THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

How Biological Subtype Affect Radiation Treatments Of Breast Cancer

Breast Cancer Radiation

Historical components of decision making

- decisions made on:
  - primary tumor size
  - lymph node status
  - margin status
  - patient age
  - ECE, LVSI

Molecular Drives of Heterogeneity

ER/PR/HER2 help distinguish disease

- prognostic importance
  - affect LRR risk without radiation
  - help define radiation indications
- predict sensitivity to radiation
  - magnitude of radiation benefit
  - fractionation schedule

Should We Be Treating Different Breast Cancers Differently?

Excellent Outcome Group: Should We Deintensify Treatment?

ER+, HER2/neu-, postmenopausal disease

- outcomes extremely good
- explore radiation omission
- explore shorter, less expensive course

LN- or ER+, HER2/neu+ treated with trastuzmab

- outcomes extremely good

Poor Outcome Group: Do We Need Radiosensitizers?

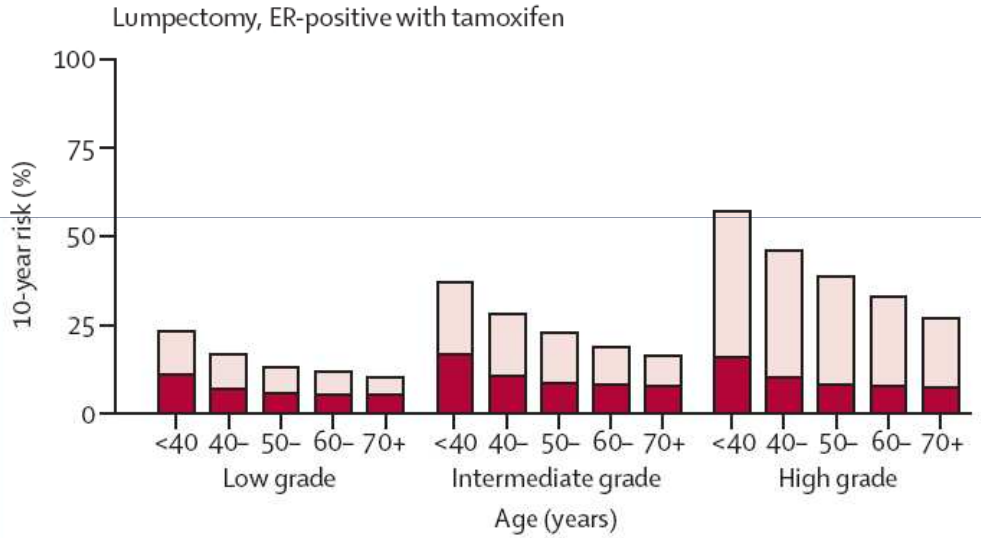
ER-Negative and Triple Negative Disease

- both prognostic and predictive
  - higher risk without radiation
  - radiation provides less proportional benefits
- risks also affected by age & stage
- risk also determined by response to NCT

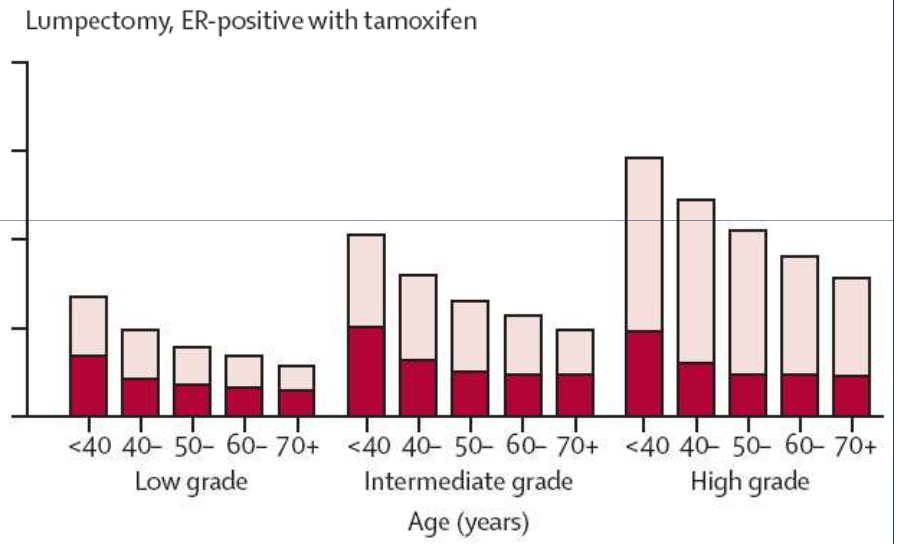
Local Regional Treatment Outcomes According to Molecular Phenotype

Oxford Meta-Analysis: ER+/tam

T1 Disease



T2 Disease



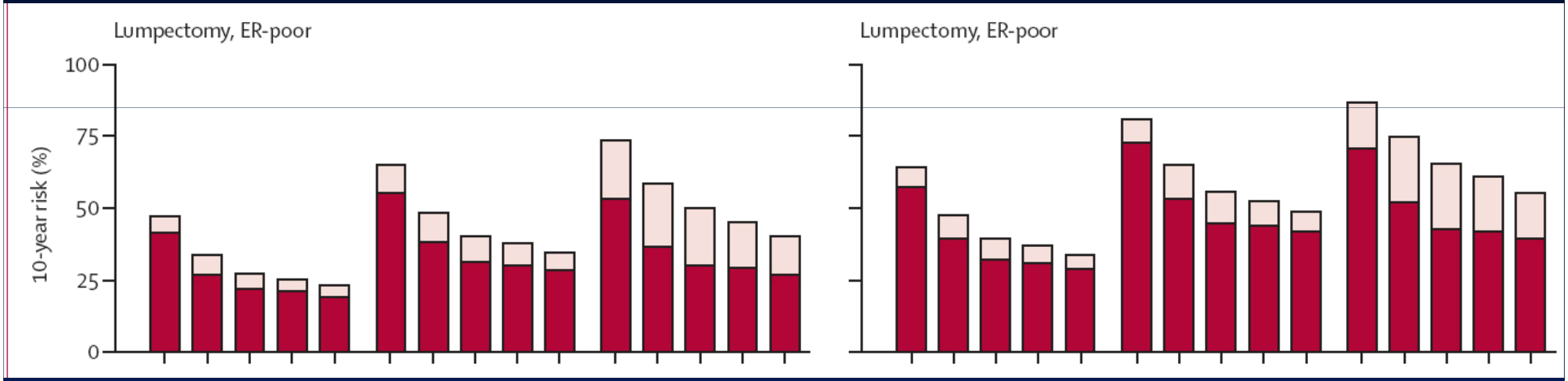
Overall risk of recurrence 15-30% without radiation

Radiation provided a 60% proportional reduction in risk

EBCTCG, Lancet, 2011

Oxford Meta-Analysis: ER-

T1 Disease **T2 Disease**



Overall risk of recurrence 30-60% without radiation

Radiation provides a 35% proportional reduction in risk

EBCTCG, Lancet, 2011

Vancouver BC: Molecular Subtypes

LRR after BCT and MRM

- **Tissue array for ER/PR/Her2/CK/EGFR**
- **profiled 3000 tumors, f/u 12 yrs**
- **Luminal A statistically improve LC and LRC**
  - **BCT and Mastectomy**
  - **basal and HER2+ had worse outcome**

Voduc et al., JCO, 2010

Vancouver BC: Molecular Subtypes

Table 4. Ten-Year LRFS After Breast-Conserving Surgery by Subtype

Subtype	No. of Patients	No. of Events	10-Year LRFS (%)	95% CI (%)
Luminal A	587	55	92	90 to 95
Luminal B	295	27	90	86 to 94
Luminal-HER2	61	5	91	83 to 100
HER2 enriched	80	15	79	69 to 89
Basal-like	134	19	86	80 to 93
TNP-nonbasal	114	9	92	86 to 97

Abbreviations: LRFS, local relapse–free survival; HER2, human epidermal growth factor receptor 2; TNP, triple-negative phenotype.

