

PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

Indications for Radiation Therapy and Selection of Treatment Fields After Preoperative Therapy

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Radiation and Preoperative Chemotherapy

Radiation Overview

- Important role in breast conservation therapy
- New questions with preoperative chemotherapy
 - indications for postmastectomy radiation
 - indications for lymph node irradiation
 - should decisions be effected by response?
 - what is the efficacy of radiation treatment?

Radiation After Mastectomy

Known facts about postmastectomy radiation

- Some patients are at risk for local recurrence
- In such patients, radiation
 - reduces the risk of local-regional recurrence
 - decreases the risk of subsequent metastases
 - improves cause-specific and overall survival
 - adds to the benefits of systemic therapy

Oxford Overview: Mastectomy +/- Postmastectomy Radiation Trials

Lymph Node-Positive Disease

Local Recurrence

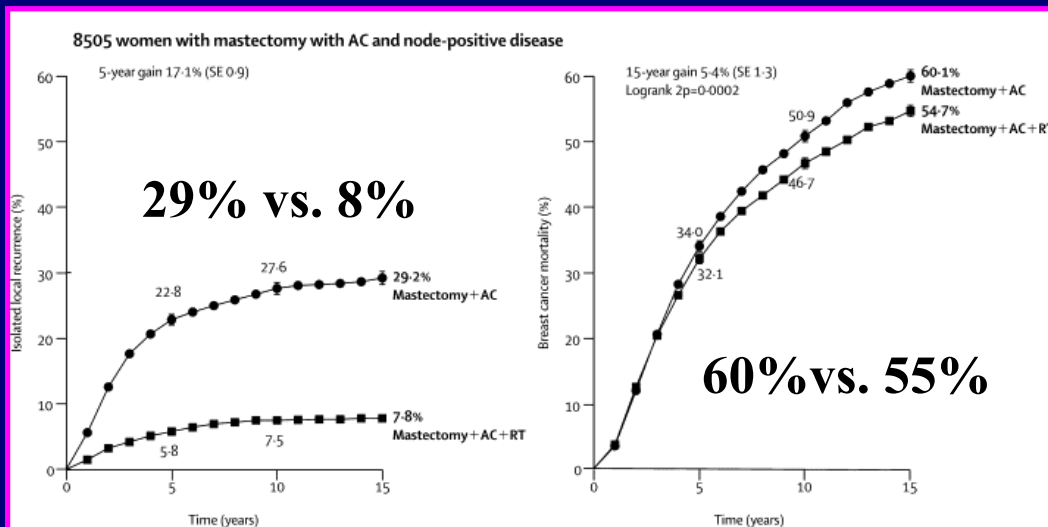
Breast Ca Deaths

Local Recurrence

- 72% reduction

Breast Ca Survival

- none in LN-
- 5% for LN+



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

Preoperative Chemotherapy Affects Radiation Decisions

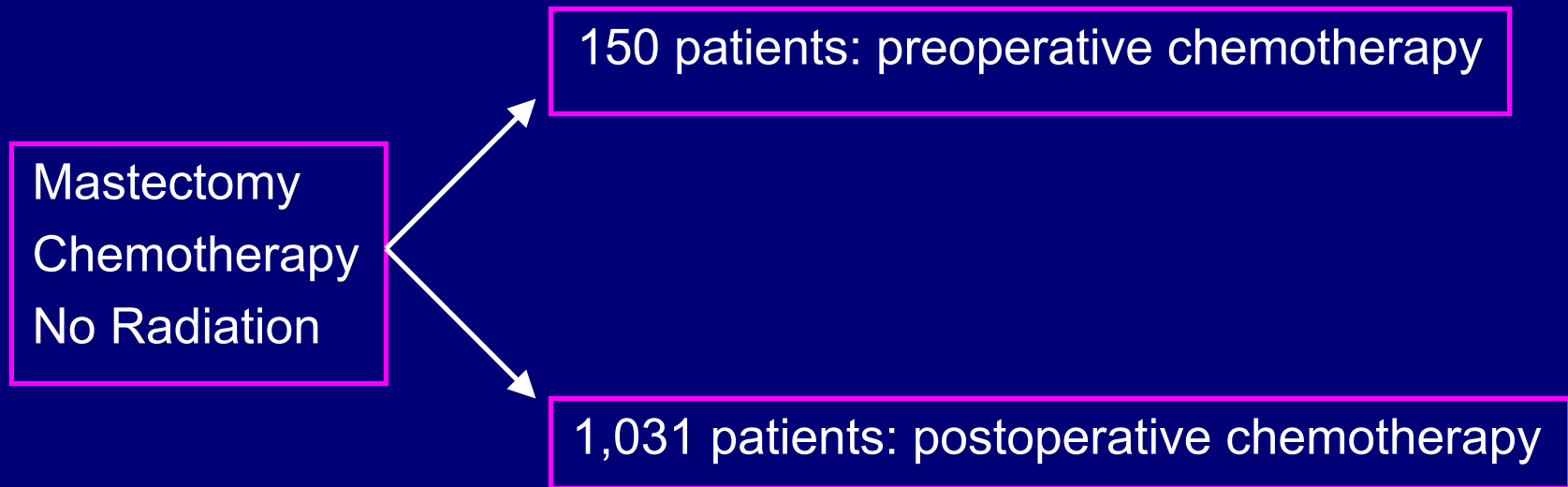
Historical indications for postmastectomy radiation

- Pathology based
- Consensus statements
 - tumor size > 5 cm
 - ≥ 4 positive lymph nodes
- Stage II w/ 1-3 +LN – unclear
- Not indicated for lymph node-negative disease

