

# Regional Nodal Radiotherapy for Breast Cancer

Reshma Jagsi, MD, DPhil

Associate Professor

Department of Radiation Oncology

University of Michigan

November 2015

# Rationale for RT

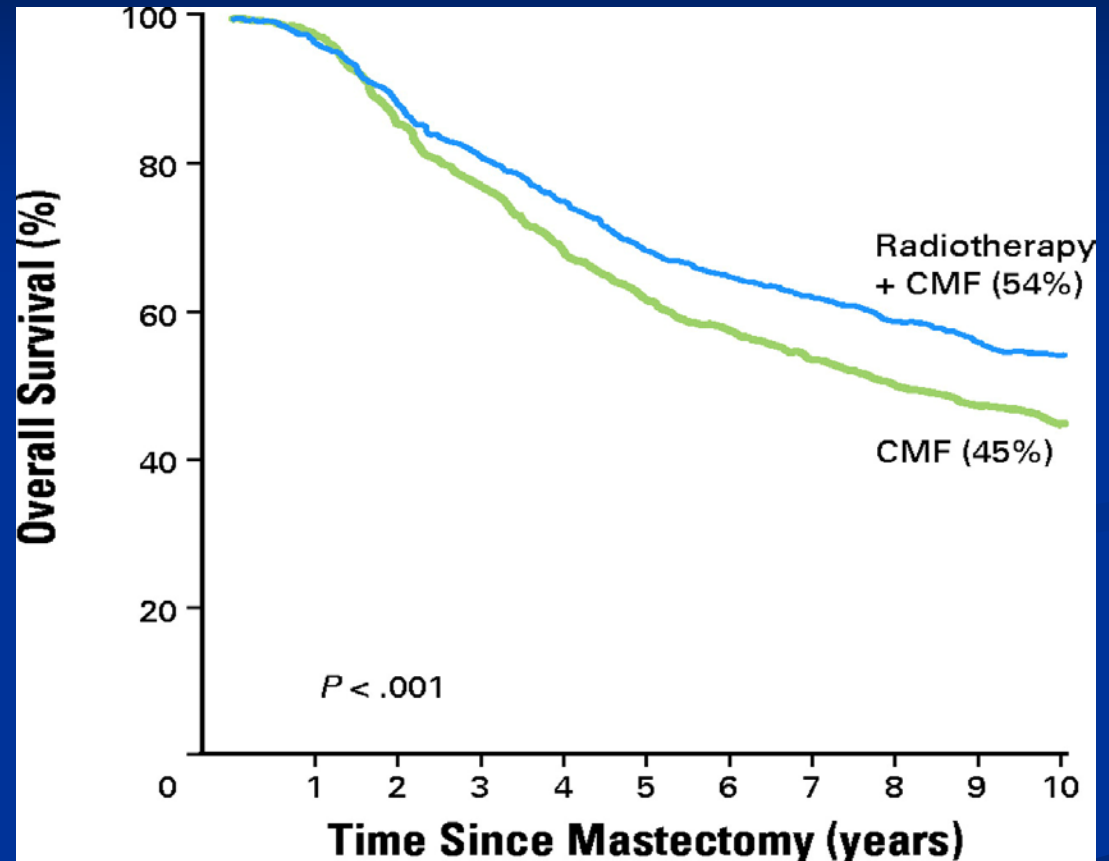
- To prevent local-regional recurrence
- To prevent seeding/re-seeding from persistent local disease

# Agenda

- Historical data from PMRT trials
  - Observation of significant survival benefits from comprehensive RT in the post-mastectomy setting led to the idea that comprehensive RT might be important for all node-positive patients
  - Reflections on how 2015 in the US differs from 1982 in Denmark...
- More recent studies specifically evaluating less and more aggressive treatment to the regional nodes

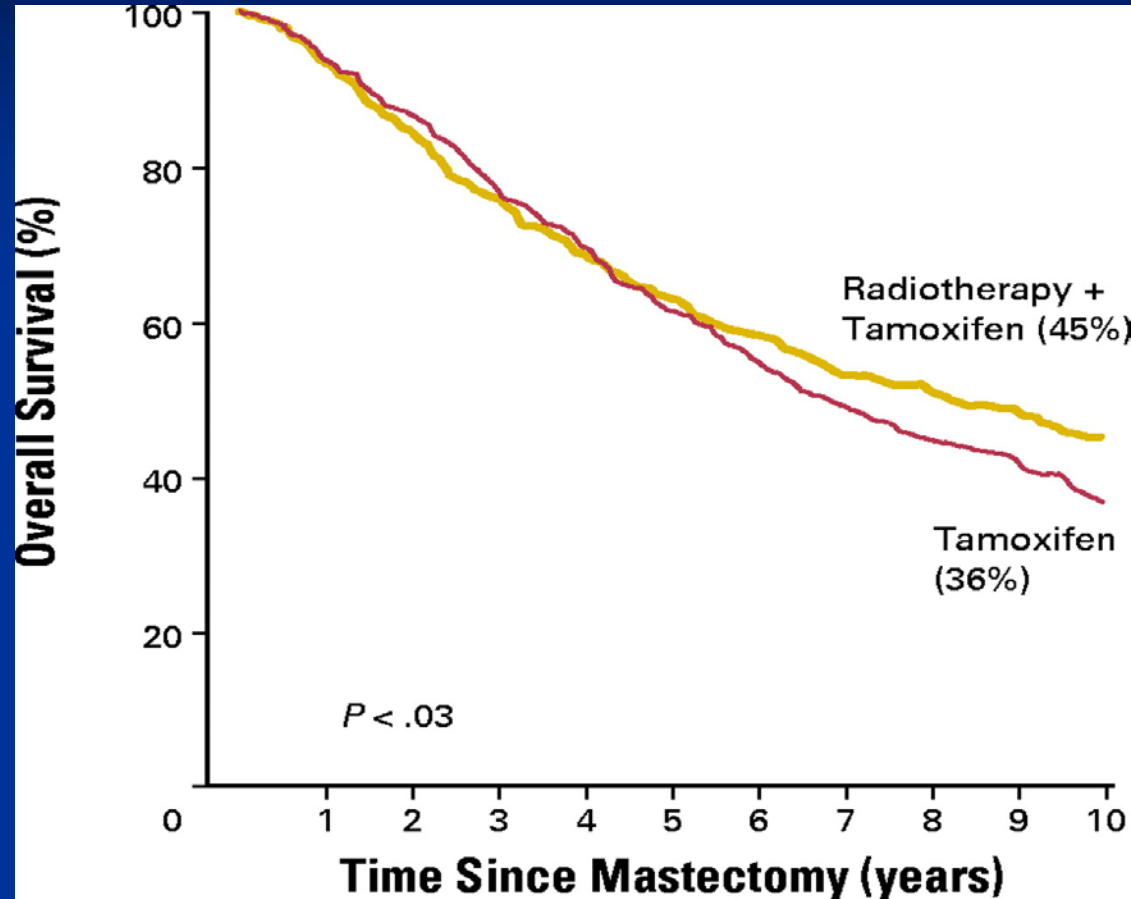
# Danish 82b Trial

- 1708 premenopausal high-risk pts with pStage II/III breast cancer randomized
  - 9 cycles CMF alone
  - vs
  - 8 cycles CMF + PMRT
- PMRT reduced LRF
  - 9% vs 32% ( $p < 0.001$ )
- PMRT improved OS
  - 54% vs 45% ( $p < 0.001$ )
- MVA revealed benefit regardless of T size or number of positive nodes