Voduc et al., JCO, 2010

MDACC BCT Experience

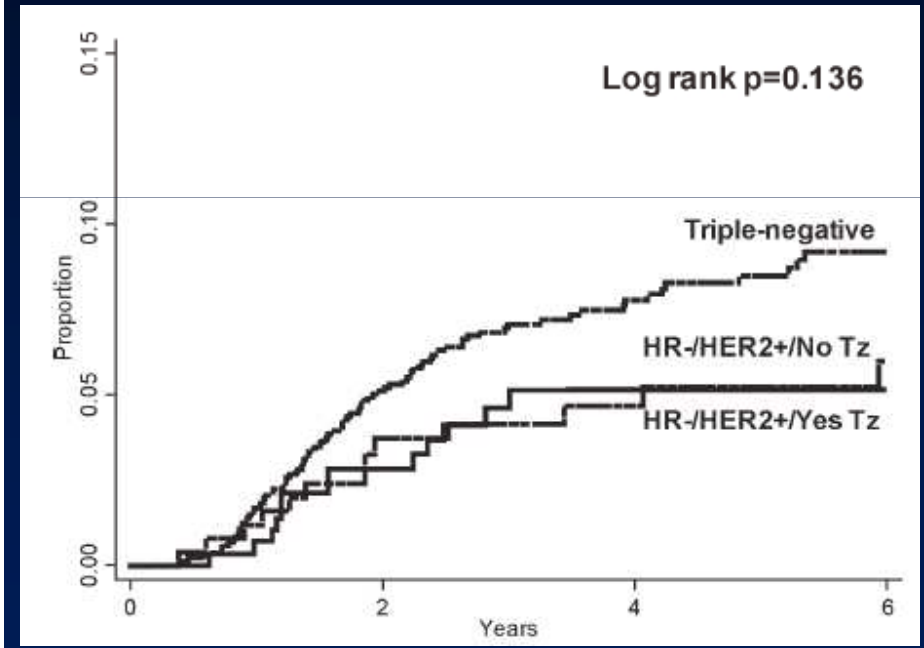
Local regional outcome according to ER stats

- **5683 patients, Rx 200-2008**
- **ER- and HER2+ predicted LR**
- **worse outcome in patients with TN disease**

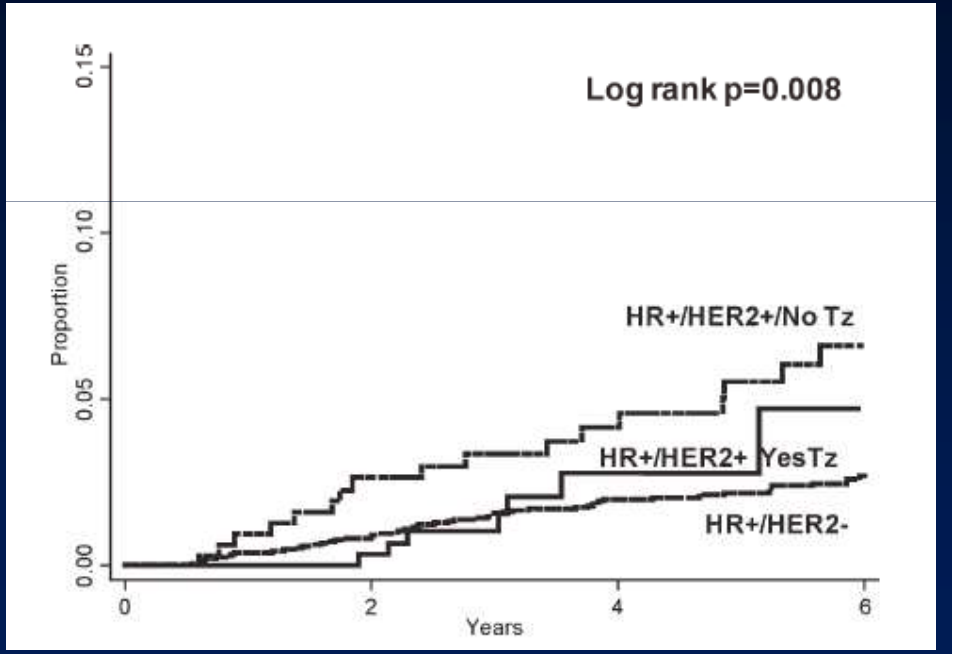
Kim et al., Cancer, 2012

Importance of TN disease

ER- disease group



ER+ disease group



Kim et al., Cancer, 2012

Harvard: Molecular Subtypes

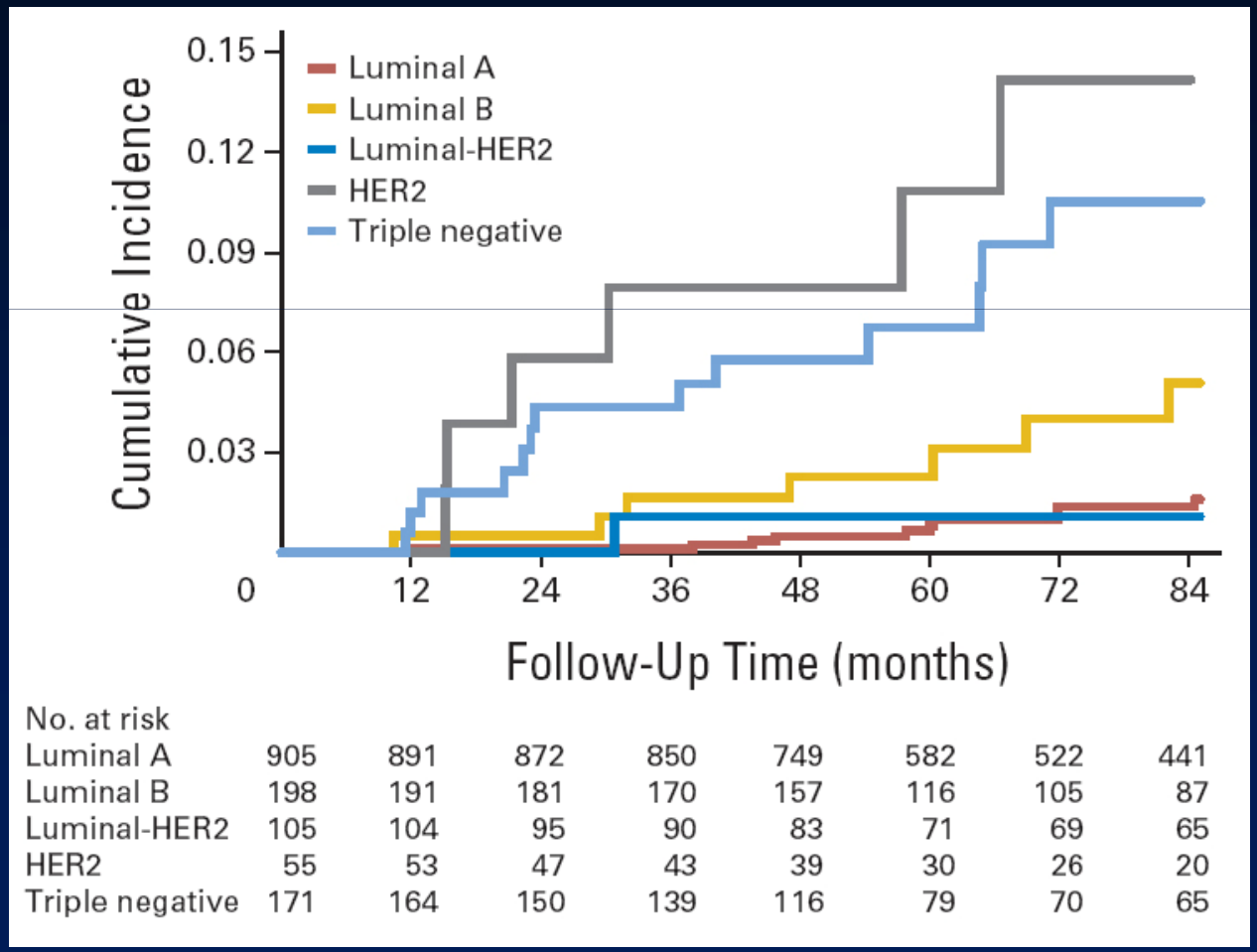
LRR after BCT

- **1434 patients treated with BCT**
- **Median f/u – 84 months**
- **Found LC dependent on**
  - **ER status/HER2**
  - **Grade**
  - **Age**

