PMRT

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PGY-2
10/24/12

Staging—Primary Tumor (T)

T1: Tumor 2cm or less in greatest dimension

- **T1mi**: Tumor < 0.1cm in greatest dimension
- **T1a:** Tumor more than 0.1cm but less than 0.5cm
- **T1b:** Tumor more than 0.5cm but not more than 1cm
- **T1c:** Tumor more than 1 cm but not more than 2cm

T2: Tumor more than 2-5cm in greatest dimension

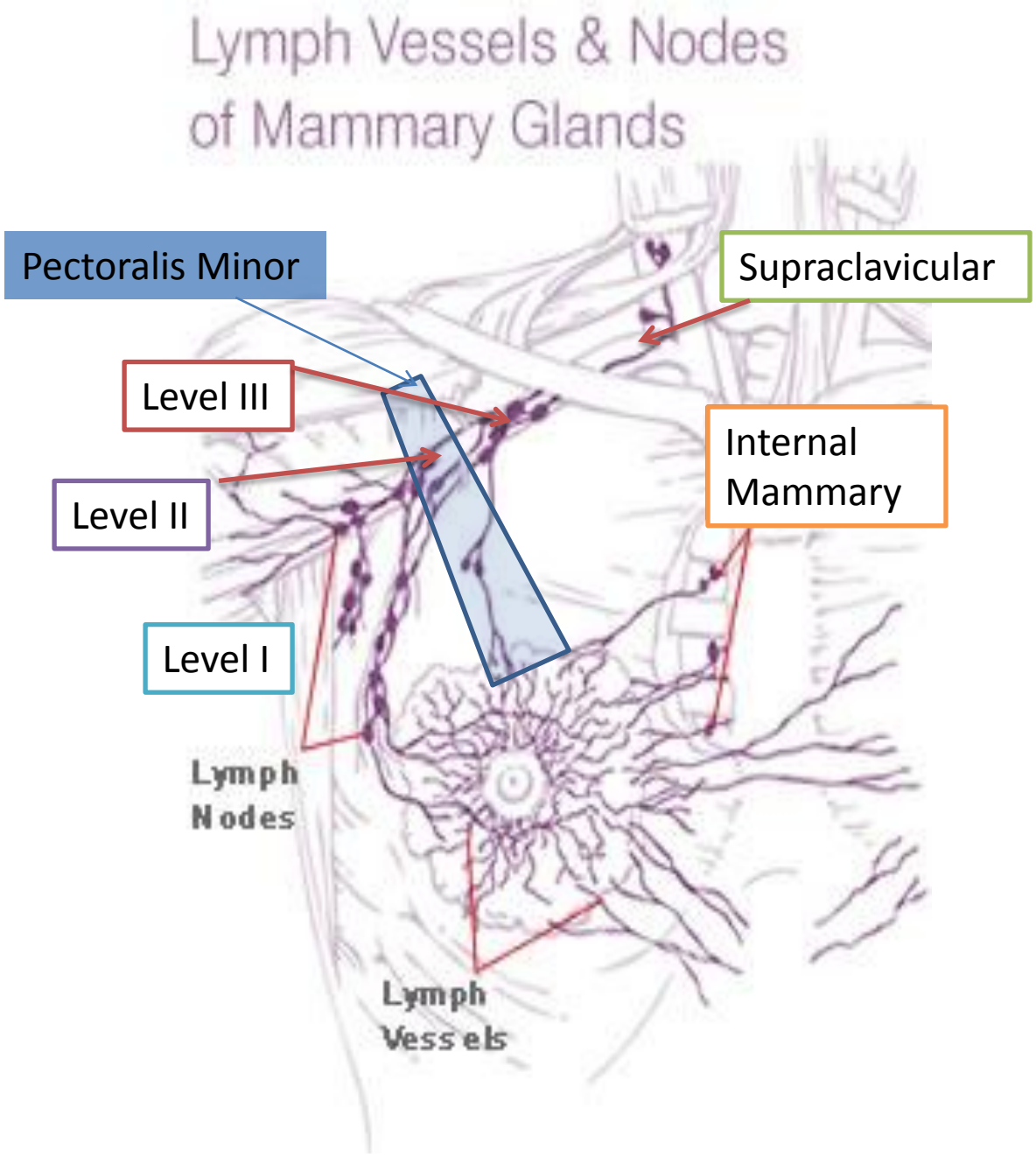
T3: Tumor >5cm in greatest dimension

T4: any size w/ direct extension to (a) chest wall or (b) skin

- **T4a**: Extension to chest wall, not including pectoralis muscle
- **T4b:** Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules not confined to the same breast
- **T4c:** Both T4a and T4b
- **T4d:** Inflammatory carcinoma