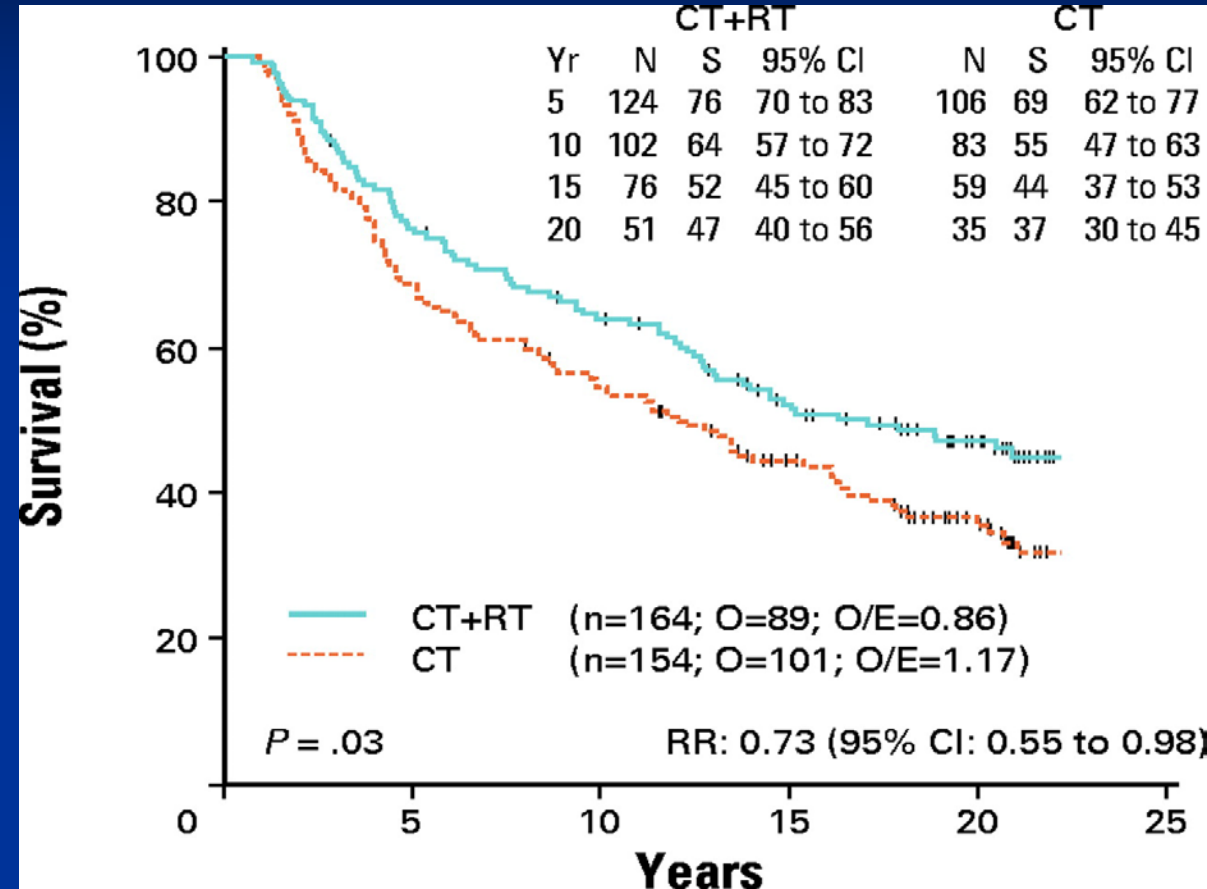
# Danish 82c Trial

- 1375 postmenopausal high-risk pts with pStage II/III breast cancer randomized
  - 1 yr Tam
- vs
- Tam + PMRT
- PMRT reduced LRF
  - 8% vs 35% ( $p < 0.001$ )
- PMRT improved OS
  - 45% vs 36% ( $p < 0.001$ )



# British Columbia Trial

- 318 premenopausal women with node-positive breast cancer randomized
  - 12 mos CMF (later reduced to 6 mos) alone
- vs
- CMF + PMRT
- PMRT reduced LRF
  - 10% vs 26% (p=0.002)
- PMRT improved OS
  - 47% vs 37% (p=0.03)
- Magnitude of benefit of XRT similar for subgroup with 1-3 vs.  $\geq 4$  LN+



# Criticisms and Concerns

- Danish Trials
  - Median # LNs removed: 7
  - Axillary Recurrence: 82b 13% (no XRT) vs. 2% (XRT)
  - Chemotherapy and hormonal therapy
    - CMF chemo era
    - Tamoxifen for 1 year in postmenopausal patients
- British Columbia Trial
  - Median # LNs removed: 11
  - CMF era

# Higher LRR Rates on the Trials Compared to Other Series

Table 6. Ten-Year Cumulative Rates of Locoregional Failure With or Without Distant Failure According to Number of Positive Lymph Nodes (LN+)

| Number LN+                           | # of pts    | 1-3 LN+ (%) | ≥ 4 LN+ (%) | Median No. of LN Dissected | Chemotherapy Used  |
|--------------------------------------|-------------|-------------|-------------|----------------------------|--------------------|
| Danish trial 82b <sup>6</sup>        | <b>856</b>  | 30          | 42          | 7                          | CMF                |
| Danish trial 82c <sup>7</sup>        | <b>684</b>  | 31          | 46          | 7                          | CMF                |
| Canadian <sup>5a</sup>               | <b>160</b>  | 33          | 46          | 11                         | CMF                |
| ECOG <sup>9†</sup>                   | <b>1099</b> | 13          | 29          | 15                         | CMF                |
| MDA <sup>10‡</sup>                   | <b>1031</b> | 14          | 25-34       | 17                         | Doxorubicin based  |
| IBCSG, <sup>11†</sup> premenopausal  |             | 19.7%       | 30-38%      | ≈15                        | CMF**              |
| IBCSG, <sup>11†</sup> postmenopausal | <b>4077</b> | 16%         | 29-35%      | ≈15                        | CMF or tamoxifen†† |
| NSABP†                               | <b>5758</b> | 13          | 24-32       | 16                         | Doxorubicin/CMF††  |



# RADIOTHERAPY FOR INVASIVE BREAST CANCER IN NORTH AMERICA AND EUROPE: RESULTS OF A SURVEY

ELIZABETH CEILLEY, M.D., RESHMA JAGSI, M.D., D.PHIL., SAVELI GOLDBERG, PH.D.,  
 LAURENT GRIGNON, B.S., LISA KACHNIC, M.D., SIMON POWELL, M.D., PH.D., AND  
 ALPHONSE TAGHIAN, M.D., PH.D.

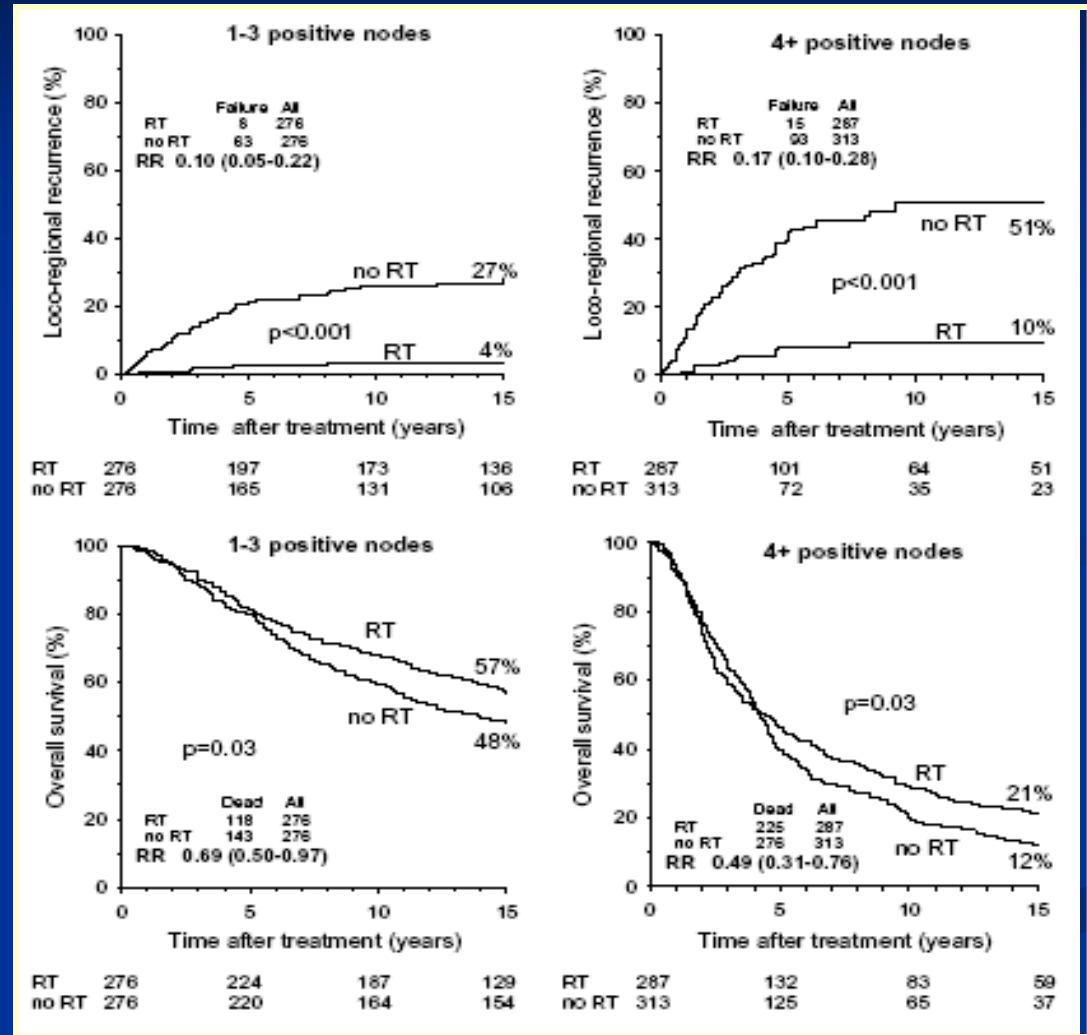
Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