Nils et al., JCO, 2011

Harvard Data

Nils et al., JCO, 2011



No. at risk								
Luminal A	905	891	872	850	749	582	522	441
Luminal B	198	191	181	170	157	116	105	87
Luminal-HER2	105	104	95	90	83	71	69	65
HER2	55	53	47	43	39	30	26	20
Triple negative	171	164	150	139	116	79	70	65

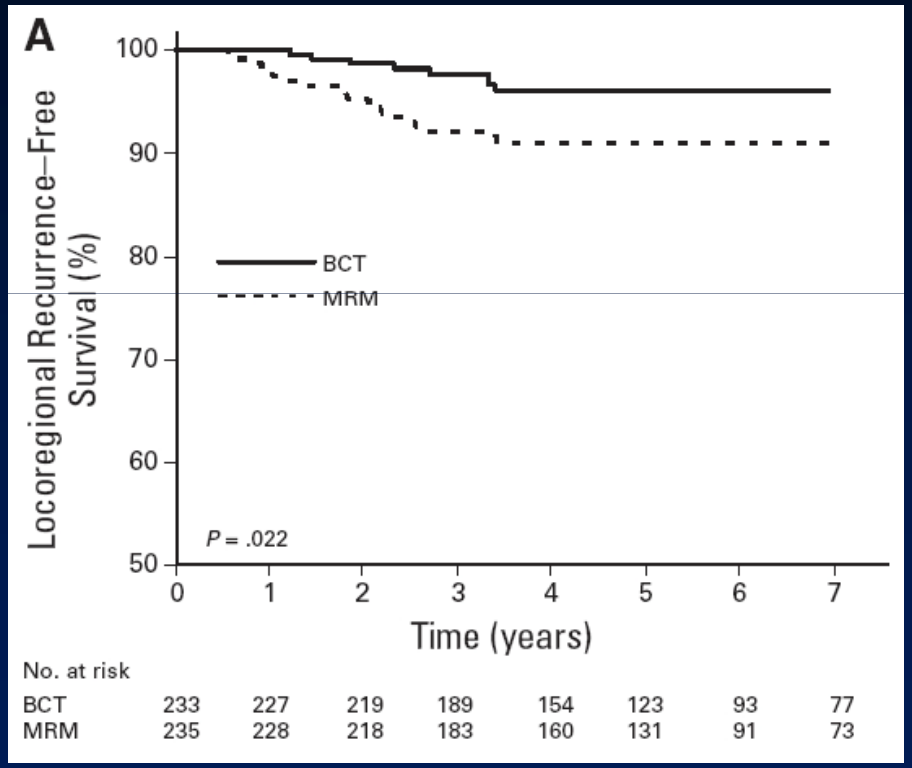
Should Patients with Triple Neg Disease Have a MRM?

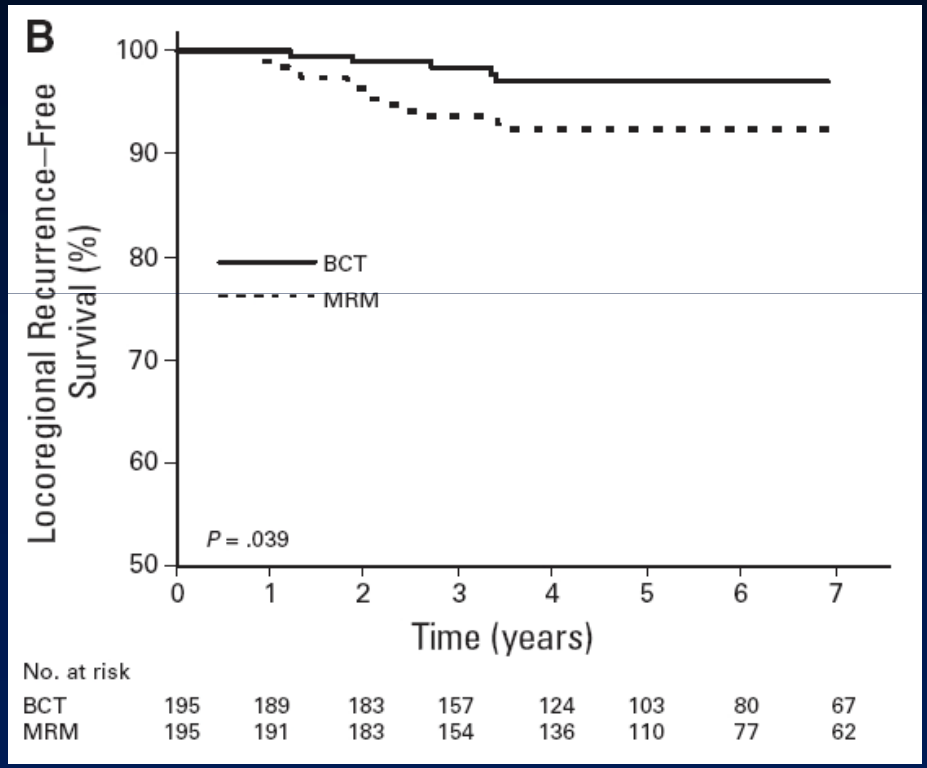
BCT vs. MRM Outcomes

- **468 pts with T1-2N0 triple negative disease**
- **BCT had better LRR and OS than MRM**

Abdulkarim et al., JCO, 2011

Should Patients with Triple Neg Disease Have a MRM?





Abdulkarim et al., JCO, 2011

Should Patients with Triple Neg Disease Have a MRM?

