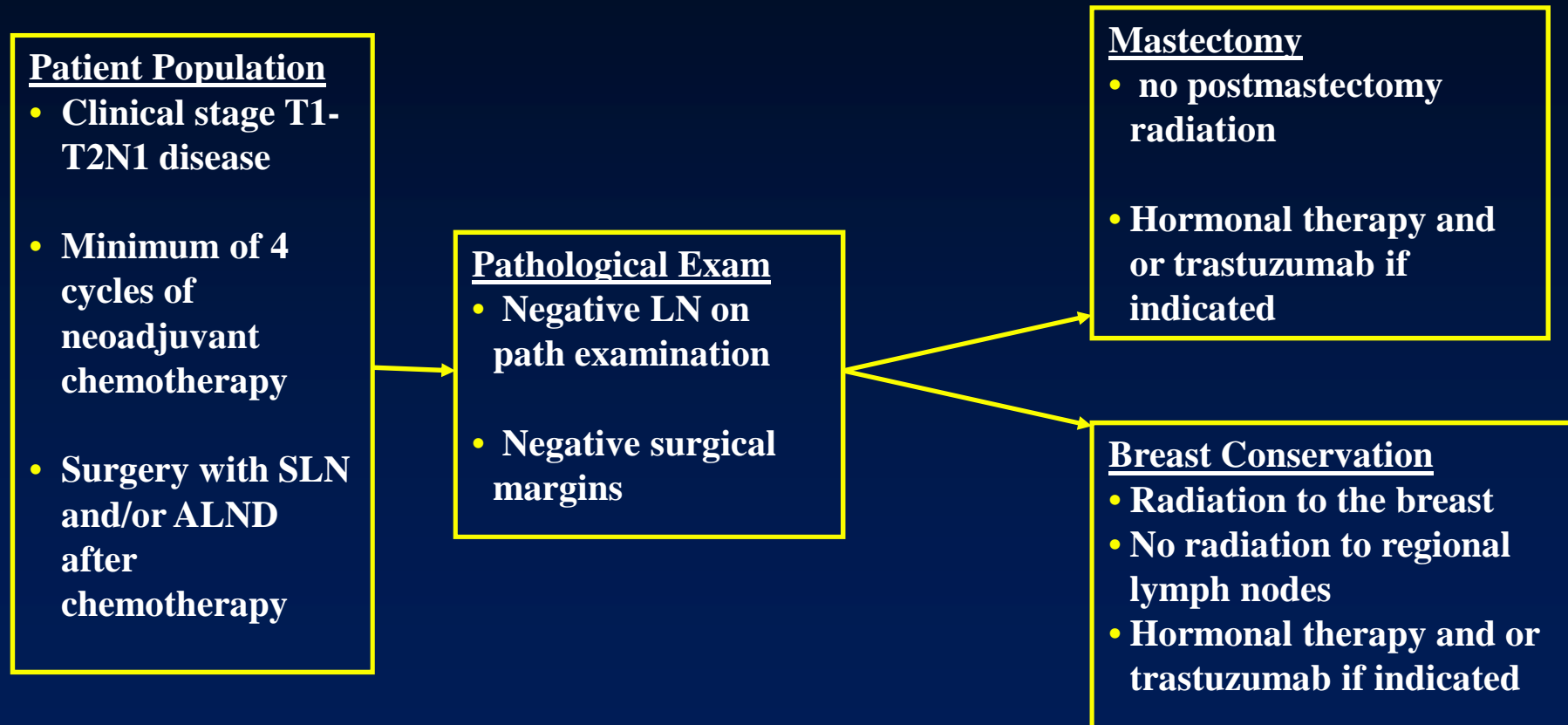
- overall LRR: 12-15%
- after modern neoadjuvant chemotherapy
 - 30-40% become LN-
 - 60-70% remain LN+
- these two groups have different LRR risk

Neoadjuvant Chemo May Allow For Tailoring of Radiation Treatment Decisions For Patients with Stage II Disease

8-Year LRF: Mastectomy, Chemo, no XRT
(Mamounas, NCI, 2007) (Garg, 2006)