Regional Lymph Nodes (N)

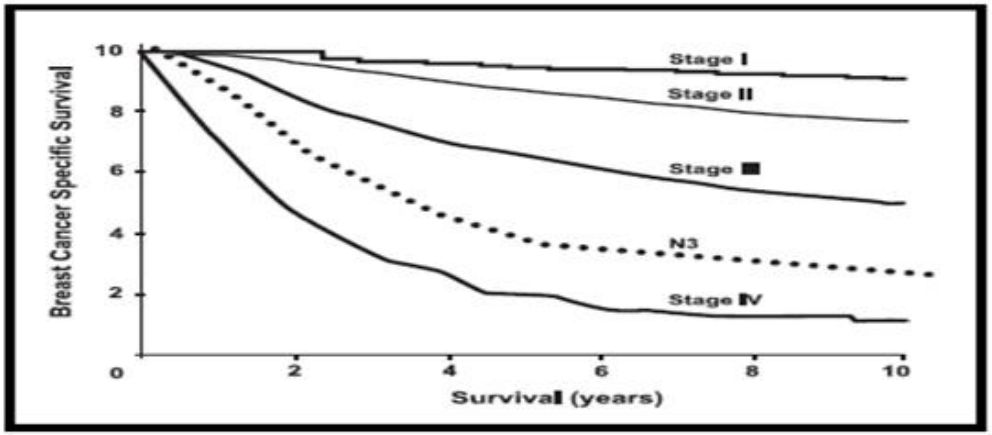
- N1 Mets to movable ipsilateral LNs
- N2
  - N2a: mets to ipsilateral axillary LNs fixed to one another (matted) or to other structures
  - N2b: Mets only in *clinically apparent* ipsilateral internal mammary nodes in the **absence** of clinically evident axillary LN mets
- N3
  - N3a: Mets in ipsilateral infraclavicular LNs
  - N3b: Mets in ipsilateral internal mammary LNs and axillary LNs
  - N3c: Mets in ipsilateral supraclavicular LNs


Lymph Vessels & Nodes of Mammary Glands
Pectoralis Minor
Supraclavicular
Level III
Internal Mammary
Level II
Level I
Lymph Nodes
Lymph Vessels

Stage Grouping

Stage IA:	**T1N0M0**
Stage IB:	**T0-1N1 (micromets)**
Stage IIA:	**T0-1N1M0**
	T2N0M0
Stage IIB:	**T2N1M0**
	T3N0M0
Stage IIIA:	**T0-3N2, T3N1M0**
Stage IIIB:	**T4N0-2**
Stage IIIC:	**TxN3M0**
Stage IV:	**TxNxM1**

	T1	T2	T3	T4
N0	* I	IIA	IIB	IIIB
N1	IIA	IIB	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIB
N3	IIIC	IIIC	IIIC	IIIC
M1	IV	IV	IV	IV



Ten-year overall survival rates in patients with breast cancer: stage IIA, 80%; IIB, 70%; IIIA, 60%; IIIB, 50%.

Mastectomy

- Simple mastectomy (or "total mastectomy"):
  - entire breast tissue is removed, but axillary contents are undisturbed with sentinel node bx
- Modified radical mastectomy:
  - The entire breast tissue + ALND
- Radical mastectomy (or "Halsted mastectomy")
  - Removing the entire breast, the axillary lymph nodes, and the pectoralis major and minor muscles behind the breast. Reserved for muscle invasion

Danish trial 82b (1982-89)

Randomized. 1708 pts.

Premenopausal high-risk pts, who had one or more of:

positive axillary LN, tumor > 5 cm, invasion of skin or pectoral fascia.