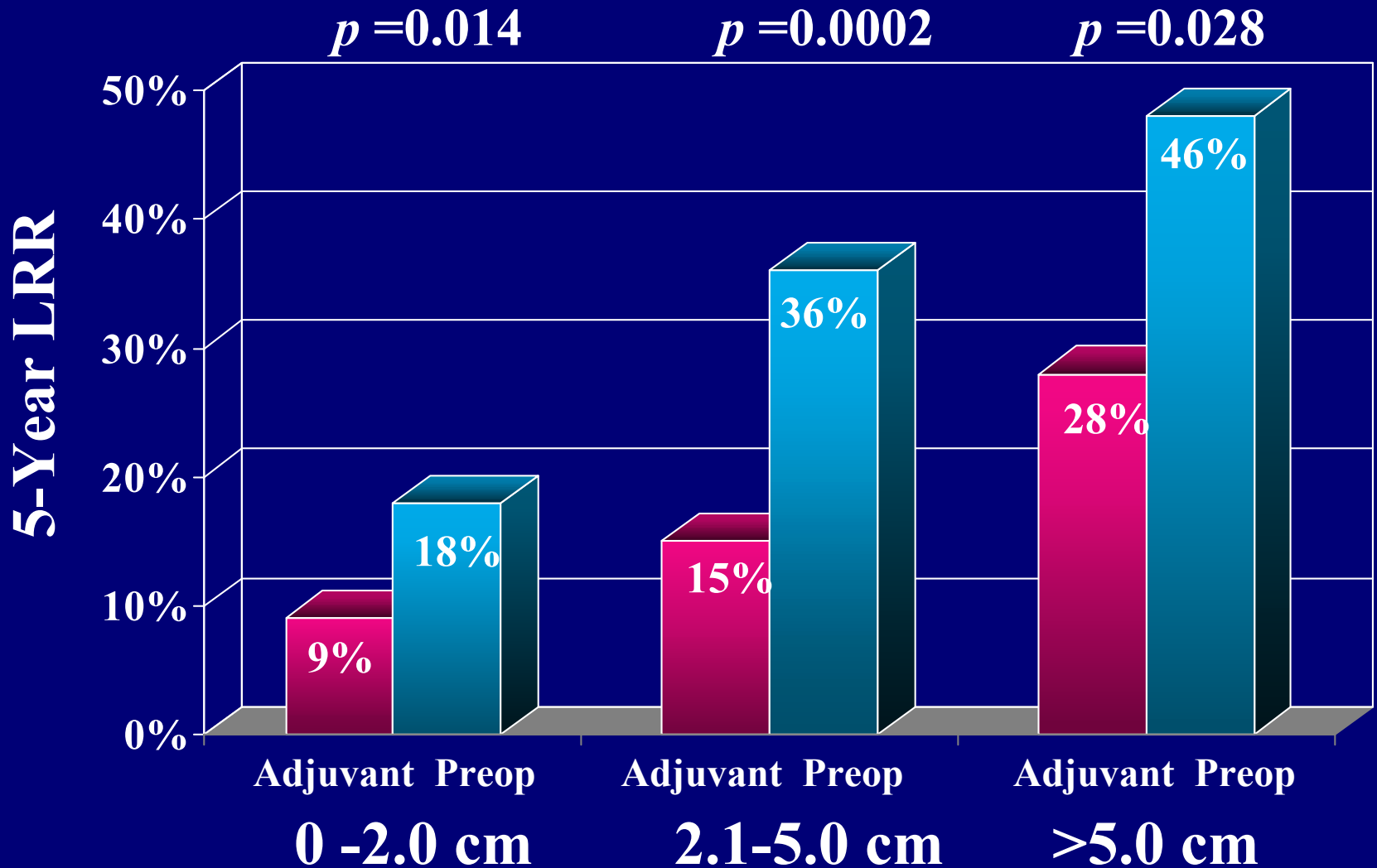
**Neoadjuvant Chemotherapy
Changes Pathological Extent
Of Disease In Most Patients**

Local-Regional Recurrence and Pathological Extent of Disease

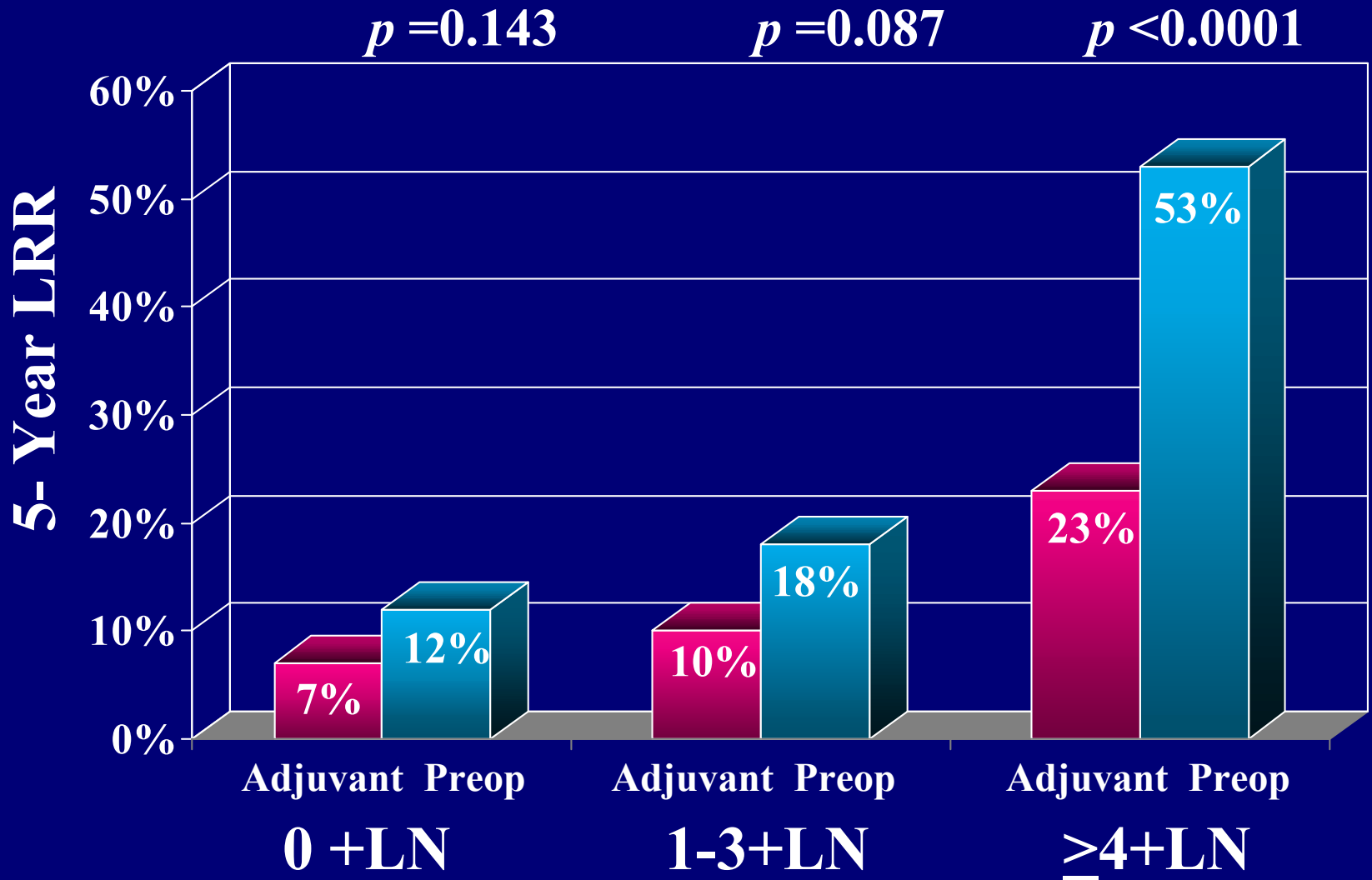
Correlated pathology and local-regional recurrence