## 1124 practicing radiation oncologists' views

|                            | <i>Chest Wall (%)</i> |               | <i>SCF(%)</i> |               | <i>Axilla (%)</i> |               | <i>IMC(%)</i> |               |
|----------------------------|-----------------------|---------------|---------------|---------------|-------------------|---------------|---------------|---------------|
|                            | <i>NA</i>             | <i>Europe</i> | <i>NA</i>     | <i>Europe</i> | <i>NA</i>         | <i>Europe</i> | <i>NA</i>     | <i>Europe</i> |
| <b>pT3N0</b>               | 88.3                  | 84.8          | 47.7          | 20.2          | 15.6              | 8.3           | 6.5           | 10.1          |
|                            |                       | NS            |               | p<0.0001      |                   | p<0.01        |               | NS            |
| <b>1-3 LN+ without ECE</b> | 61.7                  | 60.9          | 50.2          | 41.6          | 18.1              | 12.6          | 9.5           | 26.1          |
|                            |                       | NS            |               | p<0.05        |                   | NS            |               | P<0.001       |
| <b>1-3 LN+ with ECE</b>    | 85.2                  | 78.8          | 84.2          | 75.1          | 63.8              | 53.3          | 14.9          | 34.2          |
|                            |                       | p<0.01        |               | p<0.001       |                   | p<0.01        |               | p<0.0001      |
| <b>≥4 LN+ without ECE</b>  | 98                    | 94.9          | 98.6          | 94            | 58.2              | 52.8          | 23.6          | 40            |
|                            |                       | p<0.01        |               | p<0.001       |                   | NS            |               | p<0.0001      |
| <b>≥4 LN+ with ECE</b>     | 98.7                  | 95.7          | 99.4          | 96.9          | 80.4              | 71.4          | 25.1          | 43.1          |
|                            |                       | p<0.01        |               | p<0.01        |                   | p<0.01        |               | p<0.0001      |

# 2007 Danish Sub-Set Analysis

- Analyzed only the 1152 node-positive pts with 8 or more nodes examined
- 15 yr OS 39% vs 29% (p=0.015)
- LRR benefit in both groups
- Survival benefit in both groups



Overgaard M et al. *Radiother Oncol* 2007;83:247-53.

## 2007 Danish Sub-Set Analysis

“[I]n patients with fewer nodes involved and a consequential lower risk of distant metastases, a larger proportion can obtain survival benefit although they have a smaller risk of local failures. Thus, the improvement in survival may not directly be linked and proportionate to the improvement in loco-regional control.”

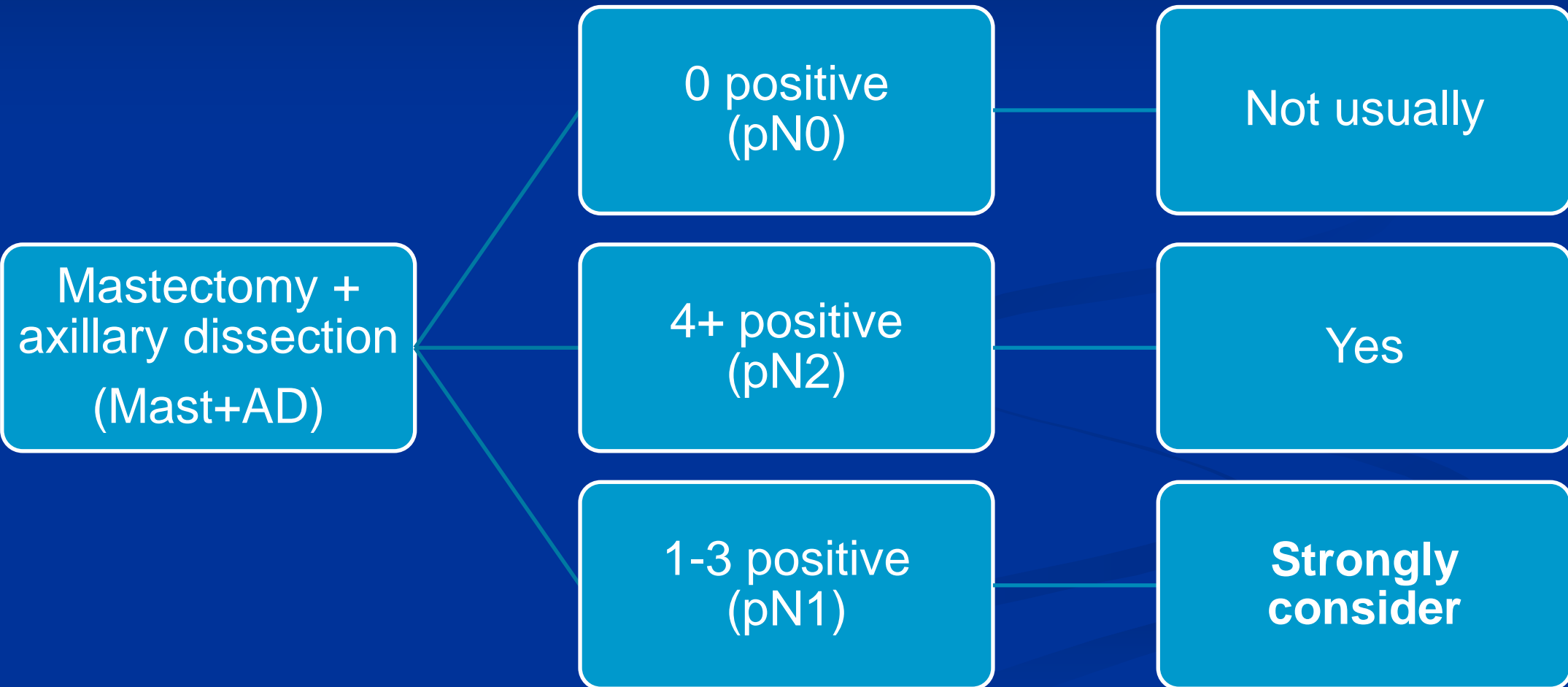
*M Overgaard et al.*

# Current Guidelines

**Surgery**

**Nodal status**

**Radiotherapy ?**



# EBCTCG's Meta-Analysis 2014

## Trials of radiotherapy after mastectomy and axillary dissection

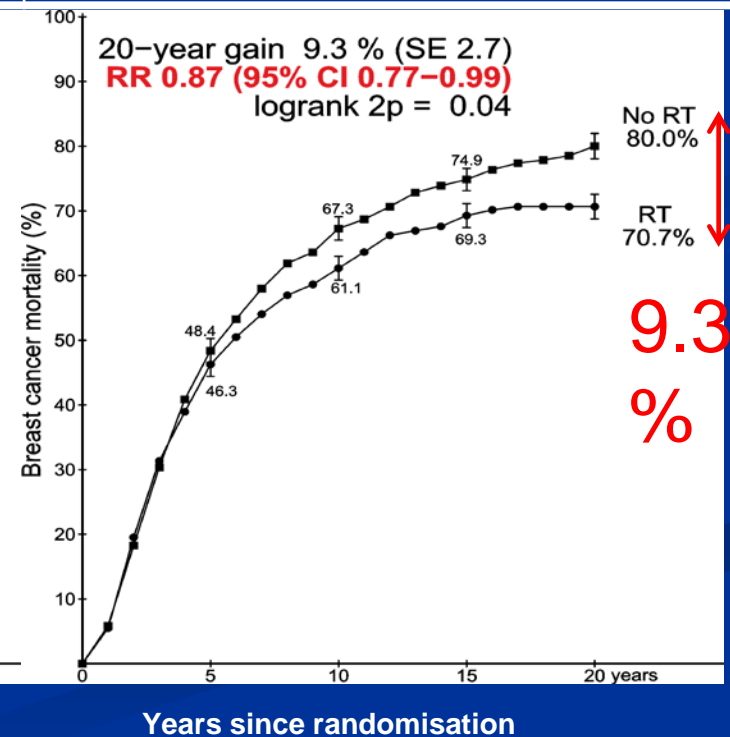
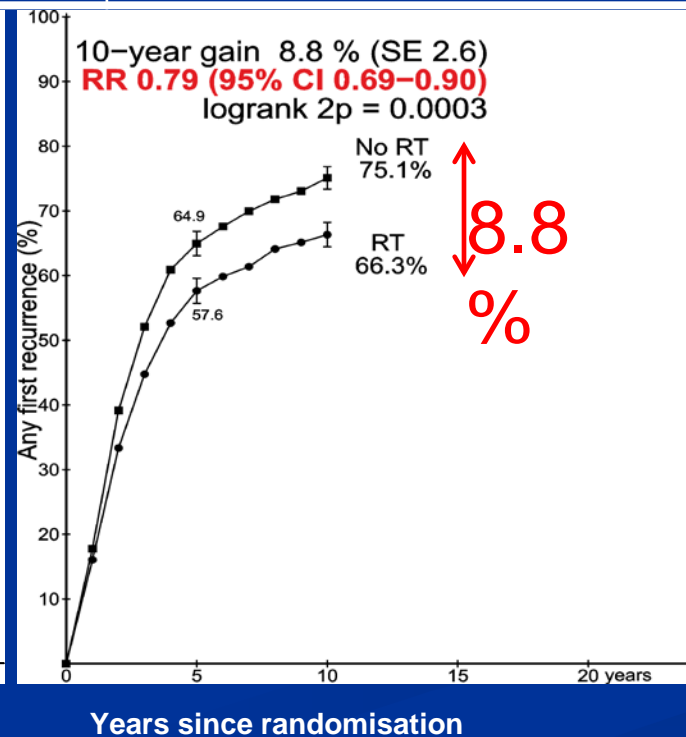
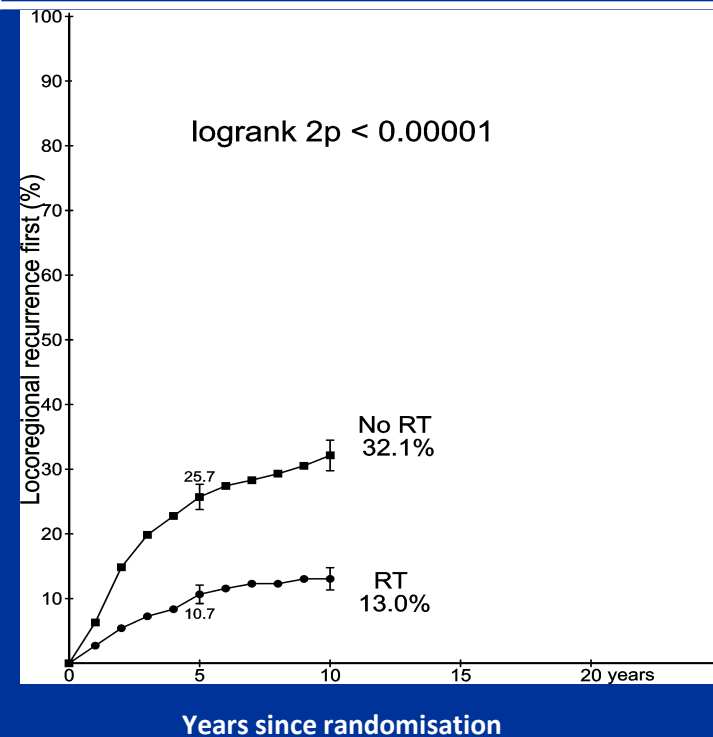
1772 pN2 women (4+ nodes)