- Randomized after surgery to: RT + CMF chemotherapy, CMF alone, or CMF + tamoxifen. (enrollment in the third group was stopped after 1986 due to higher mortality).

- Surgery consisted of total mastectomy + axillary node dissection (level I and part of level II). Median # of LN removed was 7. RT was to chest wall, SCLV fossa, infraclavicular LN, and IMN in first 4 intercostal spaces. 50 Gy in 25 fx (or 48 Gy in 22 fx, 4days/wk). Recommended use of anterior electron field to treat CW and IMN.

- Chemo: 8 cycles of CMF with RT, or 9 cycles if given alone. RT was sandwiched between first 2 cycles of chemo.

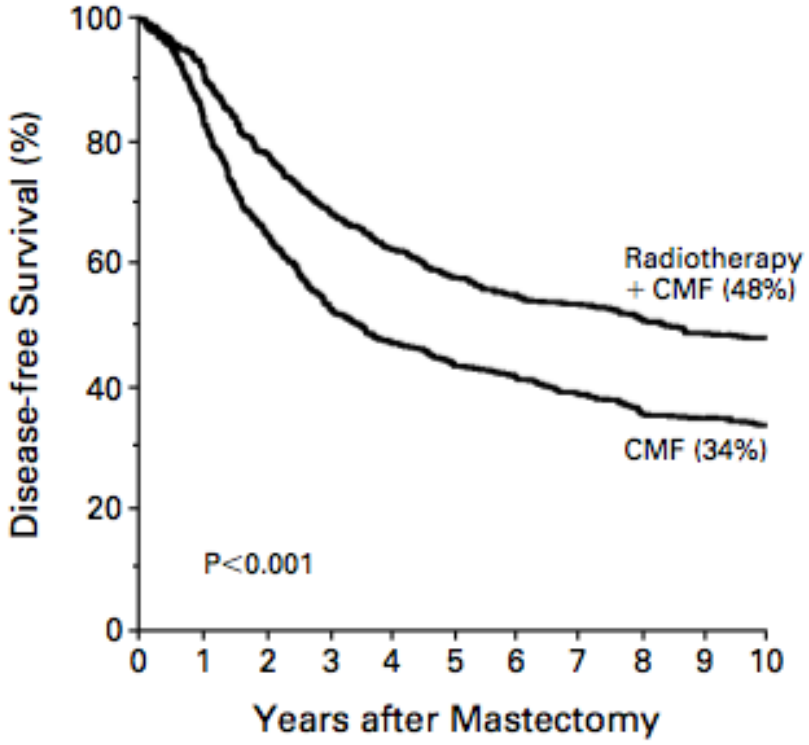
Overgaard M et al. N Engl J Med. 1997 Oct 2;337(14):949-55.

Danish trial 82b (1982-89)

- Median f/u: 114 months. LRR 9% (RT+CMF) vs 32% (CMF). 10-yr DFS 48% vs 34%. 10-yr OS 54% vs 45%.
- RT improved DFS and OS irrespective of tumor size, number of positive LN, or grade, in these high risk pts. More than 50% of local recurrence were on the chest wall.
- **Conclusion: improved survival with post-op RT**
- number of positive LN is difficult to determine from this study because few nodes were removed (median: 7) and many pts had fewer than 4 nodes sampled.

Overgaard M et al. N Engl J Med. 1997 Oct 2;337(14):949-55.