Pathological Size of the Primary Tumor



Pathological Nodal Status



**The Risk of Local-Regional
Recurrence According to a
Pathological Extent of Disease
is Different in Patients Treated
with Preoperative Chemotherapy
Compared to the Risk in Patients
Treated with Initial Surgery**

Local-Regional Recurrence Risk After Preoperative Chemotherapy + Mastectomy

150 patients, 1974-1998 at MDACC

- treated on prospective clinical trials
- preoperative chemotherapy
- modified radical mastectomy
- no radiation therapy

Factors Associated with Local-Regional Recurrence

Pretreatment Factors

- clinical stage
- clinical T stage
- clinical N stage

Postoperative Factors

- number of positive lymph nodes
- primary tumor size
- tamoxifen use

Multivariate Analysis: Both Pre- and Post-Chemotherapy Factors are Important

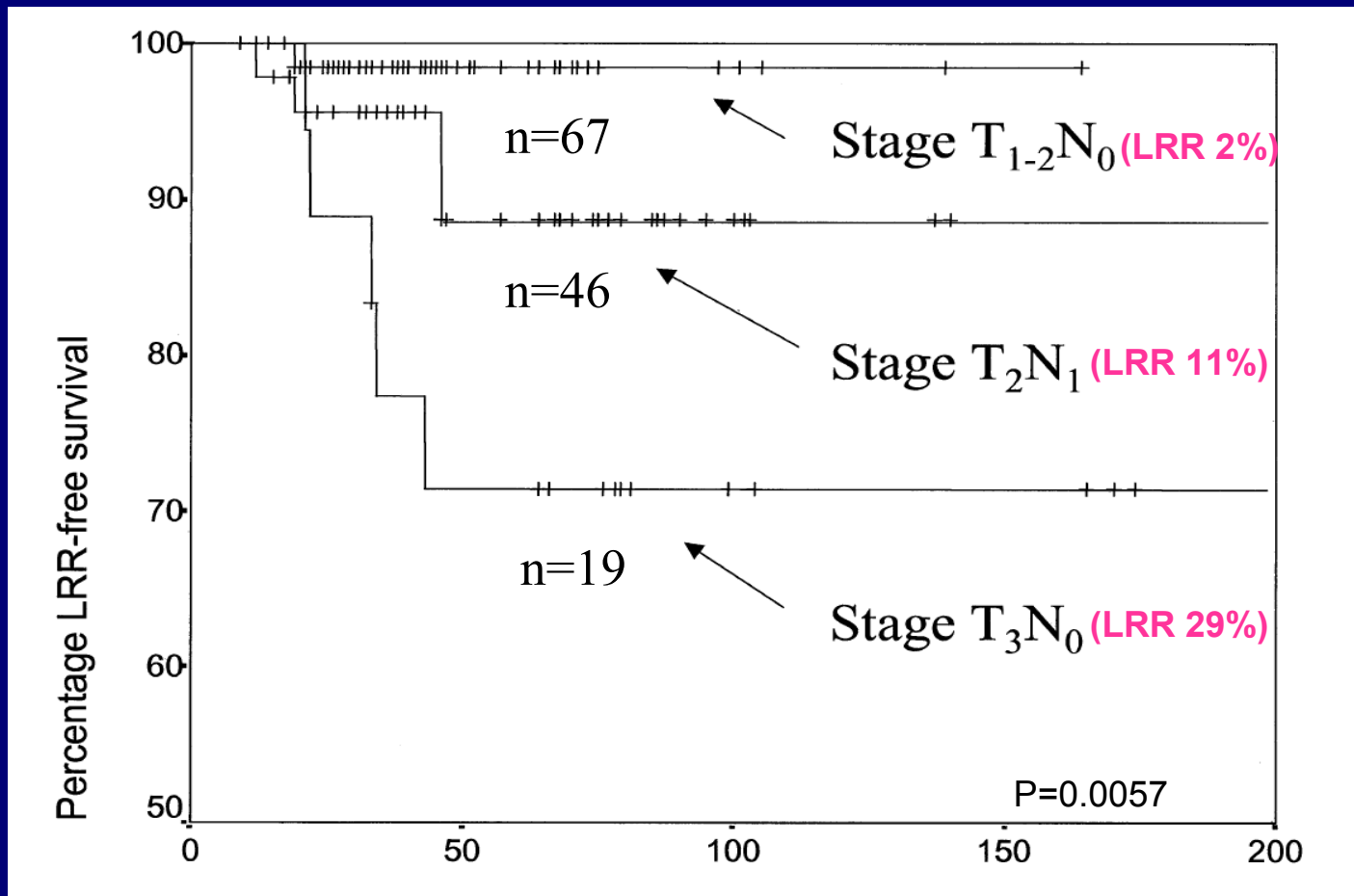
<u>Factors</u>	<u>p value</u>	<u>hazard ratio</u>
• pretreatment stage III	<0.001	4.5
• ≥ 4 positive lymph nodes	0.008	2.7
• no tamoxifen use	0.027	3.9