RT: Significant benefit

### Locoregional recurrence first

### Any first recurrence

### Breast cancer mortality

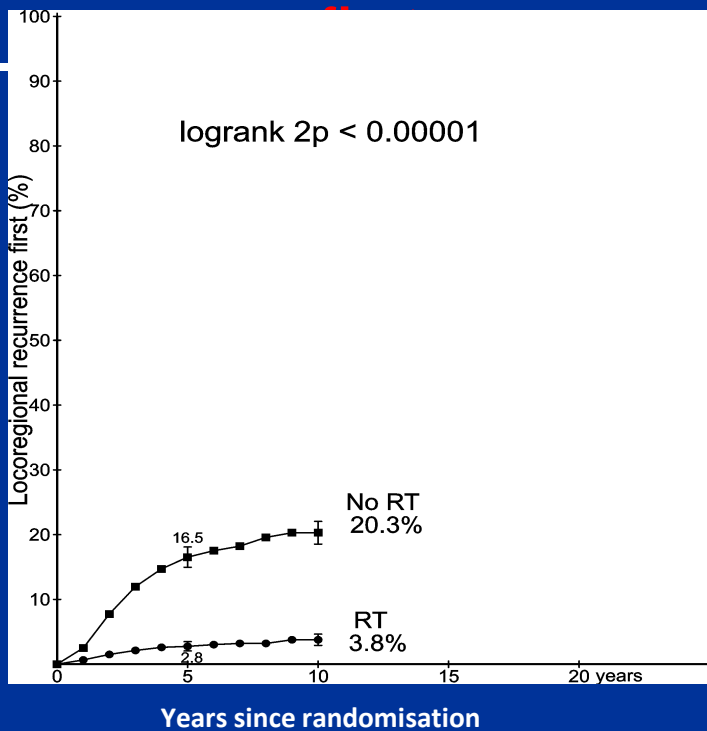


# Trials of radiotherapy after mastectomy and axillary dissection

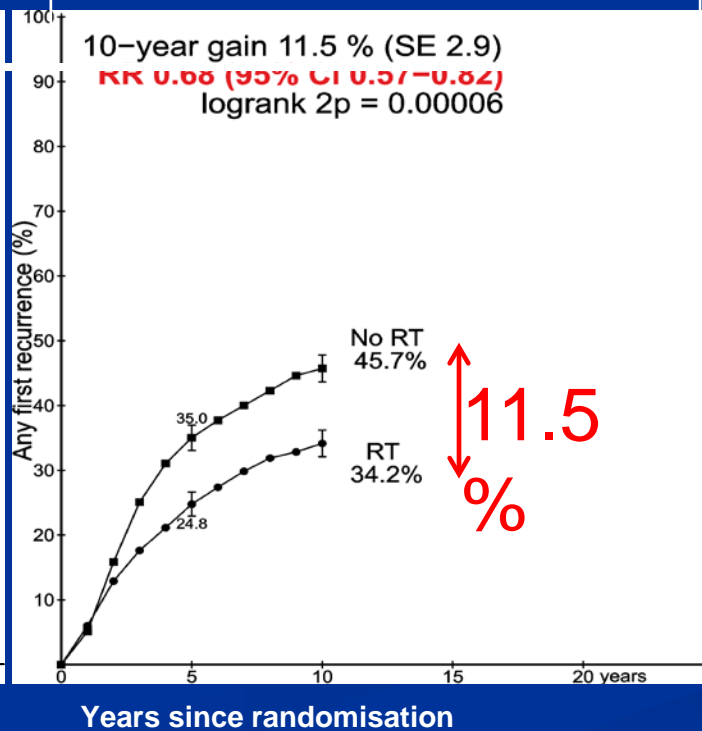
1314 pN1 women (1-3 nodes)

RT: Significant benefit (and similar results in the subset of 1133 with systemic rx)