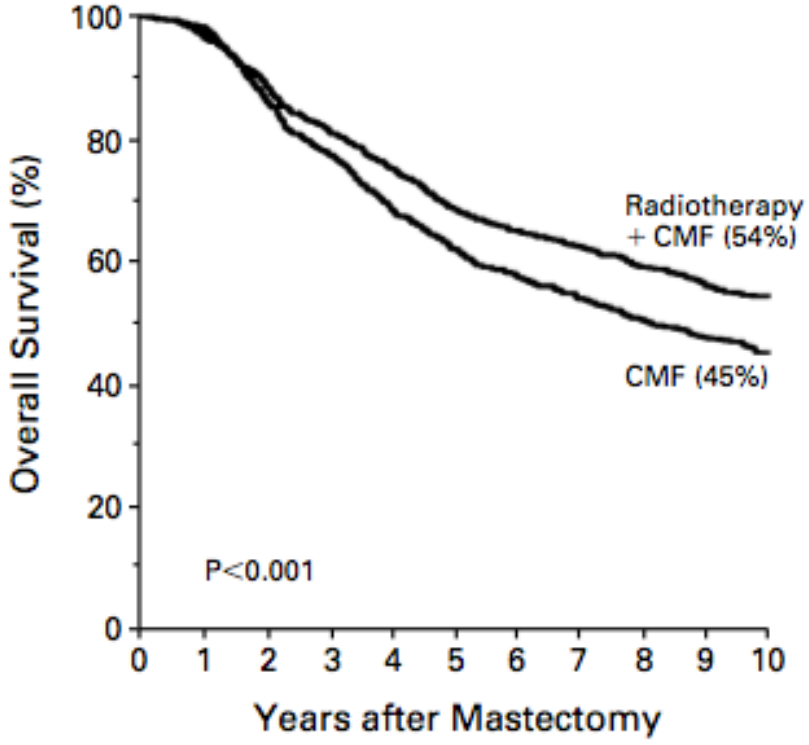
Danish trial 82b (1982-89)



Radiotherapy + CMF	852	643	505	429	308	102
CMF	856	537	382	327	216	74

Figure 1. Kaplan–Meier Estimates of Disease-free Survival among Women Treated with Radiotherapy plus CMF and CMF Alone.

Values in parentheses are disease-free survival at 10 years.



Radiotherapy + CMF	852	755	641	555	392	188
CMF	856	738	587	494	329	163

Figure 2. Kaplan–Meier Estimates of Overall Survival among Women Treated with Radiotherapy plus CMF and CMF Alone.

Values in parentheses are overall survival at 10 years.

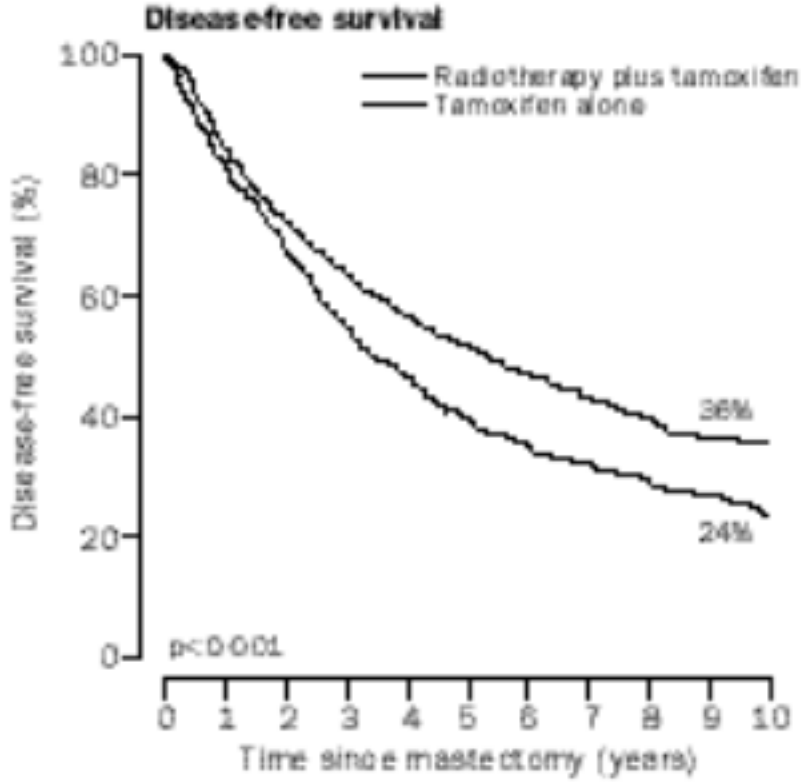
Overgaard M et al. N Engl J Med. 1997 Oct 2;337(14):949-55.