Take Home Message

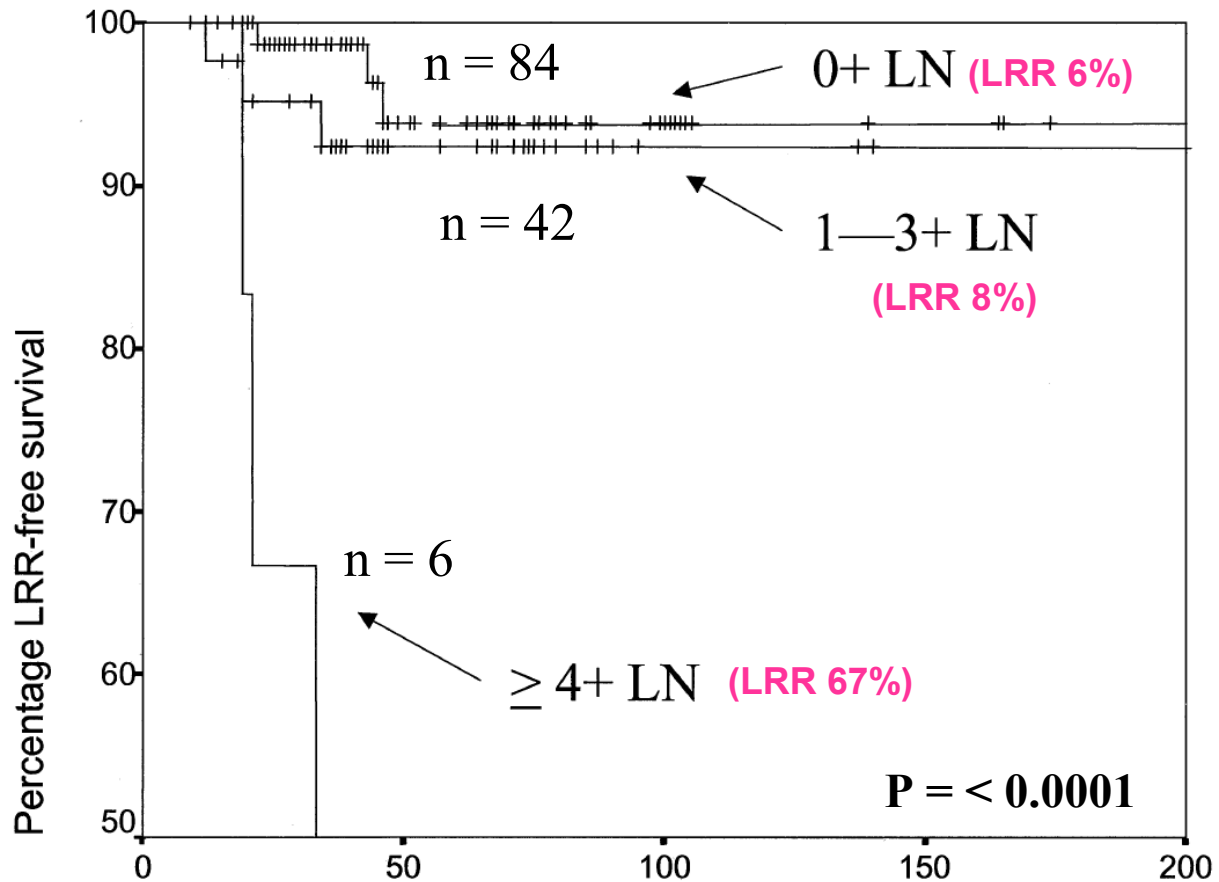
Risk for local-regional recurrence depends in part on the pretreatment stage of disease

- **Stage III has relevant risk**
- **What about stage II?**

Recurrences in Clinical Stage I/II



Recurrences in Stage II



NSABP B-18 (Mamounas, SABCS, 2003)

B-18 Study

- Mastectomy patients did not receive radiation
- 87% of pts in the trial had T1, T2 tumors
- 239 patients were treated with preoperative chemotherapy + mastectomy

Local-Regional Recurrence According to Response

10-yr LRR by Pathological Response

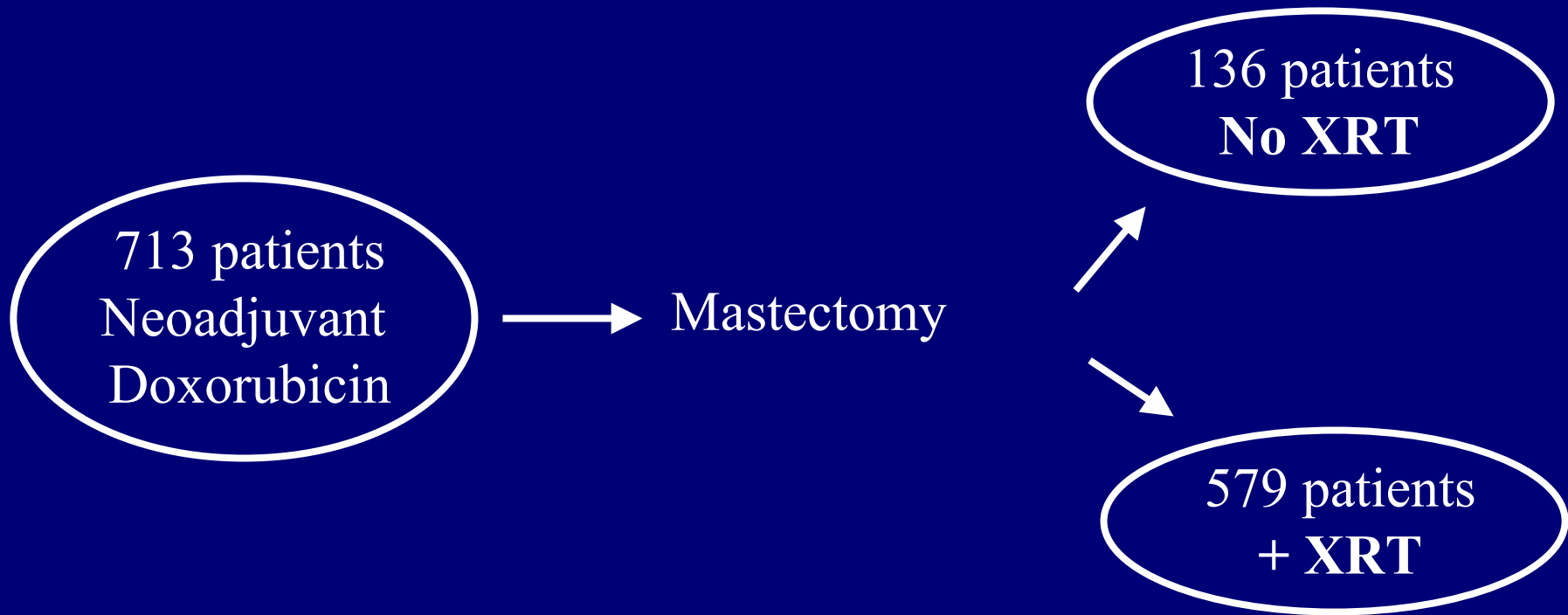
- breast pCR w/ LN- or LN+ (n=13) 0%
- residual disease w/ LN- 10.5%
- residual disease w/ LN+ 20.3%

Patients with 1-3+LN had similar risk as those
with ≥ 4 +LN

Is Postmastectomy Radiation Therapy Effective?