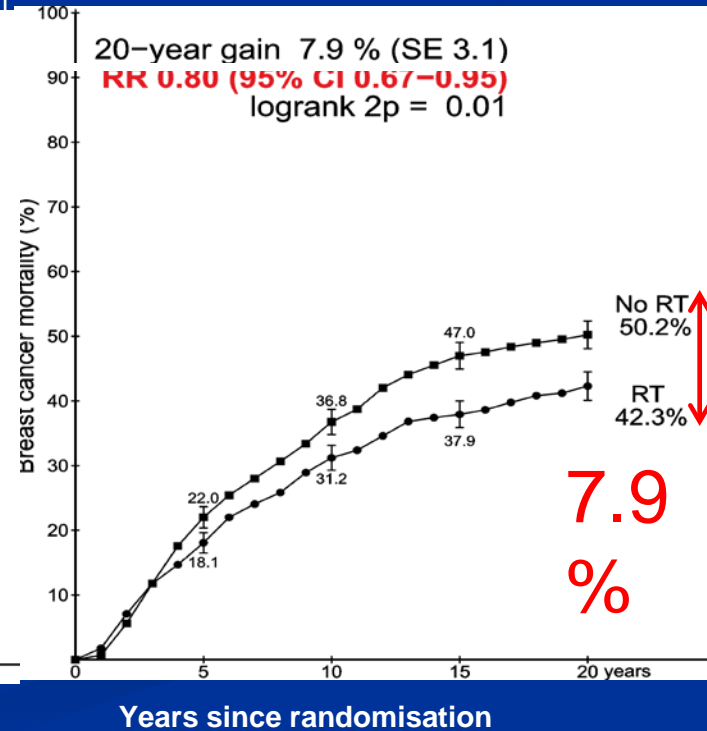
## Locoregional recurrence



## Any first recurrence



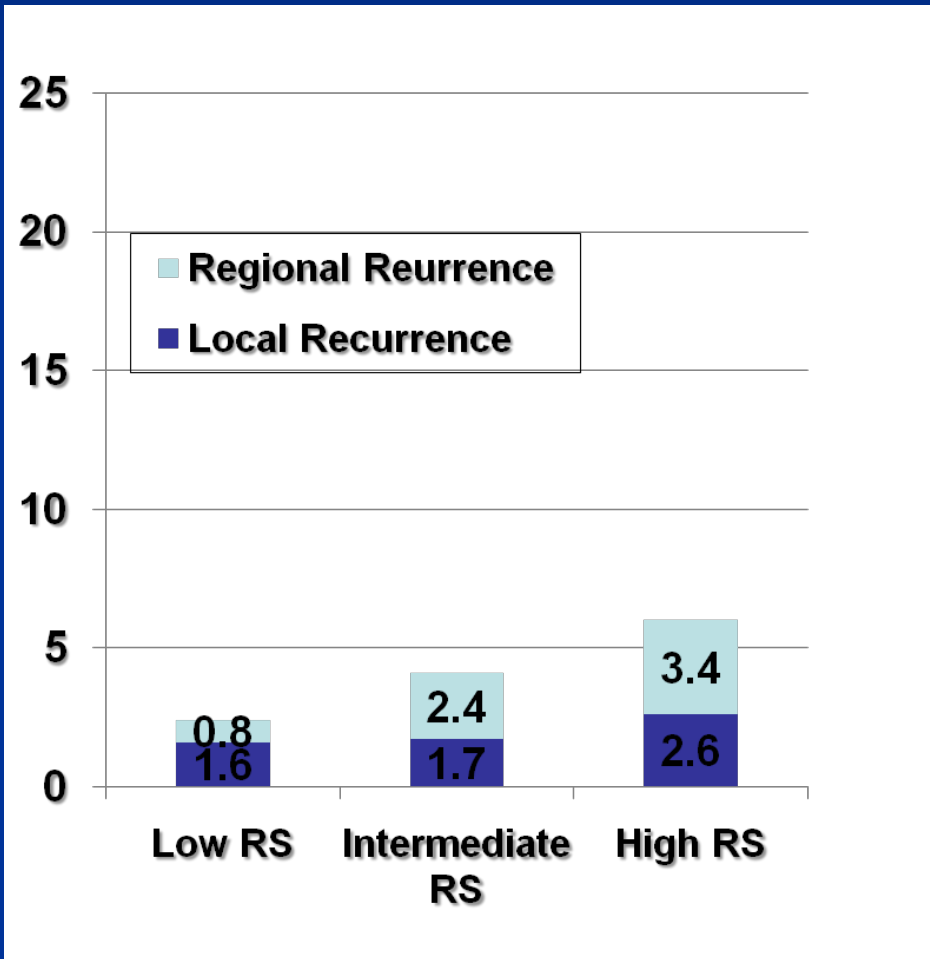
## Breast cancer mortality



# Must Acknowledge Decreasing LRR Over Time

- Screen detected cancers
- Surgical and pathologic advances
  - SLNB detects small amounts of nodal involvement
- Better systemic therapies
  - Taxanes
  - Aromatase inhibitors
  - Herceptin

# LRR in N1 Patients



Patients undergoing mastectomy for N1 disease on NSABP B28 (received no RT)

Mamounas et al. SSO 2013



# Not Every Node-Positive Patient Requires PMRT in 2015

- Select node-positive patients do very well with surgery and systemic therapy alone
- And if that's true, then not every node-positive patient undergoing lumpectomy should require comprehensive regional nodal RT either
- But some do appear to benefit
- How do we sort this out?

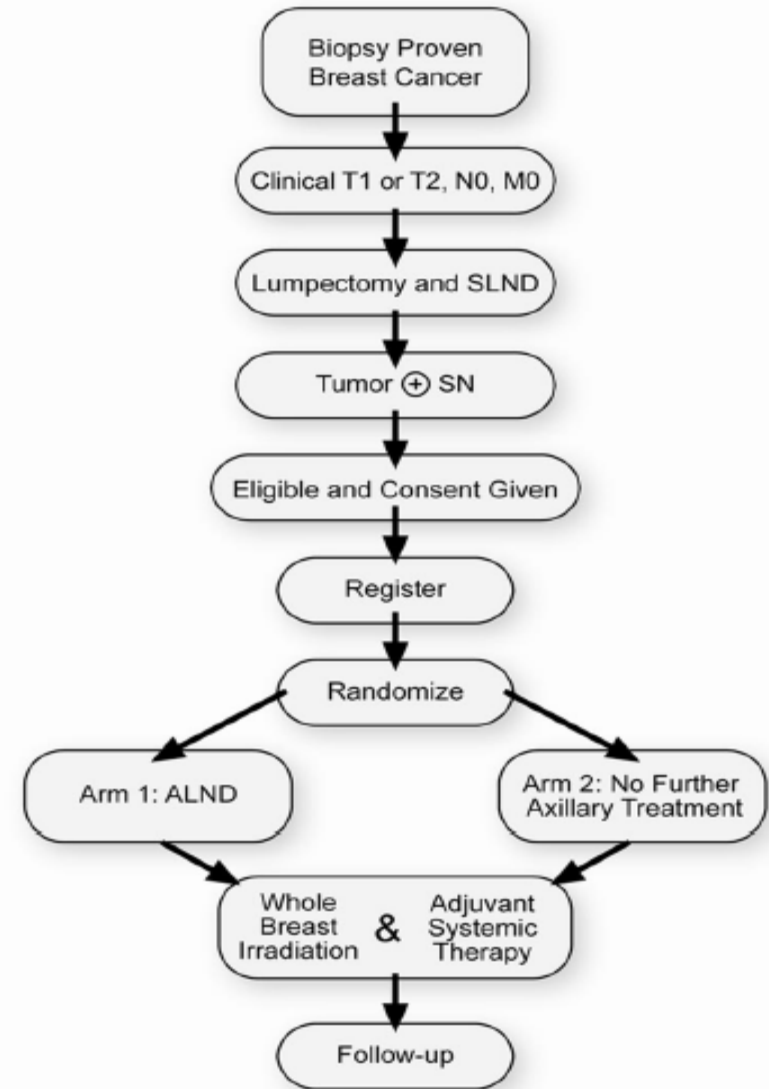
# Who Really Benefits from Comprehensive Nodal Coverage in 2015?

- PMRT trials were all or nothing
- Must consider more recent studies and try to understand what may initially appear to be conflicting results
  - ACOSOG Z0011 & IBSCG 23-01
    - The selected patients with limited node-positive disease on these trials had extremely low risks of regional nodal failure even with less aggressive surgery
  - MA20 & EORTC 22922
    - Yet patients with mostly N1 disease and even medial node-negative disease enrolled on these trials and treated with ALND appeared to benefit from regional nodal RT

# Randomized Trial of ALND vs. Observation for a Positive SLN

## ACOSOG Z0011

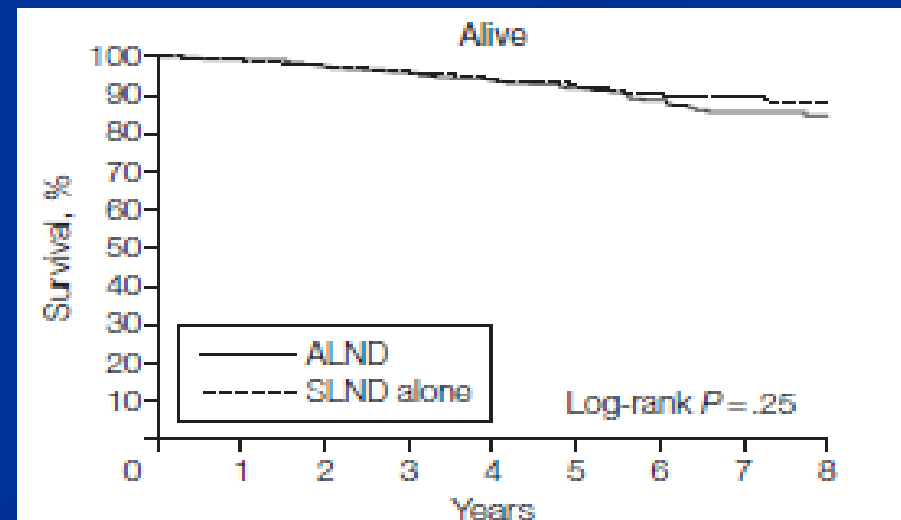
Z0011 Study Design Schema



# ACOSOG Z0011

- 891 pts (1900) 1999-2004
- 96% received systemic tx
- Median f/u 6.3 yr
- Lower AEs with SLN alone
- ALND not necessary in this pt population