Danish trial 82c (1982-90)

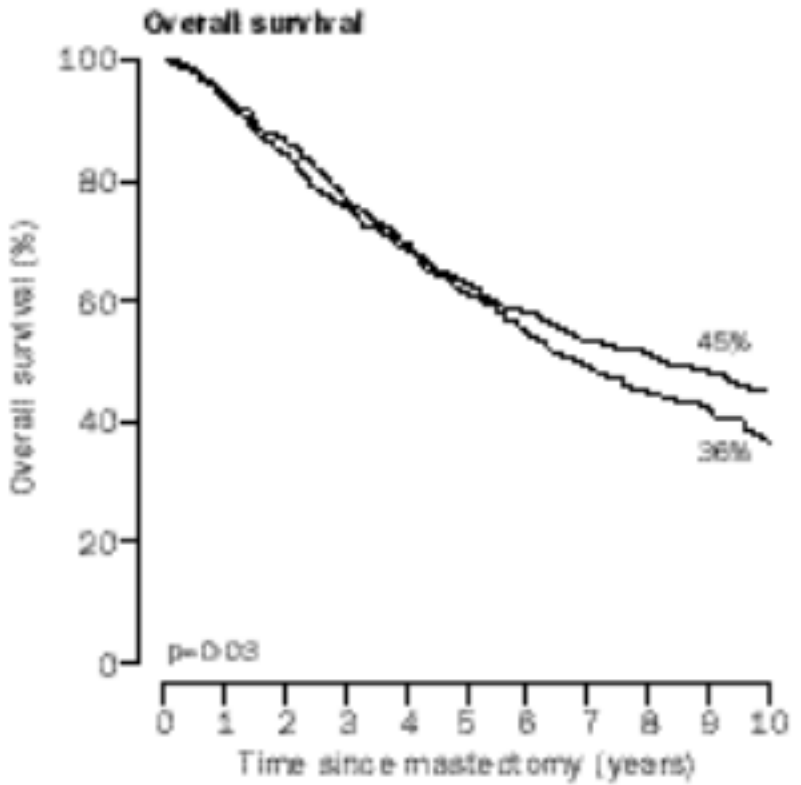
- 1375 pts. Stage II or III
- Postmenopausal high-risk pts. Randomized to post-mastectomy: tamoxifen (for 1 yr), or to tam + RT.
- Median f/u 123 months. LRR 8% (RT) vs 35% (No RT). DFS 36% vs 24%. 10-yr OS 45% vs 36%.
- The endpoints were first site of recurrence (locoregional recurrence, distant metastases, or both), and disease-free and overall survival.
- Conclusion: Improved survival with post-op RT

Overgaard M et al. Lancet. 1999 May 15;353(9165):1641-8.

Danish trial 82c (1982-90)



Patients at risk						
Radiotherapy plus tamoxifen	686	486	373	296	194	62
Tamoxifen only	689	465	307	226	150	39



Patients at risk						
Radiotherapy plus tamoxifen	686	580	469	398	285	175
Tamoxifen only	689	566	479	378	251	136

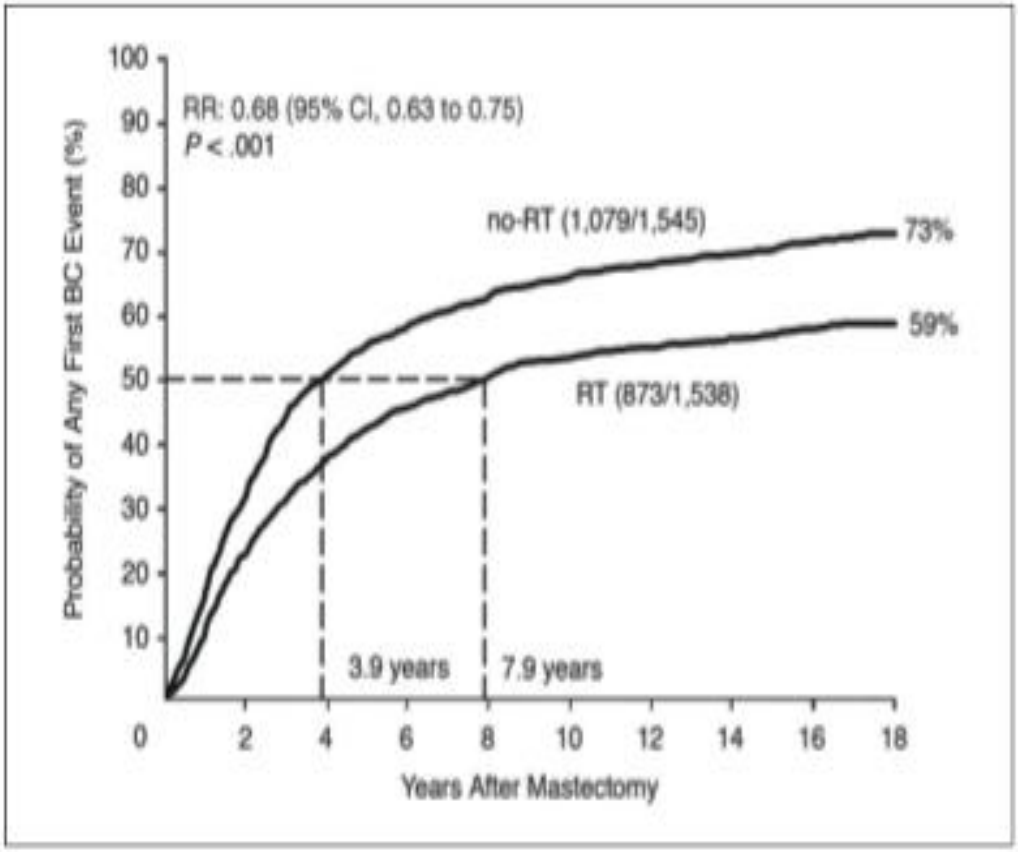
Figure 2: **Effect of radiotherapy on disease-free survival and overall survival**