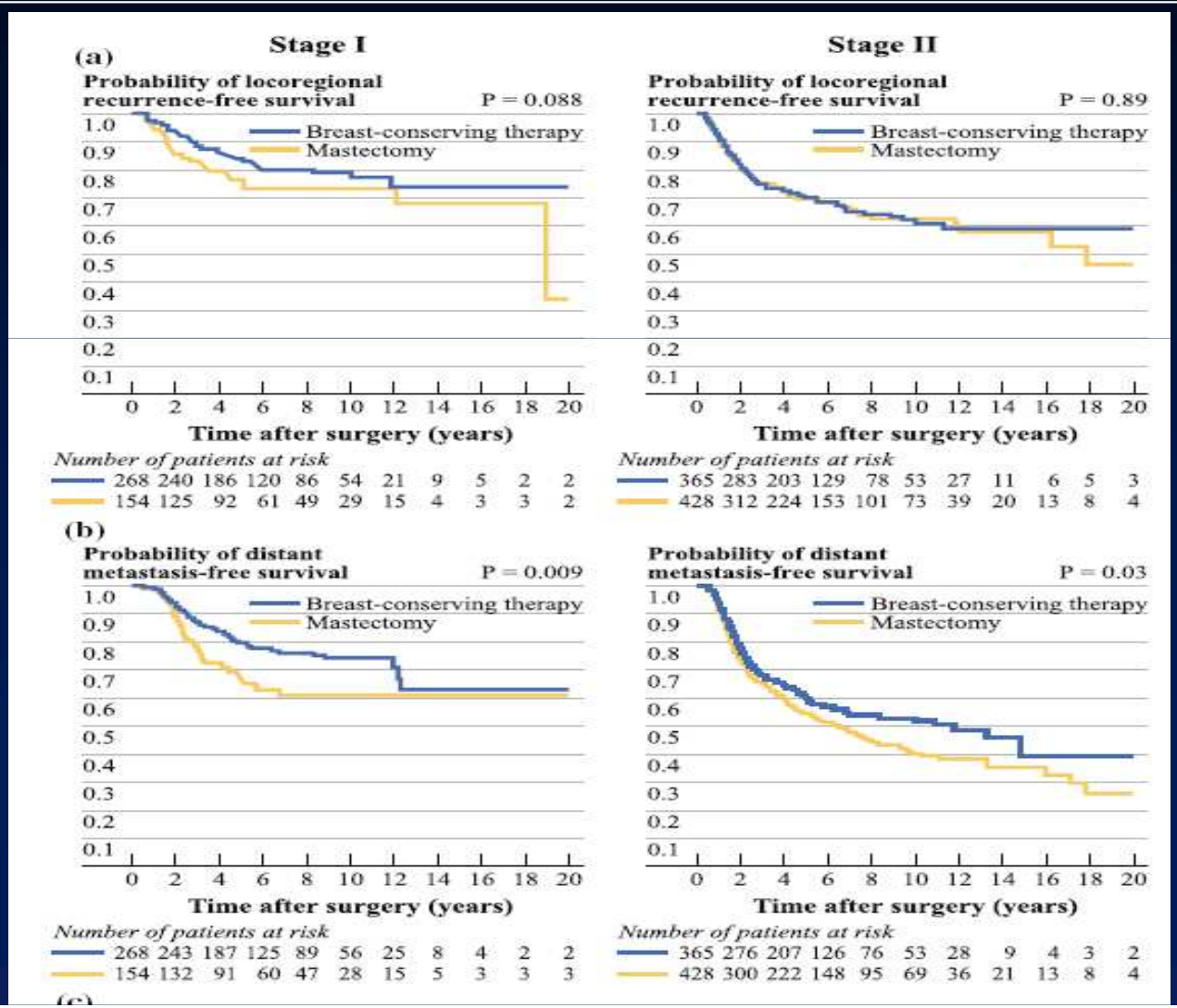
BCT vs. MRM Outcomes: MDACC Data

- **1325 pts triple negative disease**
- **BCT had better DMFS and OS than MRM**

Adkins et al., Ann Surg Oncol, 2011

Reduced DM with BCT

Adkins et al., Ann Surg Oncol, 2011



TN Disease Affects the LRR Risk after Mastectomy (no Radiation)

MDACC 5 year LRR Data

- **HR+, HER2-** **1%**
- **triple negative, LN-** **7.8%**
- **triple negative, LN+** **23.4%**

Diminici et al., Breast Cancer Res, 2012

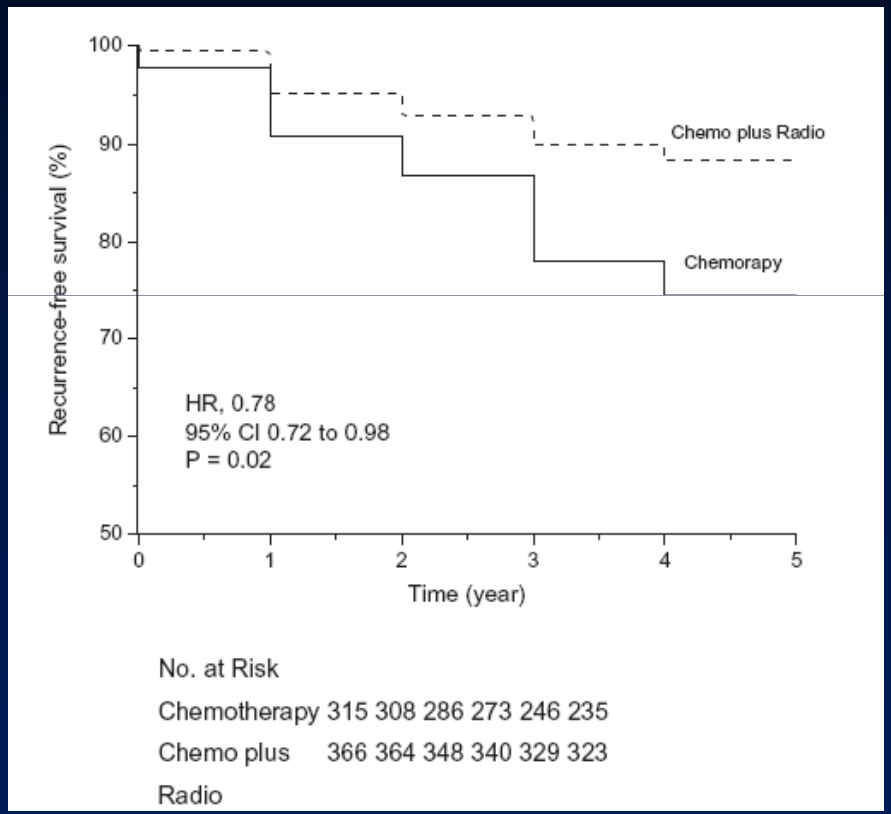
Triple Negative Prospective Trial

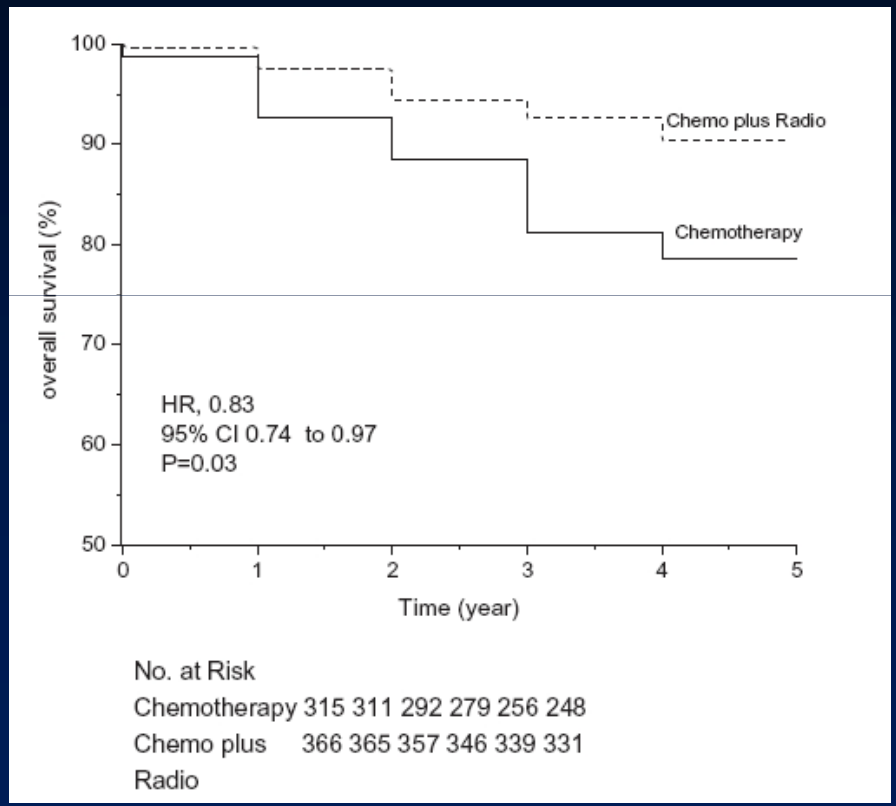
Multicenter Chinese PMRT trial in triple negative