(In the Setting of Neoadjuvant Chemotherapy)

Limited Available Data



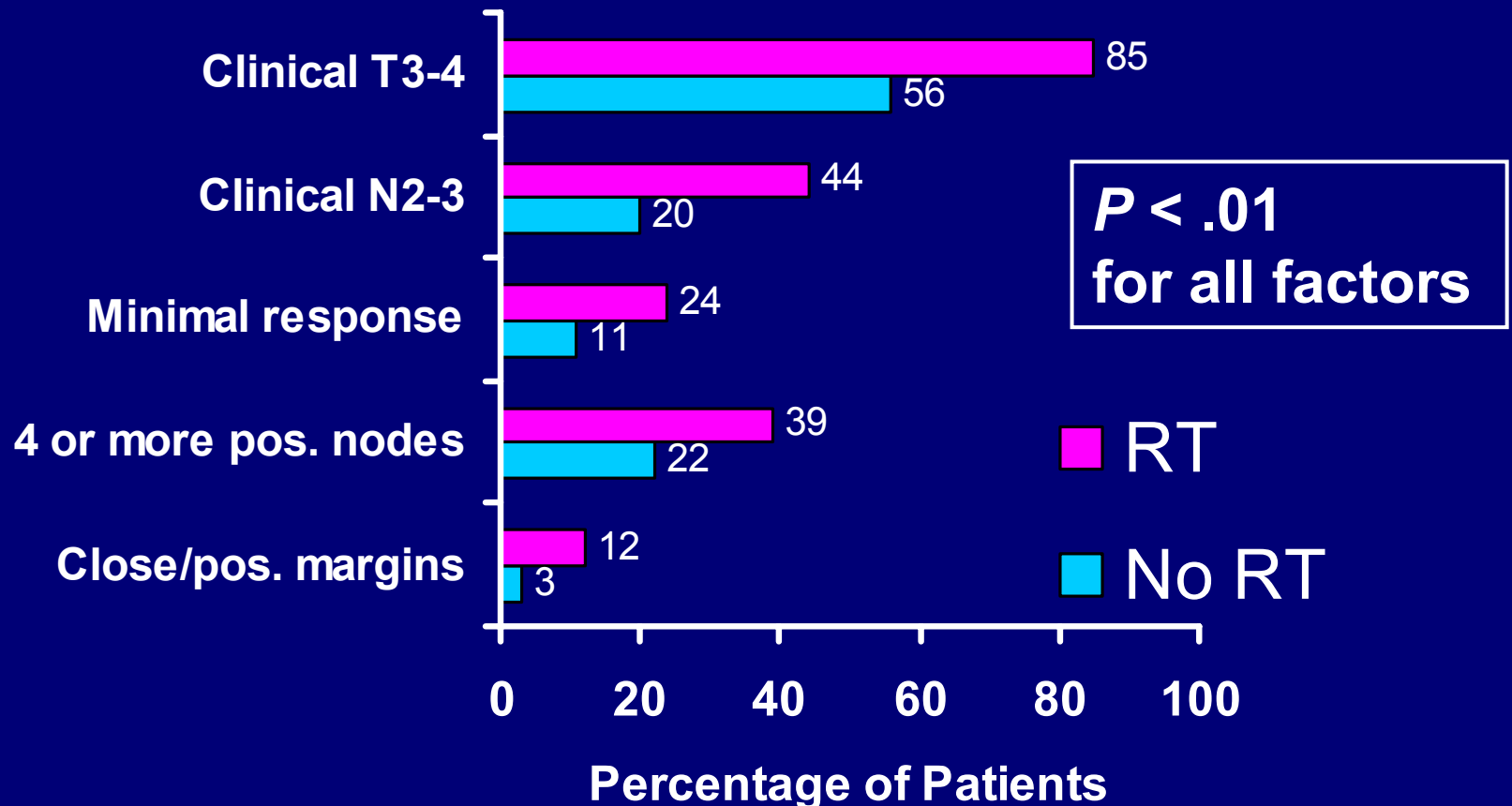
XRT: Non-randomized

6 consecutive prospective MDACC trials

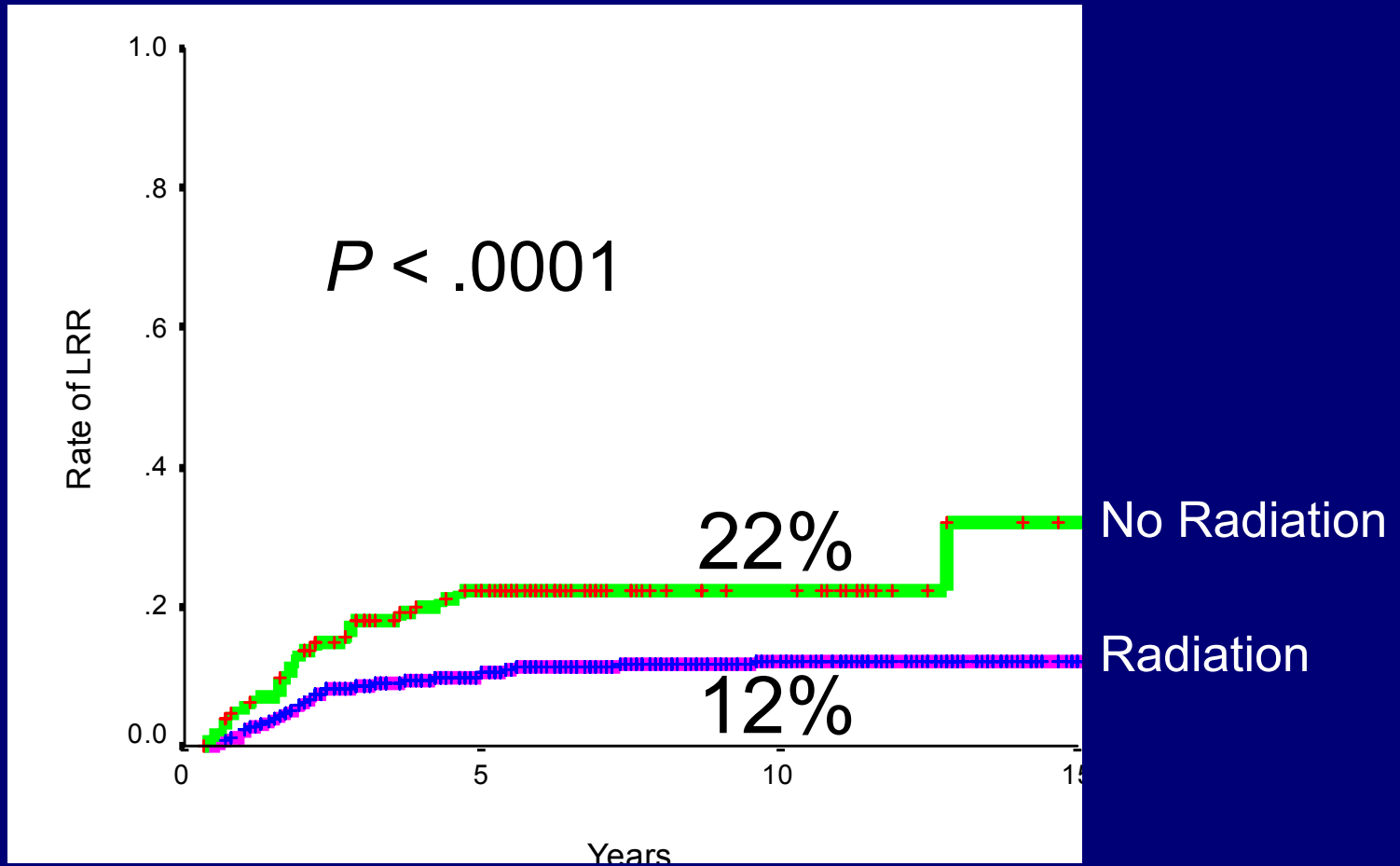
1974-1998

Comparisons Between Groups

Irradiated patients had significantly worse:



Local-Regional Recurrence



Local-Regional Recurrence By Extent of Disease