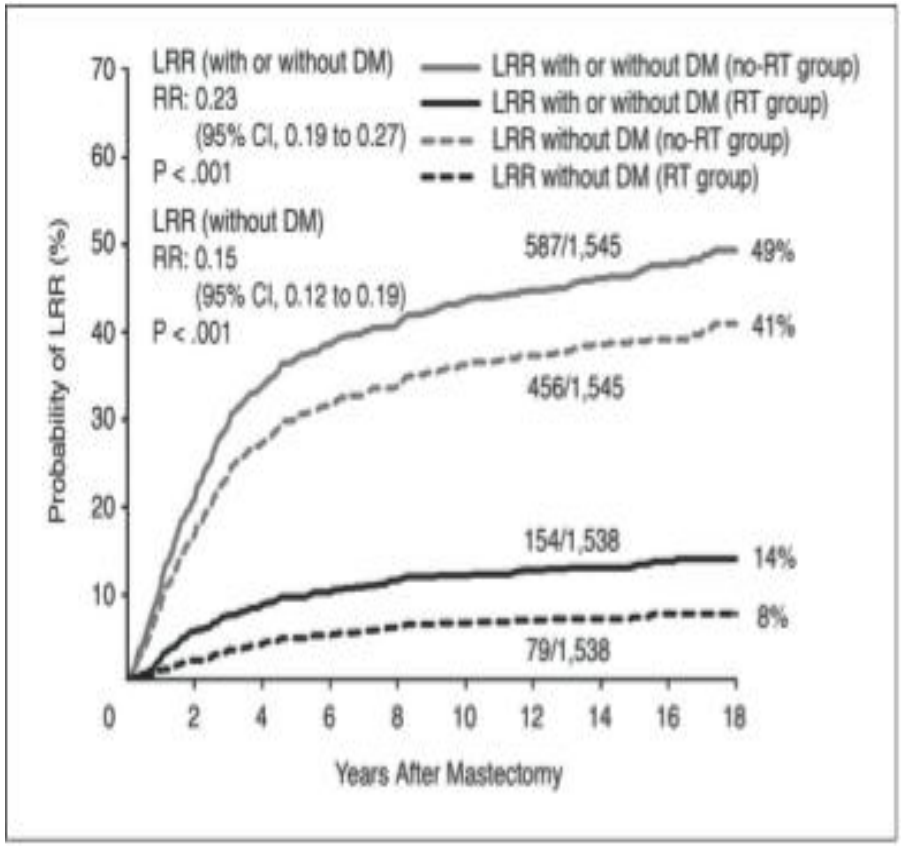
Overgaard M et al. Lancet. 1999 May 15;353(9165):1641-8.