|    | ALND | SLND |
|----|------|------|
| LR | 3.6% | 1.8% |
| AR | 0.5% | 0.9% |
| LE | 13%  | 2%   |



# IBCSG 23-01

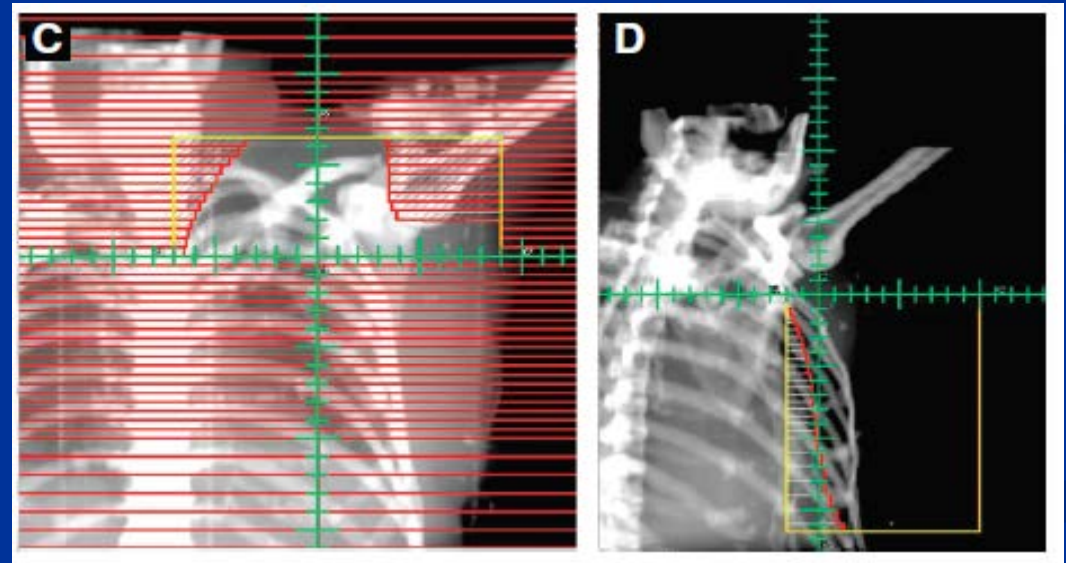
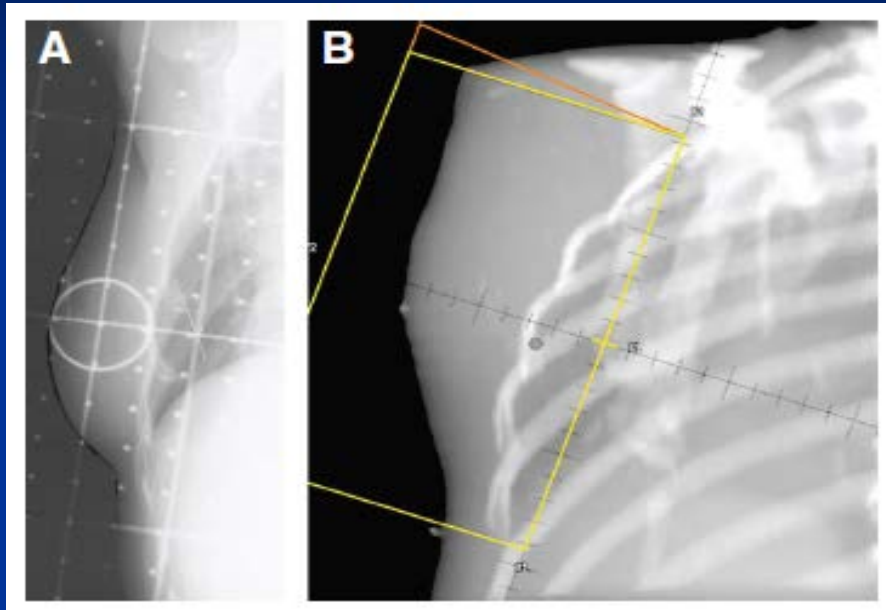
- 931 pts 2001-2010
- Very similar except
  - Only N1mi
  - L+RT 63%
    - MTX 9%
    - L+IORT 24%
- Median f/u 5 y
- Few AEs and LE overall with SLND
- ALND can be avoided in this pt population

|                                      | Axillary dissection (n=464) | No axillary dissection (n=467) |
|--------------------------------------|-----------------------------|--------------------------------|
| <b>Disease-free survival events*</b> |                             |                                |
| Total                                | 69 (15%)                    | 55 (12%)                       |
| <b>Breast cancer events</b>          |                             |                                |
| Local                                | 10 (2%)                     | 8 (2%)                         |
| Regional                             | 1 (<1%)                     | 5 (1%)                         |
| Distant                              | 34 (7%)                     | 25 (5%)                        |
| Contralateral breast                 | 3 (<1%)                     | 9 (2%)                         |
| <b>Non-breast cancer events</b>      |                             |                                |
| Second (non-breast) primary†         | 20 (4%)                     | 6 (1%)                         |
| Death without cancer event           | 1 (<1%)                     | 2 (<1%)                        |
| <b>Deaths</b>                        |                             |                                |
| Total                                | 19 (4%)                     | 17 (4%)                        |

# What Radiation Fields Are Appropriate?

- In Z0011, RT was supposed to be “tangential” to the whole breast:
  - No third-field nodal radiation was to have been administered
  - More specific dosing, frequency and field definition guidelines not described
  - QARC analysis of actual RT fields showed that substantial minority (15-19%) received third field RT
  - “High tangents” may have covered much of levels I and II (used in about half of patients, but NO difference by treatment arm)
- So, applying Z0011 does not necessarily mean that it is wrong to radiate nodal fields in select patients who meet Z0011 eligibility criteria

# Regional RT: Many Shades of Gray



# MA.20

- pN+ or T2N0 & G3 or ER- or LVI
- BCS + ALND + systemic tx
- RNI = IMNs, SCV, ICV  $\pm$  axilla
- 85% 1-3 + LN
- 91% chemo (86% A or 26% T), 76% endocrine tx

2000-2007

R  
A  
N  
D  
O  
M  
I  
Z  
E



Breast only

Breast + RNI

N=1,832

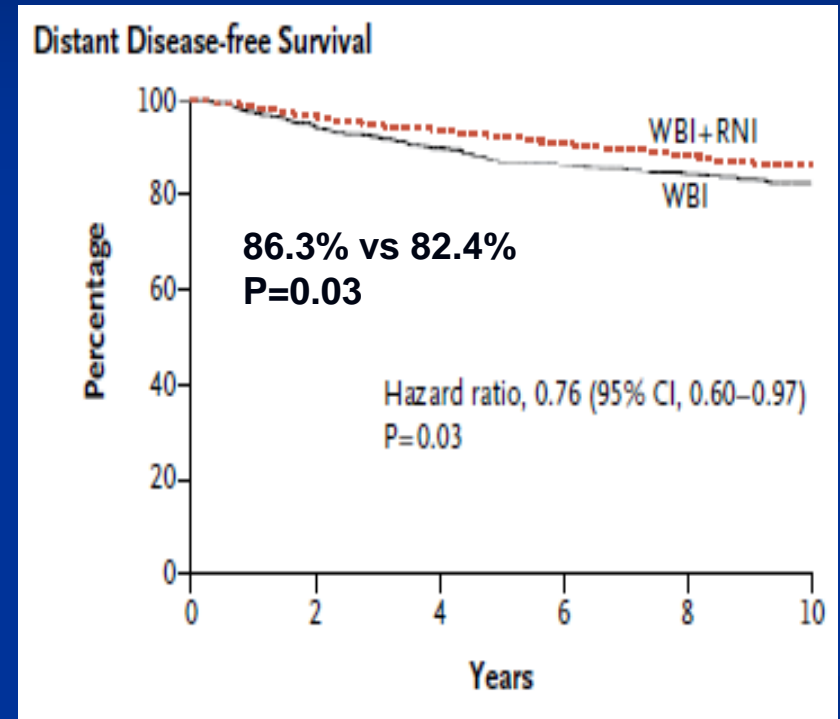
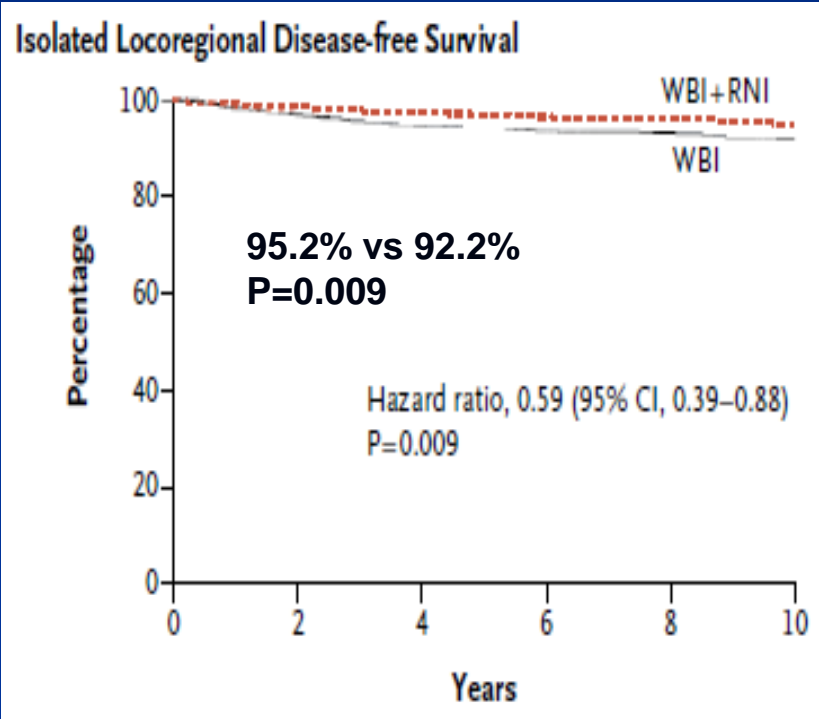