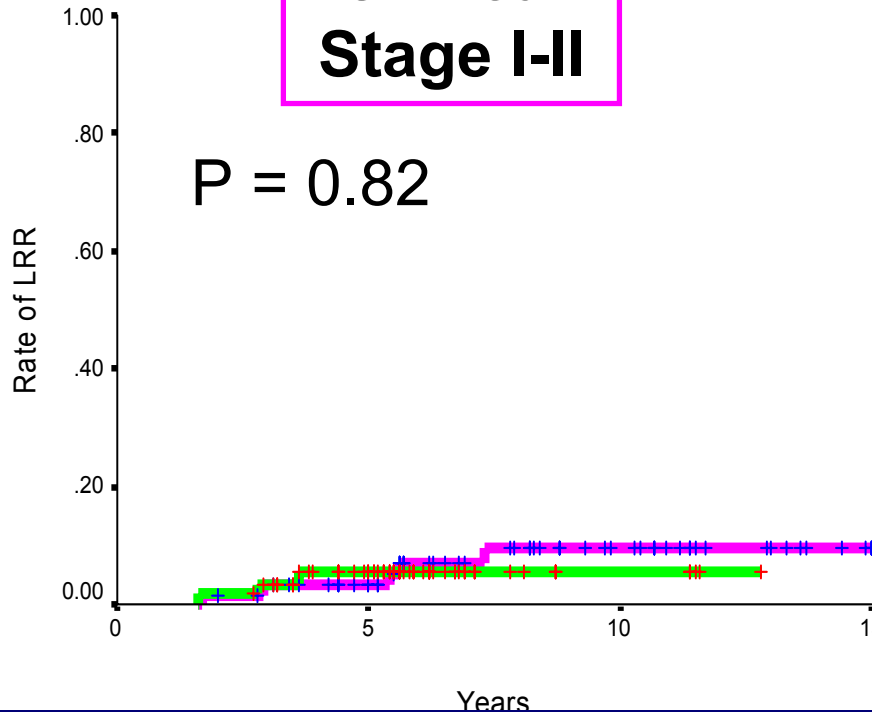
Table 3. Ten-Year Actuarial Rates of LRR According to Clinical and Pathological Disease Status

Factor	10-year LRR Rate		P
	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
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

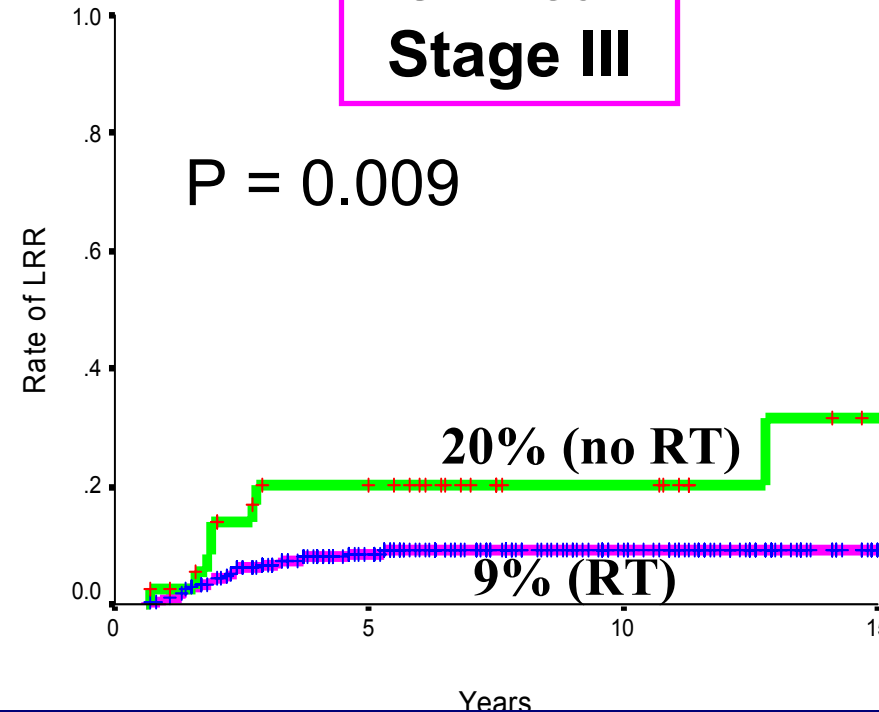
Abbreviation: LRR, local regional recurrence.