- **681 with stage I-II**
- **81% LN-, 15% with 1-3 +LN**
- **all treated with mastectomy and chemotherapy**
- **most randomized to XRT received it to CW only**
- **median f/u of 86.5 months**

Wang et al., Radiotherapy Oncol, 2011

Triple Negative Prospective Trial



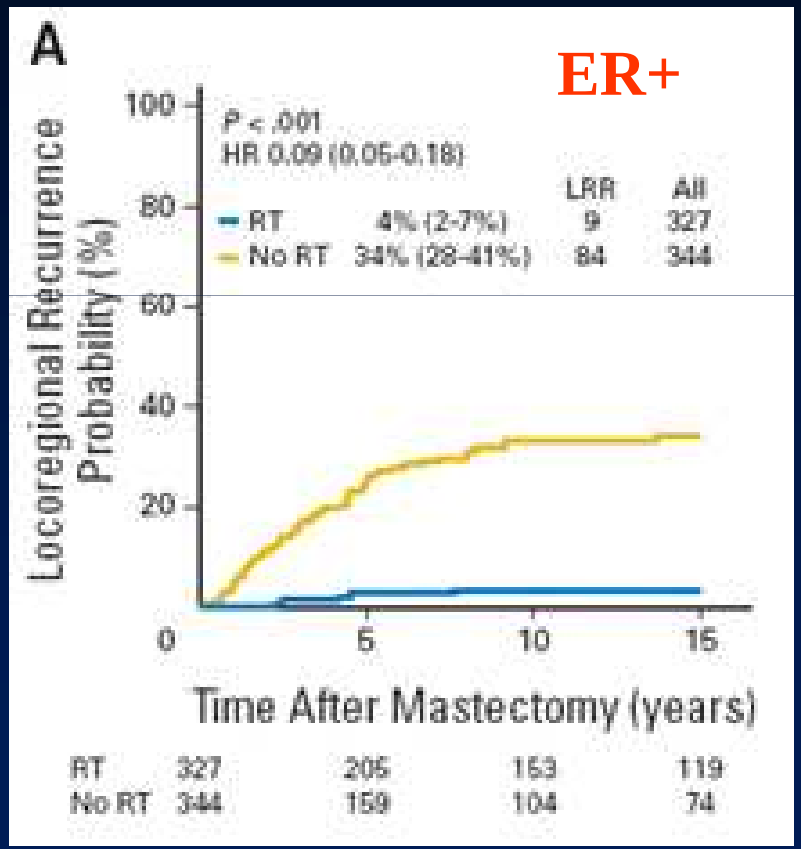


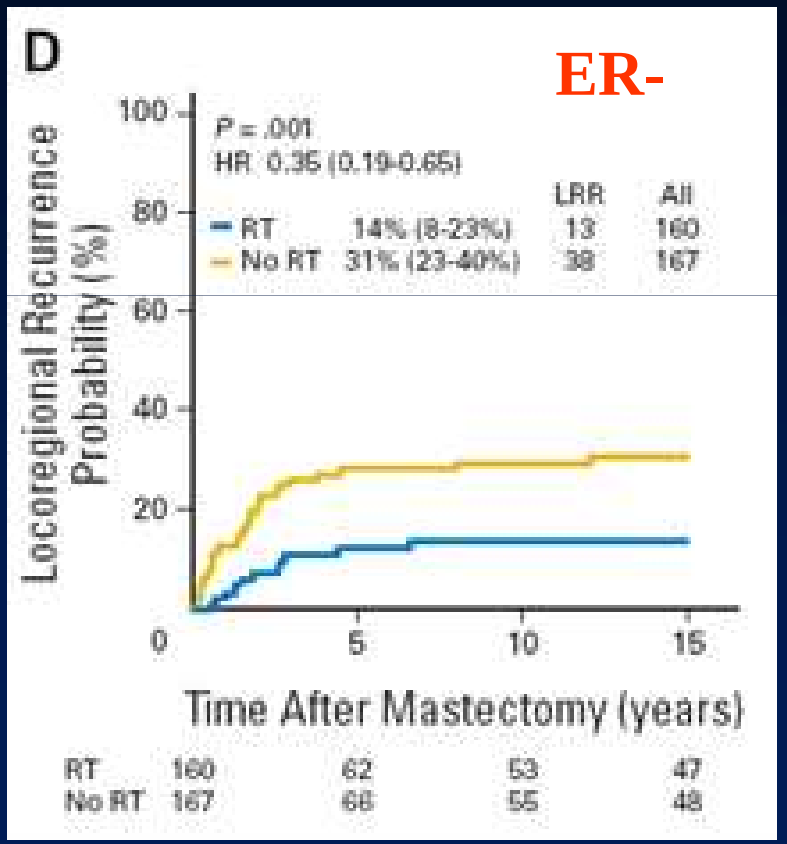
Wang et al., Radiotherapy Oncol, 2011

Efficacy of PMRT In More Advanced Triple Negative Disease

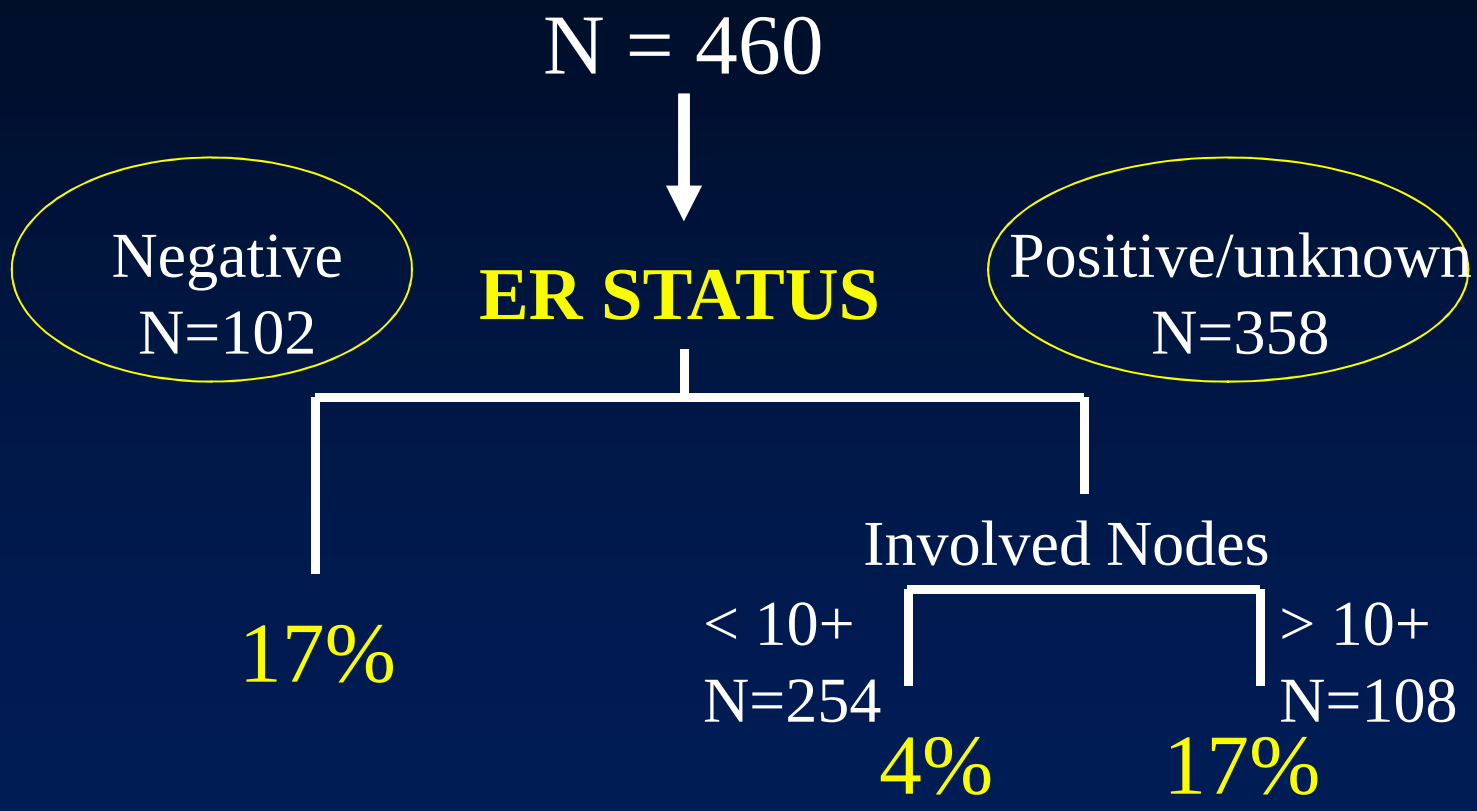
Danish Trials Postmastectomy LRR

Kyndi et al., J Clin Oncol, 26:1419, 2008





Recursive Partitioning Analysis LRR after XRT (MDACC)

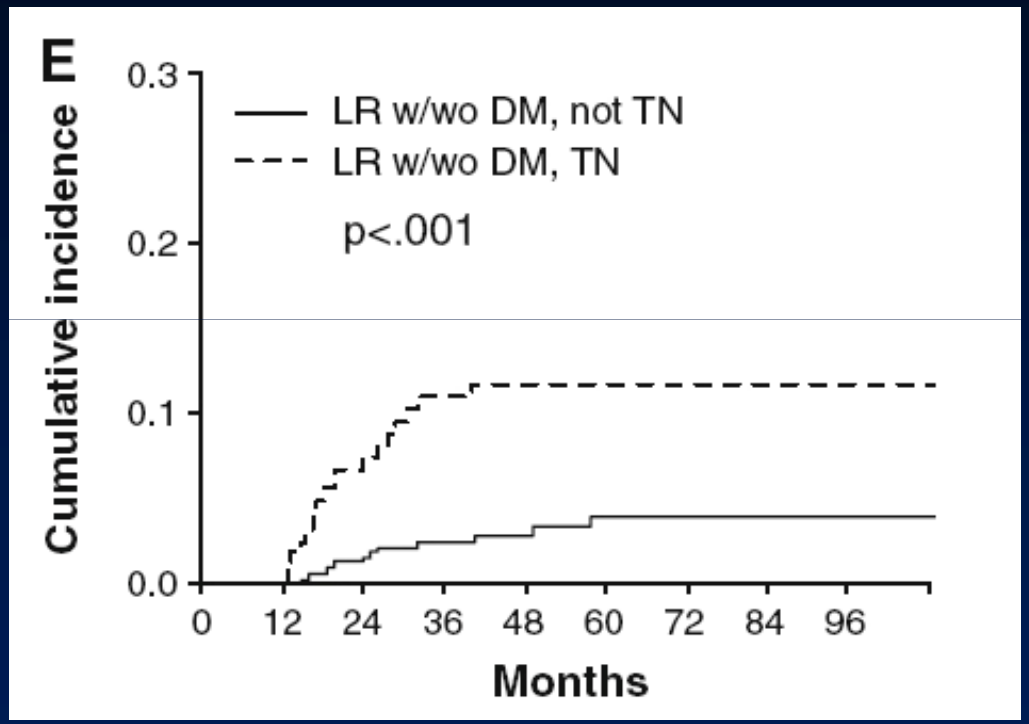