# MA.20: 5 y Follow Up

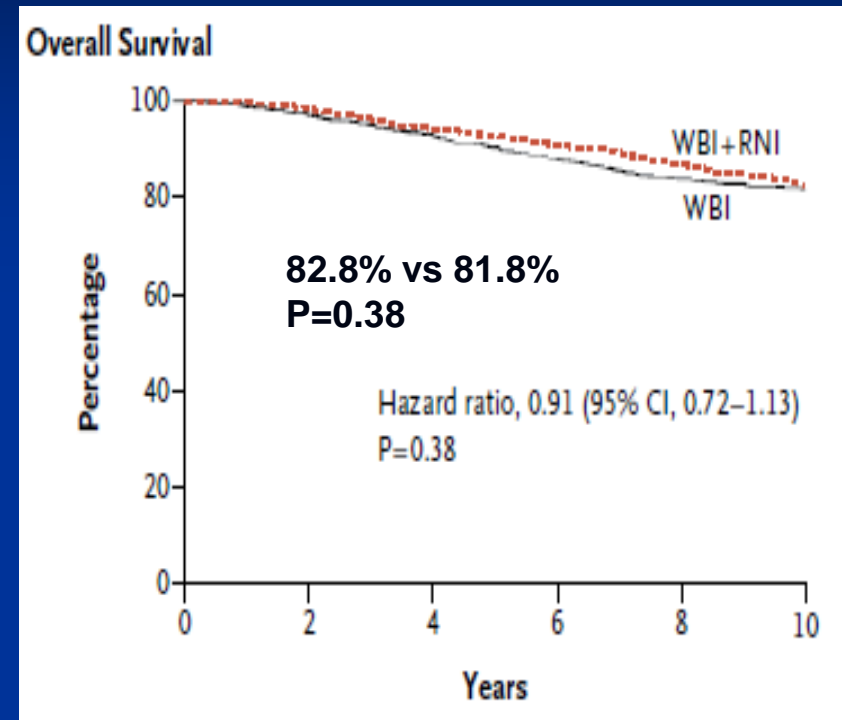
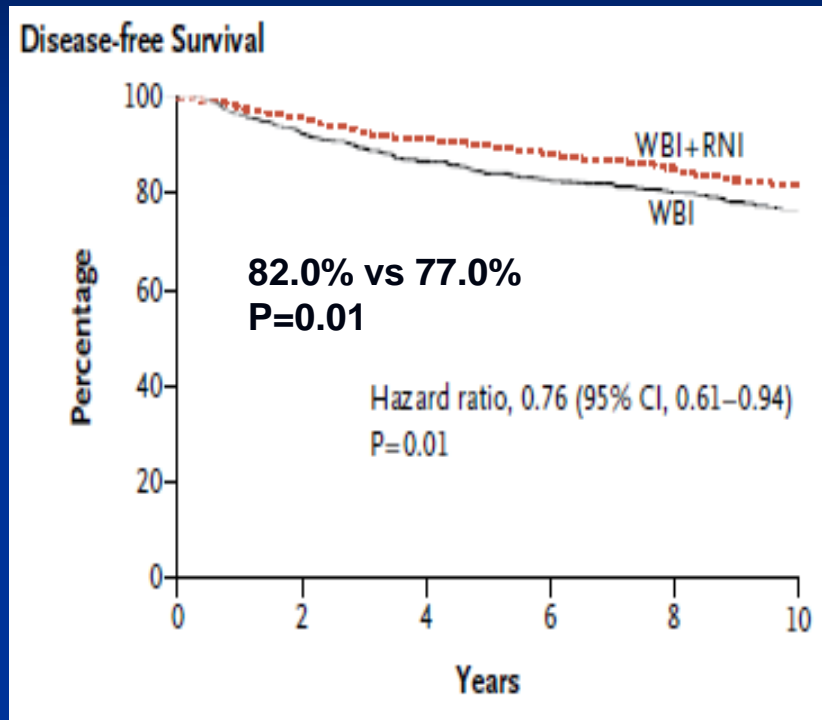
|                  | WBI   | WBI + RNI | p    |
|------------------|-------|-----------|------|
| Isolated LR DFS* | 94.5% | 96.8%     | .02  |
| Distant DFS      | 87.0% | 92.4%     | .002 |
| DFS              | 84.0% | 89.7%     | .003 |
| OS               | 90.7% | 92.3%     | .07  |

- LE 4.1% vs 7.3%, pneumonitis 0.2% vs 1.3%

# MA.20: 10 y F/U



# MA.20: 10 y F/U



- Prespecified subgroup analysis showed that pts with ER – had higher OS (81.3% vs 73.9% p=0.05)

# EORTC 22922: 10 y F/U

- BCS or MTX + ALND
- Medial/central N-/+ or lateral N+
- RNI = IMNs, SCV, ICV  $\pm$  axilla
- BCS 76%, MTX 24%
- pN0 44%, pN1 43%
- Chemo 25%, horm 30%, both 30%

1996-2004

R  
A  
N  
D  
O  
M  
I  
Z  
E

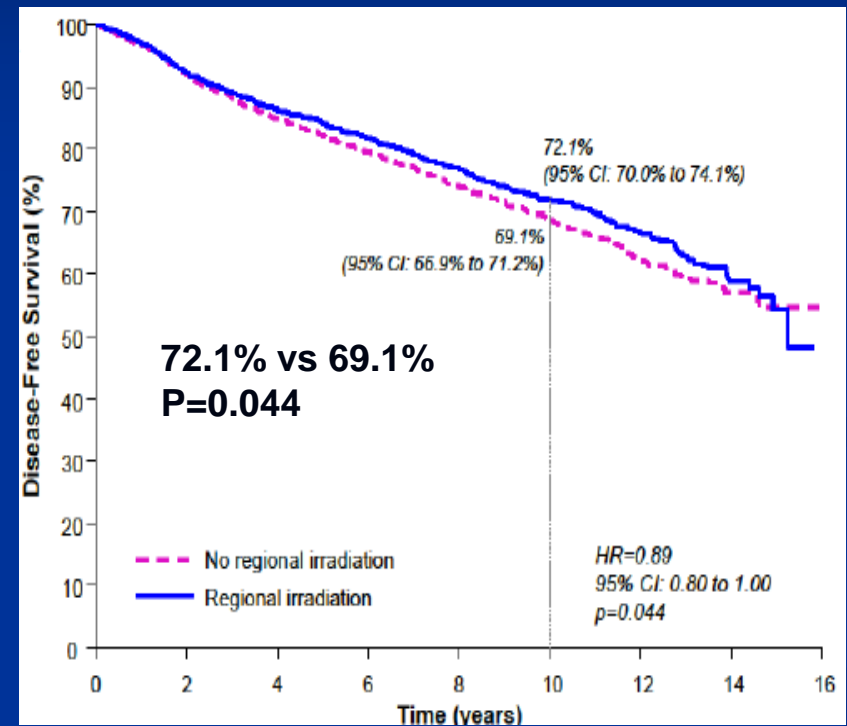
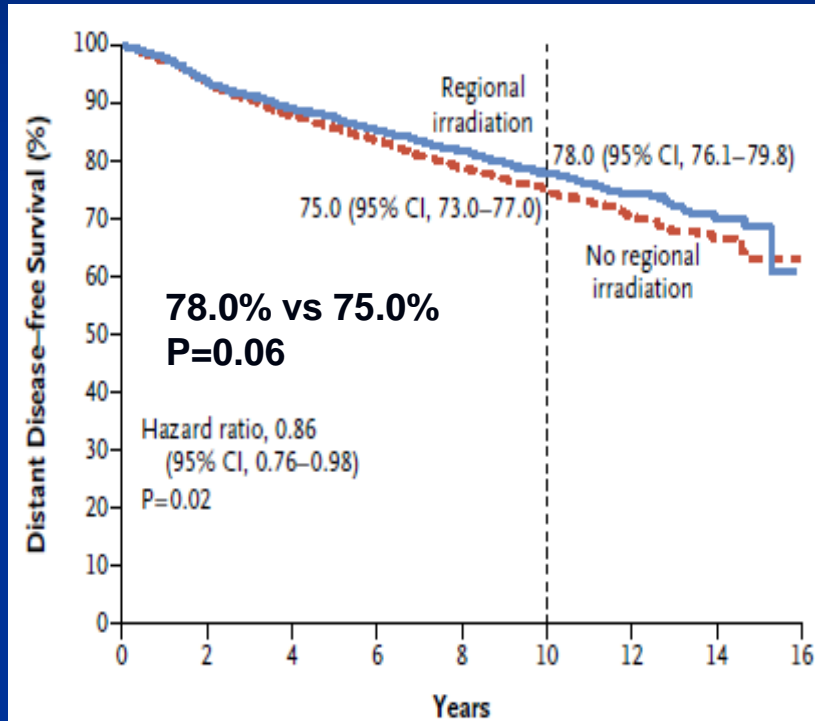