Local-Regional Recurrence

**Clinical
Stage I-II**



**Clinical
Stage III**



**Good pathologic response to chemotherapy
(0-5cm tumor, 0-3 nodes)**

Local-Regional Recurrence

<u>Multivariate analysis</u>	<u>Hazard</u>	<u>P-value</u>
No radiation	4.1	.0001
≥20% pos. nodes	2.9	.0001
Stage ≥ IIIB	2.3	.001
Nodes sampled < 10	2.0	.005
No tamoxifen	1.9	.034
ER negative	1.8	.014
Path size >2cm	1.7	.026

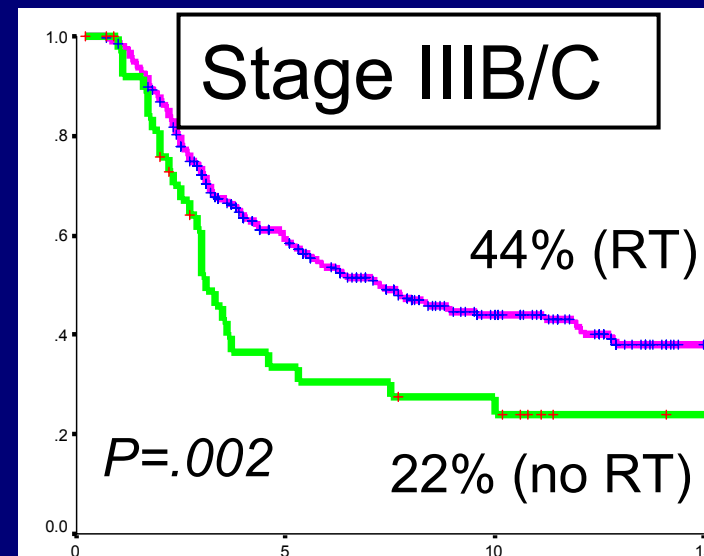
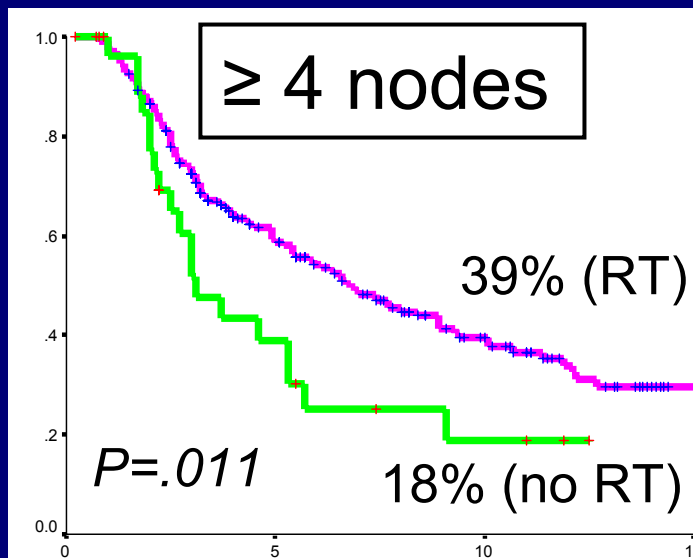
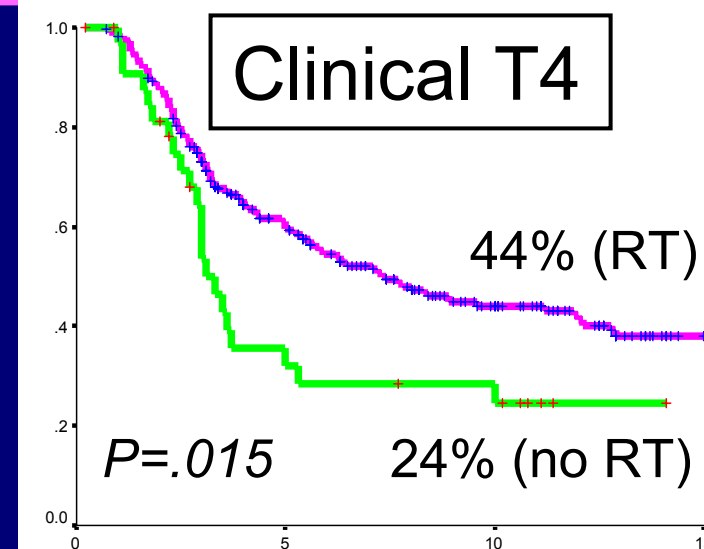
Cause-Specific Survival

<u>Univariate subset analysis</u>	<u>P-value</u>
• clinical stage IIB/C	0.002
• clinical T4 tumors	0.015
• 4 or more positive nodes	0.011

Radiation improved CSS ~ 20%

Cause-Specific Survival

Univariate Subset Analyses
Radiation improved CSS ~
20%



Cause-Specific Survival

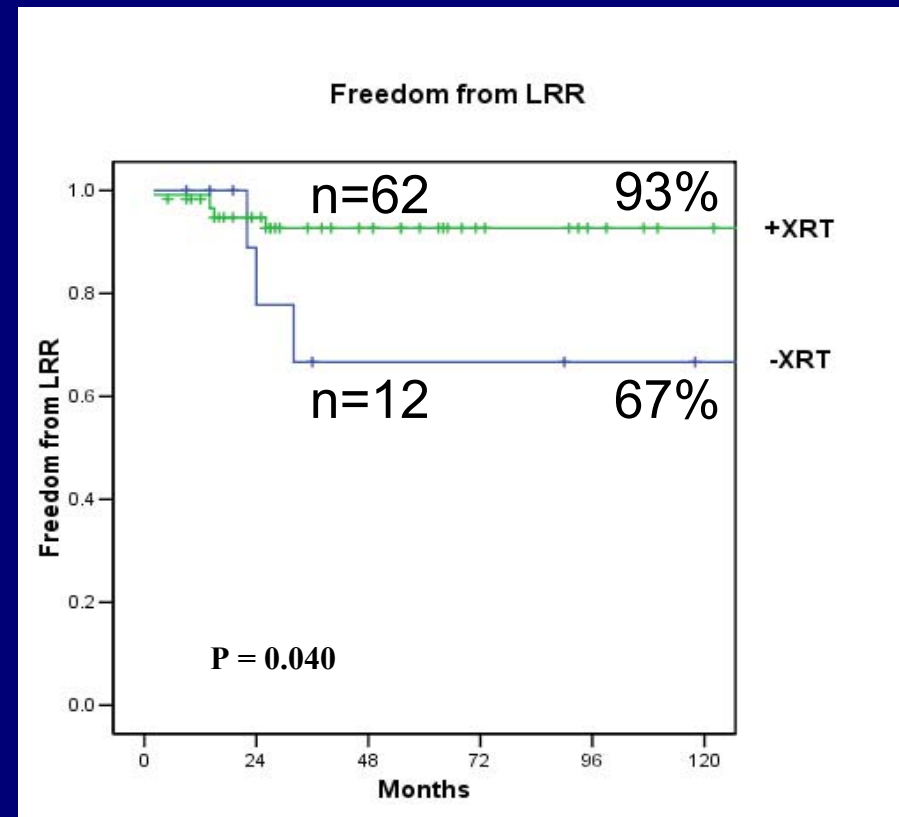
<u>Multivariate analysis</u>	<u>Hazard</u>	<u>P-value</u>
Stage \geq IIIB	2.4	.0001
Path. tumor size >0 cm	2.3	.001
≥ 4 positive nodes	2.1	.0001
No radiation	1.8	.001
Nodes sampled <10	1.5	.004
ER negative	1.5	.003