Woodward et al., Int J Radiat Oncol Biol Phys, 26:1419, 2008

Unv Miami PMRT Outcomes in TN

PMRT Outcomes

- 582 PMRT pts



Panoff et al., Breast Cancer Res Treat, 2011

Triple Negative Disease Appears to Be Prognostic Predicting Need For Radiation But Simultaneously Is Predictive of Less Benefit From Radiation

Triple Negative Disease: Particular Subtypes

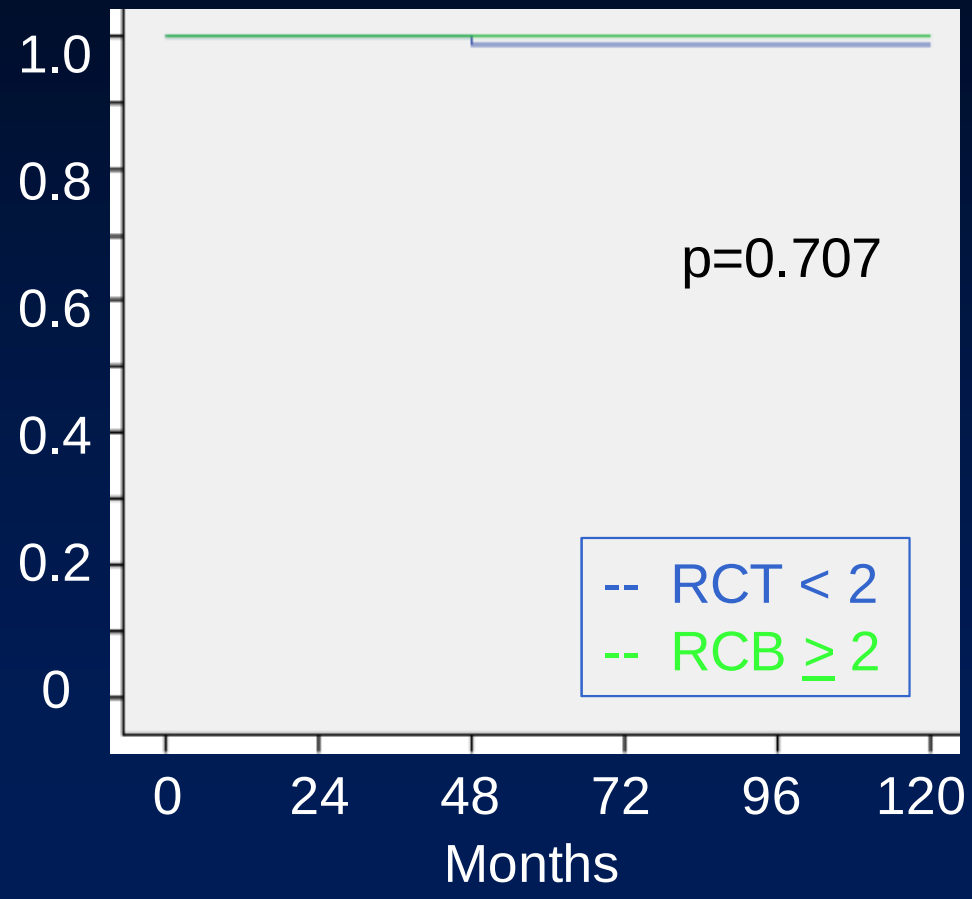
Triple Negative Subtypes

Rare subtypes of bresat cancer most often are TN

- **medullary (BRCA1 like) – do well**
- **adenoid cystic, squamous cell ca – do well**
- **sarcomatoid – do poorly w/ and w/o radiation**
  - **metaplastic carcinoma**
  - **angiosarcoma**
  - **claudin low**