Arm of a Trial Schematic



Patients with a Poor Response

Selected Pts Have Poor LRR Outcome

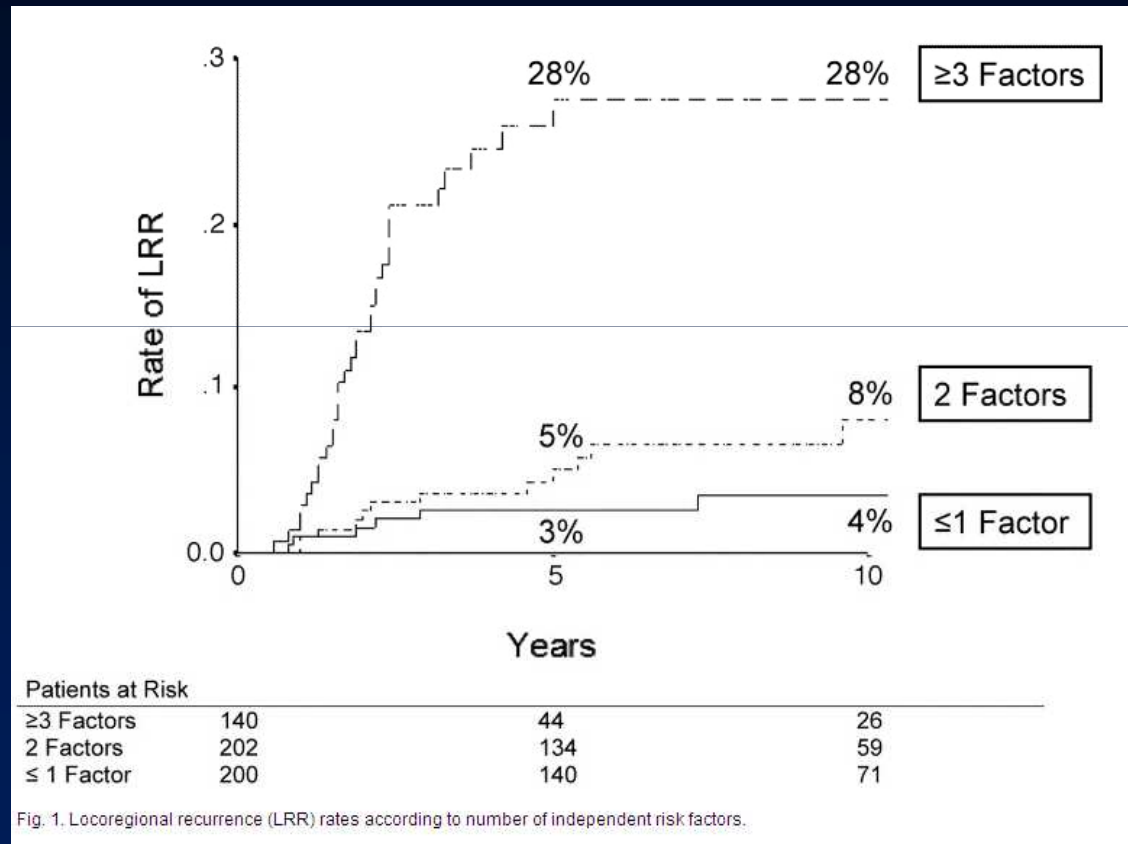
Multivariate for LRR after NCT and Radiation

Table 6. Multivariate analysis of locoregional recurrence

Factor	Hazard ratio	95% Confidence interval	<i>p</i>
Skin or nipple involvement	2.8	1.5–5.2	0.001
Supraclavicular nodal involvement	2.7	1.3–5.6	0.009
No tamoxifen use	2.7	1.2–6.0	0.019
Extracapsular extension	2.1	1.1–4.0	0.020
Estrogen receptor negative disease	2.1	1.2–3.7	0.013