Local-Regional Recurrences in Patients with a pCR

Clinical Stage II Disease

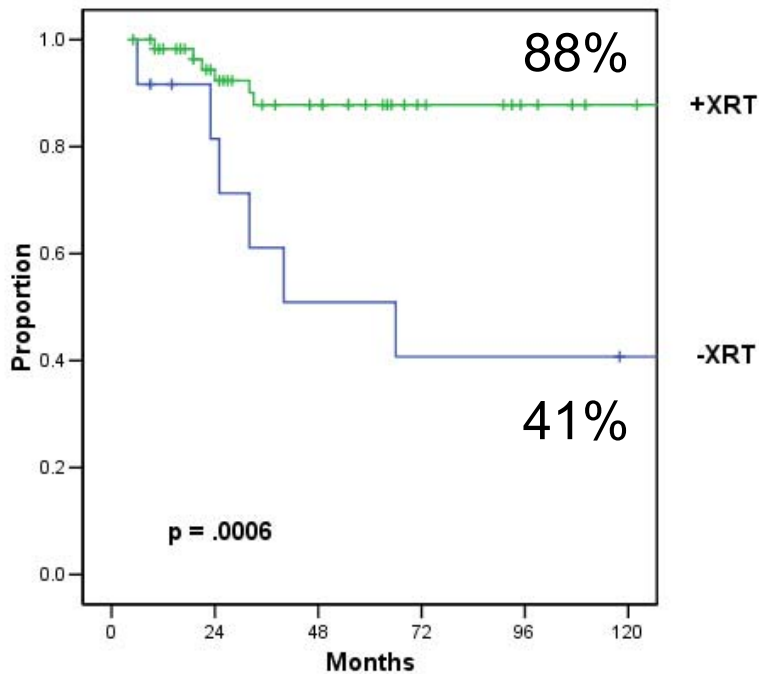
- no radiation: 0/20
- radiation: 0/10
- no LRR events

Clinical Stage III Disease

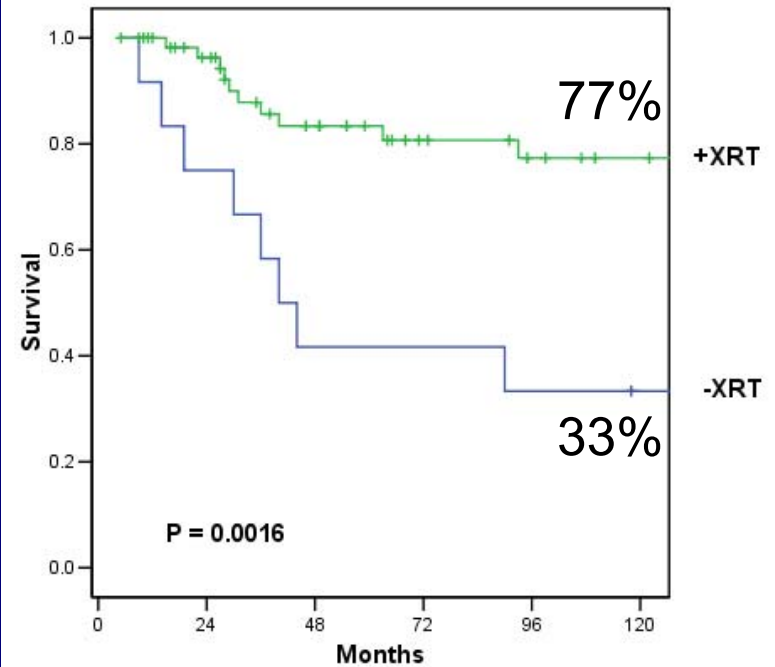


Patients with Stage III Disease and a pCR

Freedom From Distant Metastases



Overall Survival



Selecting Radiation Treatment Fields

(There is no data to guide clinicians in patients treated with neoadjuvant chemotherapy)

Postmastectomy Radiation and Treatment Field Selection

Postmastectomy Radiation and Lymphatic Radiation

- preoperative stage III disease - yes
- higher risk preoperative stage II disease – yes
cofactors to consider: >2 cm residual primary, LVSI, extracapsular extension, close margins, ≥20% + LN
- lower risk preoperative stage II – risks/benefits
- stage II with pCR – most likely no

Possible Clinical Trial

Postmastectomy Radiation

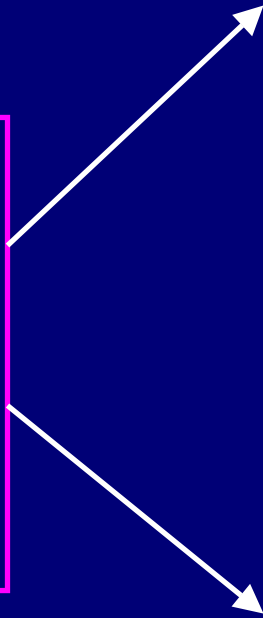
Eligibility

Pretreatment Stage II/III

Postoperative

- >4 cm primary
- -LN

Observation



Conclusions

After preoperative chemo and mastectomy:

- reduces local-regional recurrence
- deaths from breast cancer for selected patients

Radiation is indicated for:

- pretreatment stage III or clinical T3 tumor
- ≥ 4 positive nodes before or after chemotherapy
- selected patients with pretreatment stage II disease