Long-Term Results: 82b and c

- Combined 82b and c: 18 year follow up
- probability of any first breast cancer event was 73%(no RT) and 59%(RT) (P < .001) (relative risk [RR], 0.68; 95% CI, 0.63 to 0.75).
- **LRR** 49% vs 14%(RT). **LRR for 1-3 +LN**: 27% vs. 4% (RT) **4+ LN**: 51% vs. 10%(RT) All SS.
- **DM** 64% vs 53%(RT). (P < .001) 73% chance of DM after developing LRR; does not depend on initial treatment.

Nielsen HM et al J Clin Oncol. 2006 May 20;24(15):2268-75.





- **Conclusion**: PMRT changes the disease recurrence pattern in high-risk breast cancer patients; fewer patients have LRR as first site of recurrence, and overall fewer patients have DM.

Nielsen HM et al J Clin Oncol. 2006 May 20;24(15):2268-75.

Long-Term Results: 82b and c

Overall Survival

- **1-3 LN**: 57%(RT) vs 48%; **4+ LN** 27%(RT) vs 12%. All SS.
- No OS benefit for patients that were ER/PR- or HER2+.

Nielsen HM et al J Clin Oncol. 2006 May 20;24(15):2268-75.

British Columbia Trial

- CMF 6-12 mo +/- RT
- 318pts With LN+, premenopausal high risk +ALN s/p mastectomy.
- Modified radical mastectomy with median 11 LN removed.
- 20 yr fu

Ragaz J et al. J Natl Cancer Inst. 2005 Jan 19;97(2):116-26

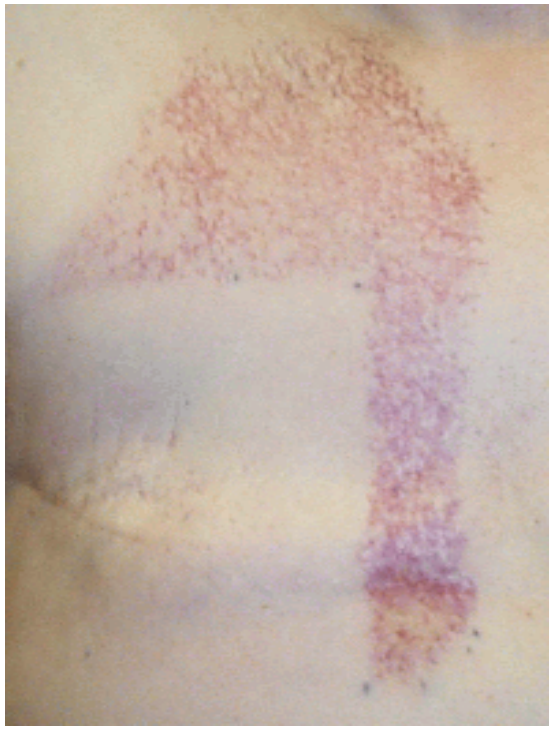
British Columbia Trial

- Radiation:
- 5 field, 37.5Gy/16f Co-60. CW with tangents, supraclavicular/axillary + PAB in 35 Gy/16, bilateral IM 37.5/16 with en face photon field. RT given between cycle 4 and 5.

Ragaz J et al. J Natl Cancer Inst. 2005 Jan 19;97(2):116-26

Treatment of the internal mammary nodes

- Classically done with an en face electron or photon field.
- This field arrangement gave dose not only to the left ventricle but also the coronary arteries.
- Field often treated the supraclavicular fossa in continuity: the "hockey stick".