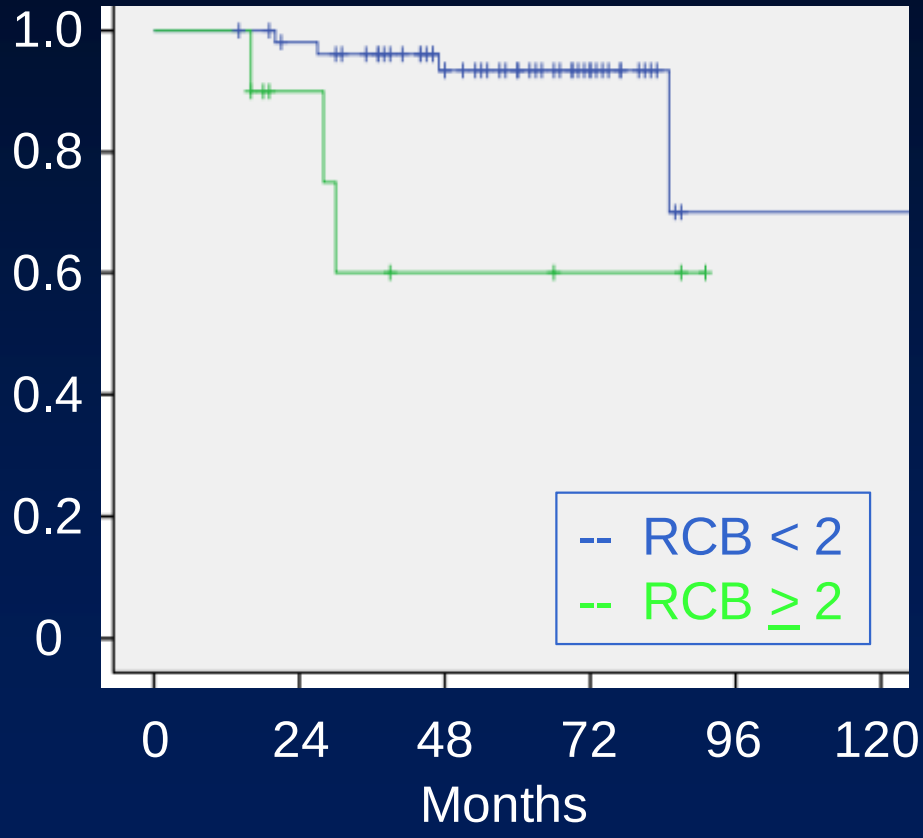
Does Chemotherapy Response Help Predict Radiation Outcome?

NCT + PMRT, Hormone Positive



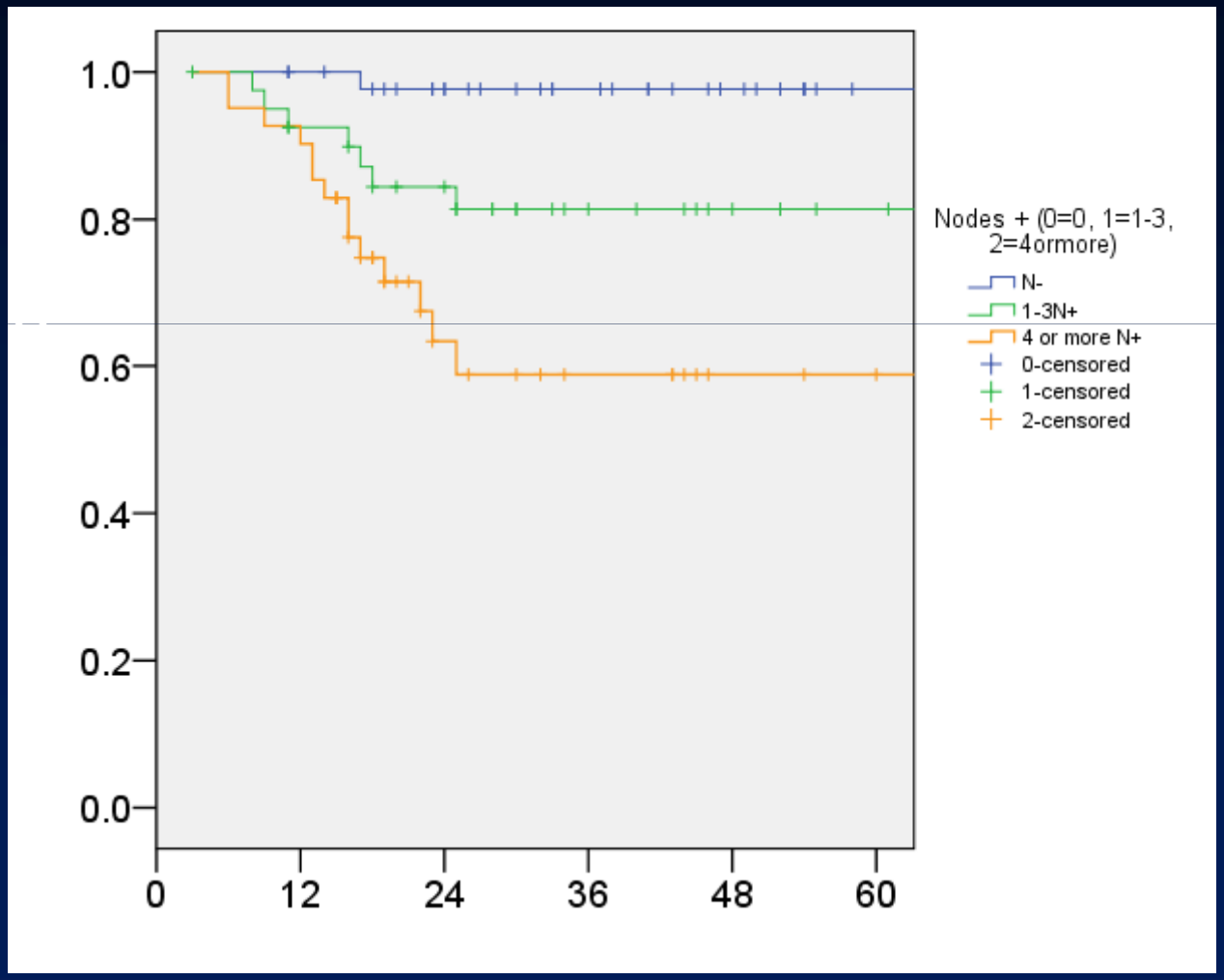
RCB < 2	5 yr LRR	0%
RCB ≥ 2	5 yr LRR	1%

NCT + PMRT, Triple Negative



RCB < 2	5 yr LRR	6.6%
RCB ≥ 2	5 yr LRR	40.0%

MDACC PMRT in Triple Negative Disease by Nodal Status



5-Yr LRC:

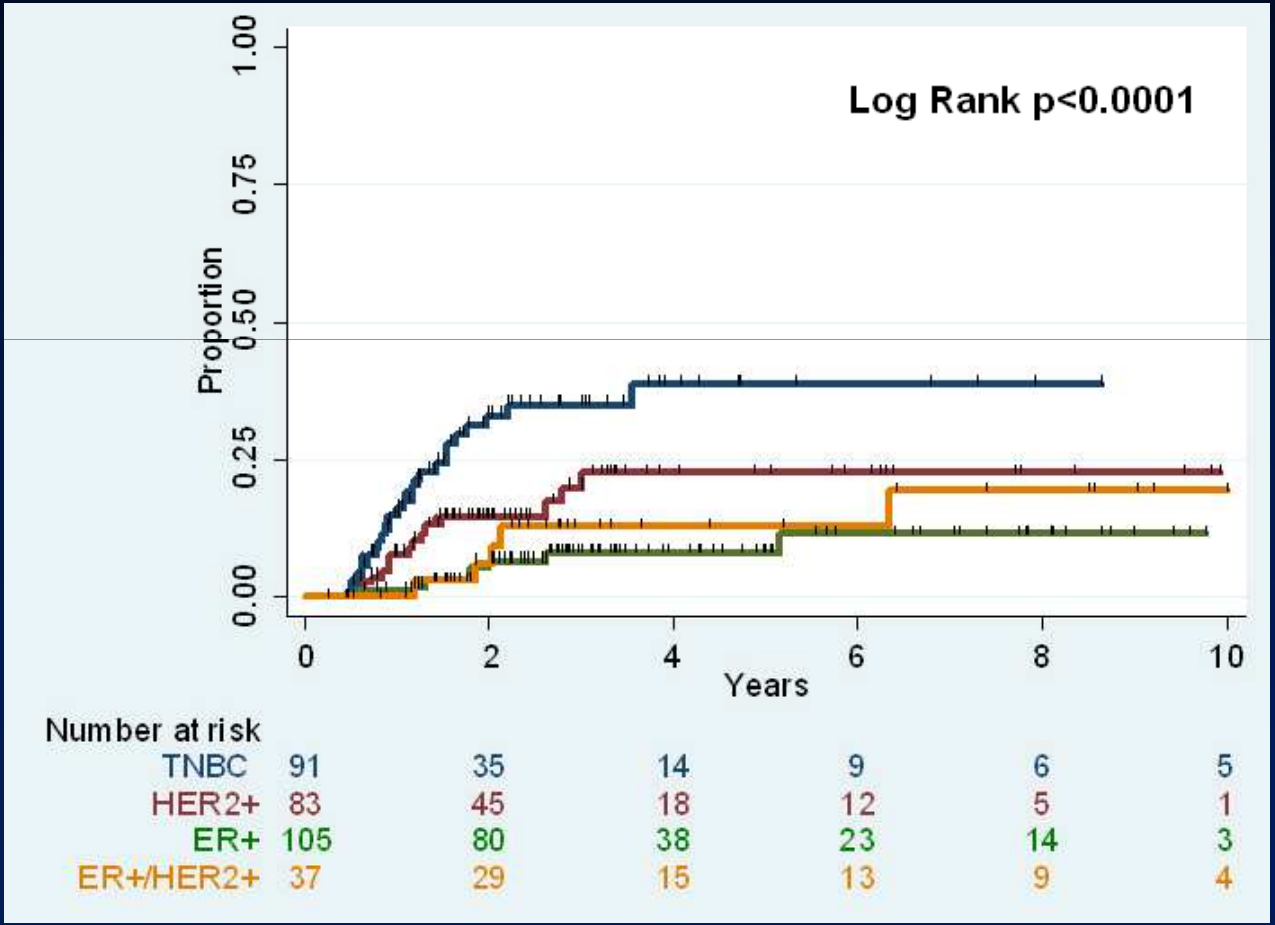
Node neg: 98%

1-3N+: 81%

4 or more N+: 59%

P<0.001

MDACC: Inflammatory Breast Cancer with PMRT



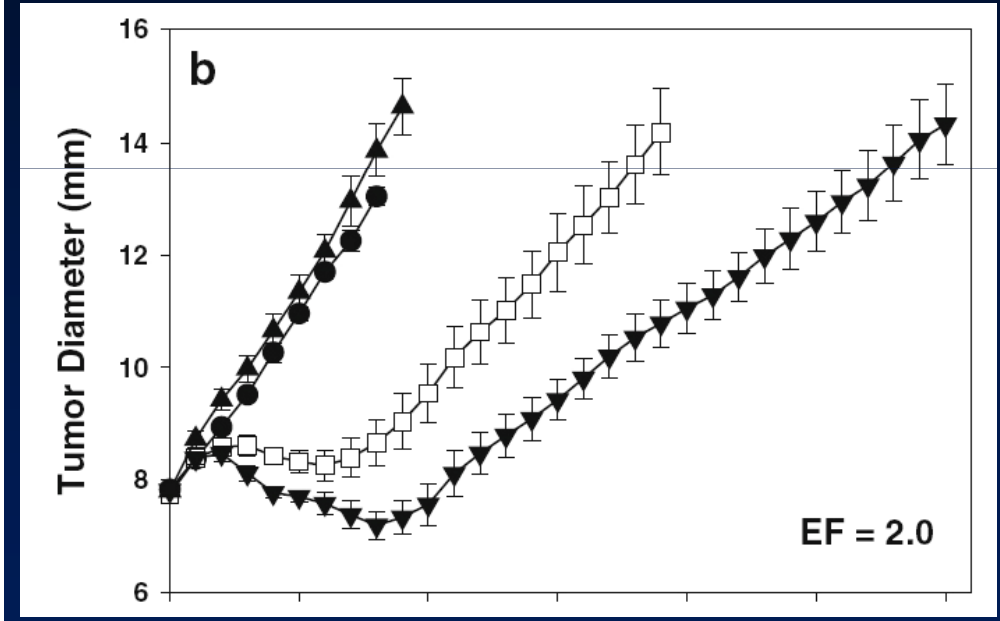
Li et al., Oncologist, 2012

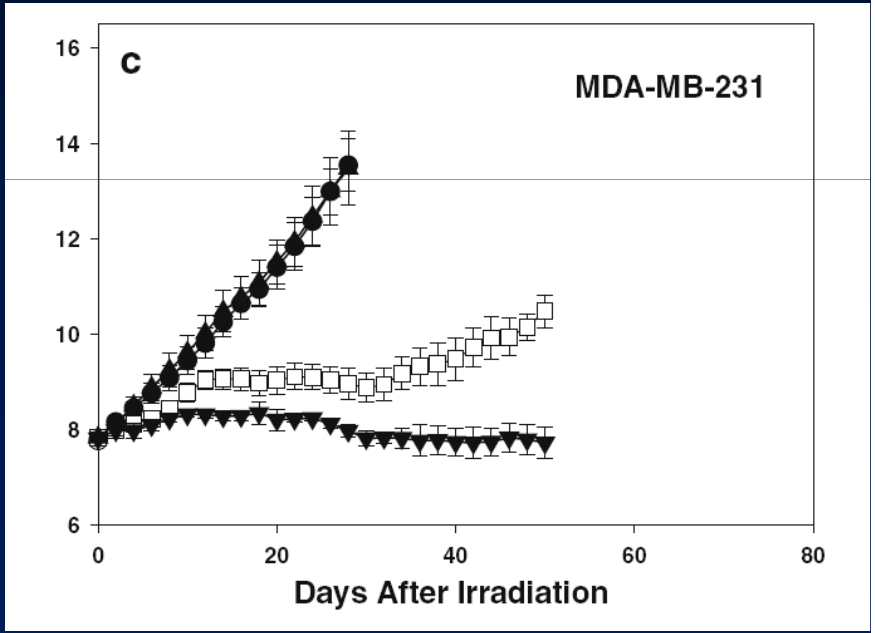
New Radiation Strategies

TBCRC Funded Phase I Trial (Jagsi, PI)

- Veliparib (parp inhibitor) + radiation
- 30 patient study
- inflammatory or recurrent breast cancer

PARP Radiosensitize Triple Negative Xenographs





Wang et al., Inv New Drugs, 2011

Other New Strategies

Triple Negative Advanced Disease

- need new strategies
  - concurrent chemotherapy
  - concurrent PARP/molecular targets
  - dose escalation
  - phenotype assays of DNA damage

Conclusion

Breast Cancer is a Heterogeneous Disease

- many subtypes do extremely well
  - focus on omission, cost, convenience
  - focus on toxicity avoidance
- selected subtypes need improvements
  - focus on new therapeutic approaches