Huang et al., Int J Radiat Oncol Biol Phys, 2005

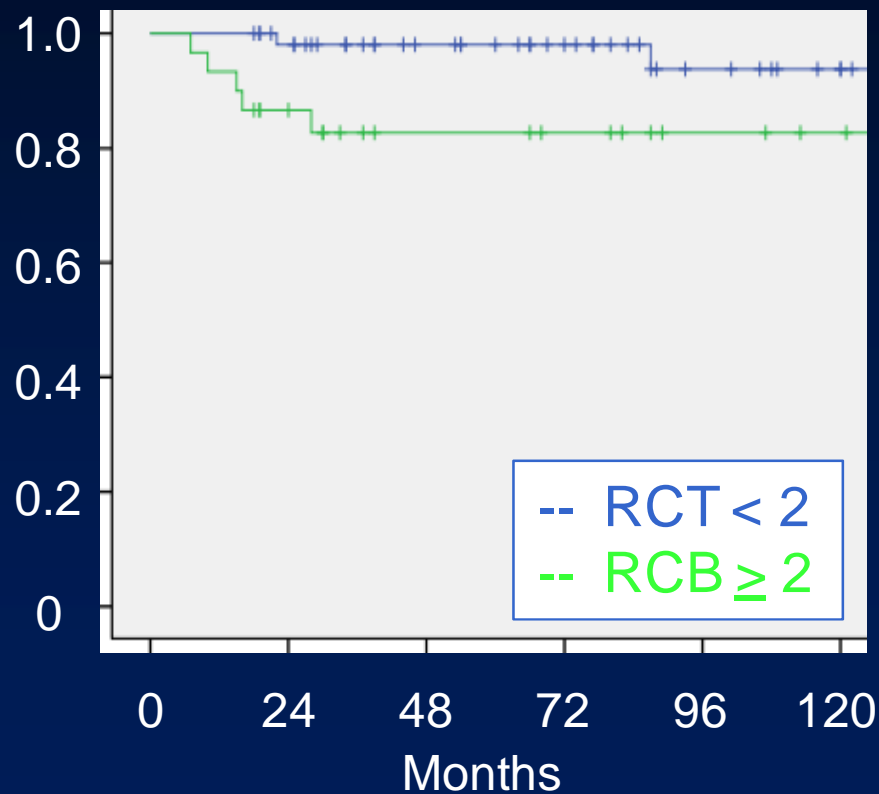
Selected Pts Have Poor LRR Outcome



Huang et al., Int J Radiat Oncol Biol Phys, 2005

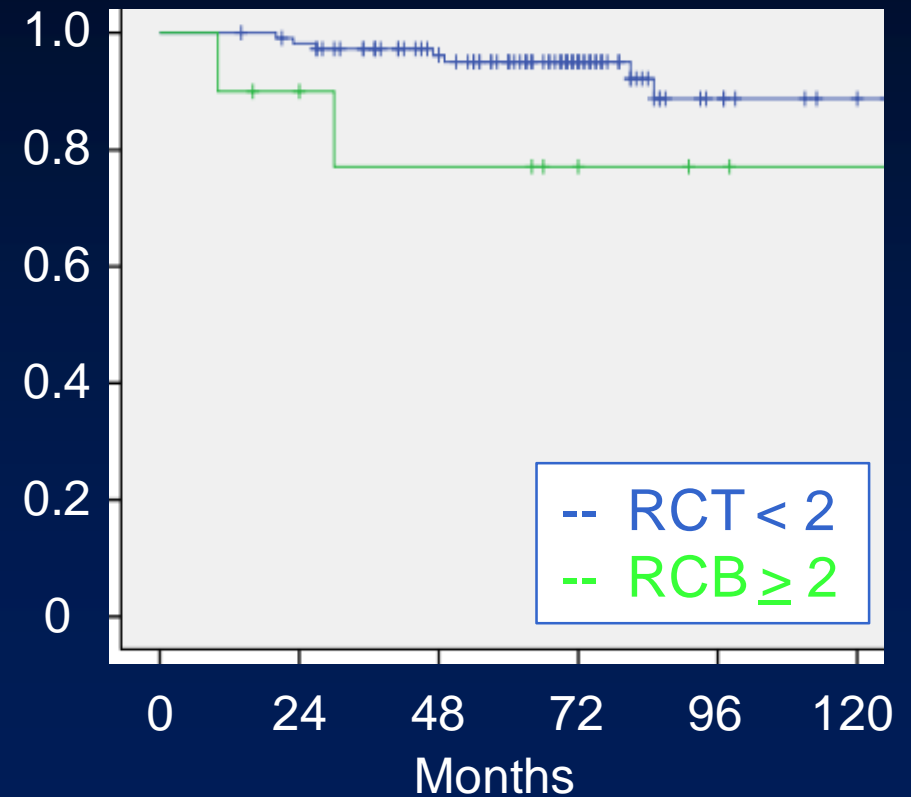
Residual Cancer Burden predicts LRR in ER-negative disease or LVSI

Mastectomy + RT



n=85

BCT + XRT



n=125

Conclusions

After neoadjuvant chemo and mastectomy:

- reduces LRR
- deaths from breast cancer for selected patients

Radiation is indicated for:

- stage III or clinical T3 tumor
- most pts with positive nodes after NCT
- selected patients with stage II disease

Conclusions

New radiation sensitizers are needed

- Pts with N3c disease/ incomplete response
- ER- disease, high residual disease burden