Breast or CW  
only

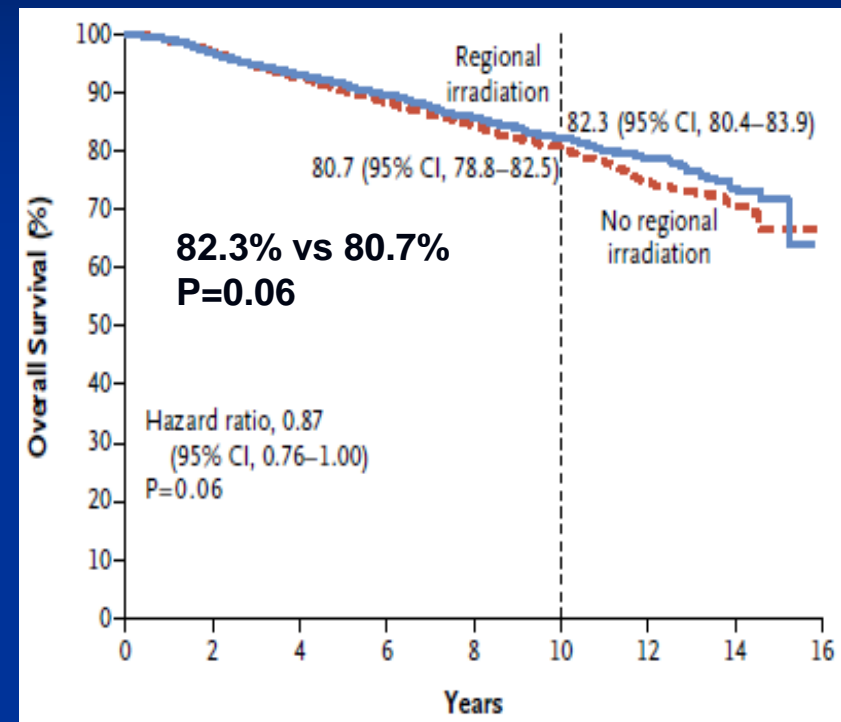
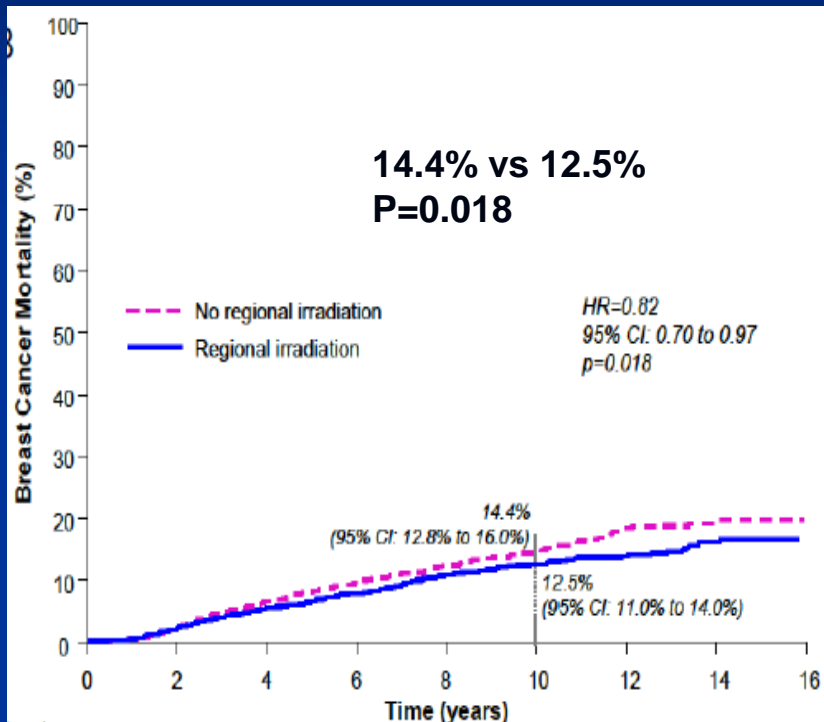
Breast or CW  
+ RNI

N=4,004

# EORTC 22922: 10 y F/U



# EORTC 22922: 10 y F/U



# Comparing the Studies

- Z0011 (1-2 nodes) & IBSCG (micromets only) included lower risk pts
  - Z0011 (all underwent SLNB, which likely identified smaller deposits of nodal disease)
    - T1 69%, ER+ 83%, N1mi 41%
  - IBSCG
    - T1 69%, ER+ 90%, N1mi 100%
- MA20 and EORTC generally appear to have included higher risk pts
  - MA 20 (only 39% underwent SLNB before ALND)
    - T1 52%, ER+ 75%
    - “at the time of our study, the size of nodal metastasis was not routinely measured, so it is difficult to generalize our findings to patients with micrometastases”
  - EORTC 22922:
    - T1 60%, hormonal rx 60%
    - “when our trial was designed, adjuvant systemic therapy was not as variable as it is today and molecular subtypes were not yet described; thus, we recorded little information about these variables”

# How similar were the patients?

|                        | <u>Z-11</u> |                       | <u>MA 20</u> |            |
|------------------------|-------------|-----------------------|--------------|------------|
|                        | ALND        | SLND                  | ALND         | ALND + RNI |
| Age (yrs)              | 56          | 54                    | 53           | 54         |
| T <sub>2+</sub> (%)    | 32          | 29.4                  | 45           | 50         |
| ER neg (%)             | 17          | 17                    | 26           | 25         |
| Grade 3                | 29          | 27.5                  | 42           | 43         |
| LN mets                |             |                       |              |            |
| 1-3+                   | 85          | 93 (majority 1 or 2+) | 85           | 85         |
| Size of LN involvement |             |                       |              |            |
| Micromets              | 35          | 45                    | ?            | ?          |
| Macromets              | 65          | 55                    | ?            | ?          |

MA 20 included patients with cl N + axilla; all Z-11 patients with clinically neg axilla.



# Toxicity of the regional nodal field: low but not zero

## ■ MA20

- Acute pneumonitis (1.2% vs 0.2%,  $p=0.01$ )
- Lymphedema (8.4% vs 4.5%,  $p=0.001$ )
- NS differences in brachial neuropathy, cardiac disease, or second cancers

## ■ EORTC 10-year results

- Pulmonary fibrosis (4.4% vs 1.7%,  $p<0.001$ )
- Cardiac fibrosis (1.2% vs 0.6%,  $p=0.06$ )
- Cardiac disease (6.5% vs 5.6%,  $p=0.25$ )
- Second cancers (191 vs 222,  $p=NS$ )
- Lymphedema (12.0% vs 10.5%,  $p=NS$ )

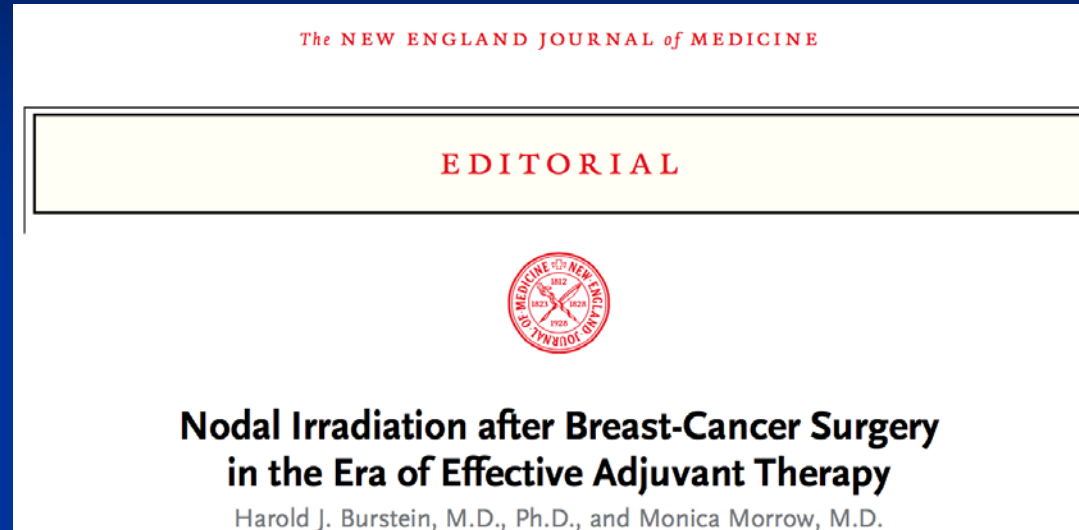
# What Do We Know?

- Z0011 and IBCSG 23-01: Low risk pts don't need surgery beyond SLNB
- MA.20 and EORTC 22922: There are some benefits from adding regional nodal RT in higher risk patients

# Estimating Risk to Guide Practice

- Consider risk factors
  - Number of nodes involved, number of nodes examined
  - Size of nodal metastasis
  - ECE
  - Young age
  - Large primary tumor size
  - Medial primary tumor location
  - LVI
  - high grade
  - triple negative subtype
  - high RS

# Words of Wisdom



“[T]he tumor subtype is now recognized as a primary determinant of local recurrence, a fact that when paired with other prognostic factors (including age and nodal stage) has enabled better risk stratification and opened the door to tailoring local-regional management strategies... Treatment selection for the individual patient is the key issue.”

# Summary: Regional Nodal RT

- Some patients with low-volume metastases to the axilla appear not to need ALND or comprehensive nodal RT in the setting of modern systemic therapy and lumpectomy with tangential breast RT
- Others with higher risk of harboring substantial residual nodal disease may benefit from comprehensive nodal RT
  - Must consider multiple other factors that affect this risk and recognize that overall risks in 2015 are much lower than they were in the past

# Summary: Regional Nodal RT

- In general, recommend regional RT for N2 disease & omit regional RT in N0 disease
- For N1 disease, consideration of tumor biology and other risk factors is critical to individualize care

# Conclusions

- Significant new evidence is emerging to help guide the management of patients with node positive disease
- Care must be individualized
  - Recognizing the importance of tumor biology is essential
  - Patients themselves should be informed and involved in making decisions together with their providers