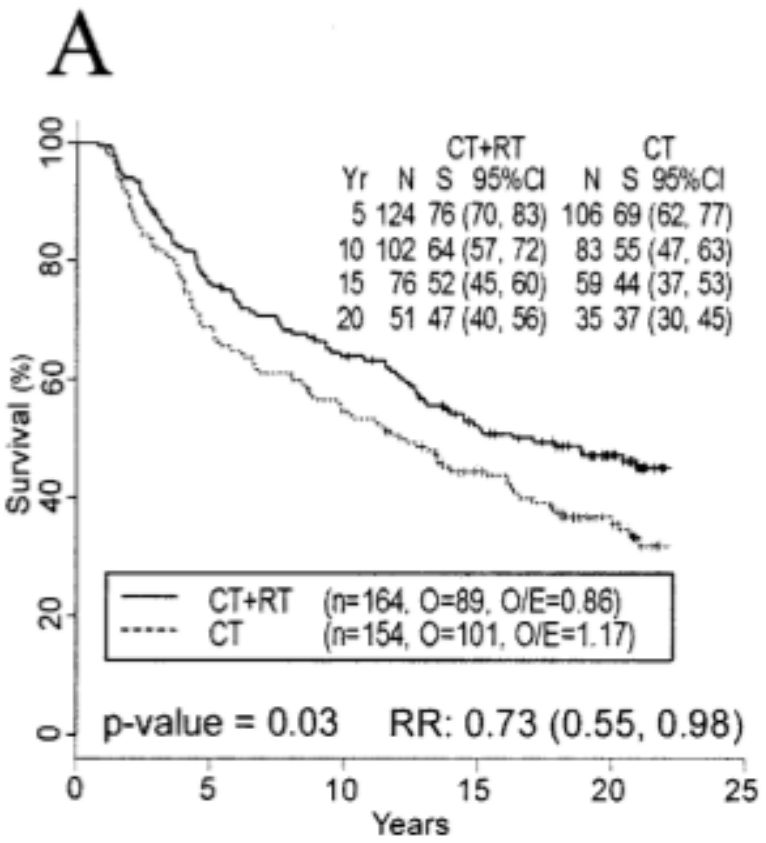
British Columbia Trial

- LRR: 26% vs 10%(RT)
- **OS: 37% vs 47%(RT) SS**
- *S*imilar results for 1-3 LN and >4 LN
- Arm edema in 3.2% vs 9.1%(RT).

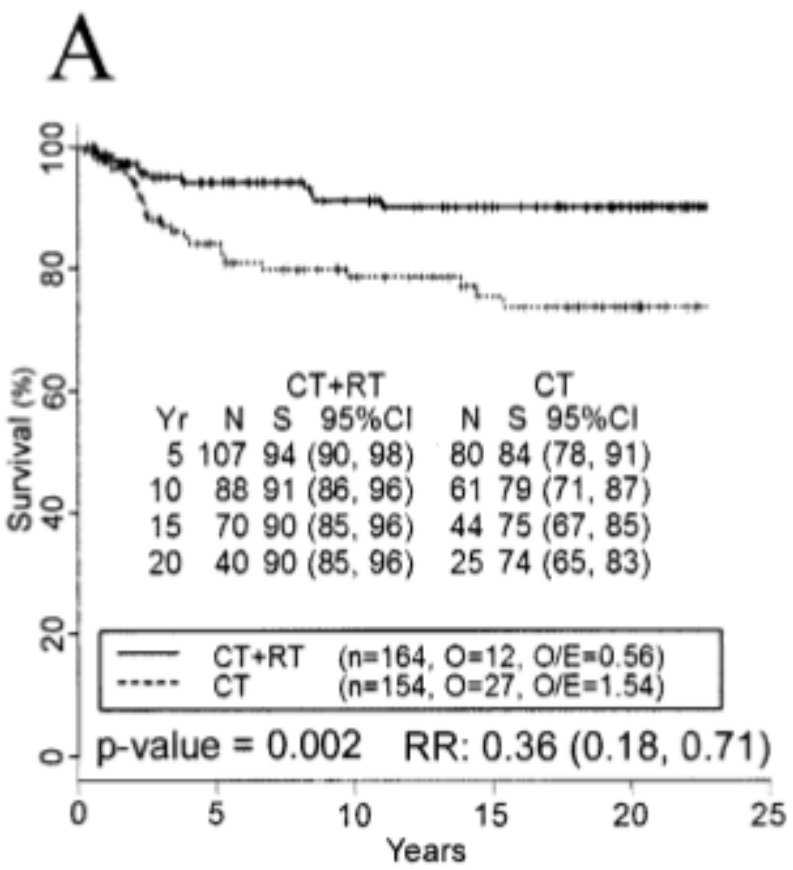
Ragaz J et al. J Natl Cancer Inst. 2005 Jan 19;97(2):116-26

British Columbia Trial

Overall Survival



Recurrence free survival



British Columbia Trial

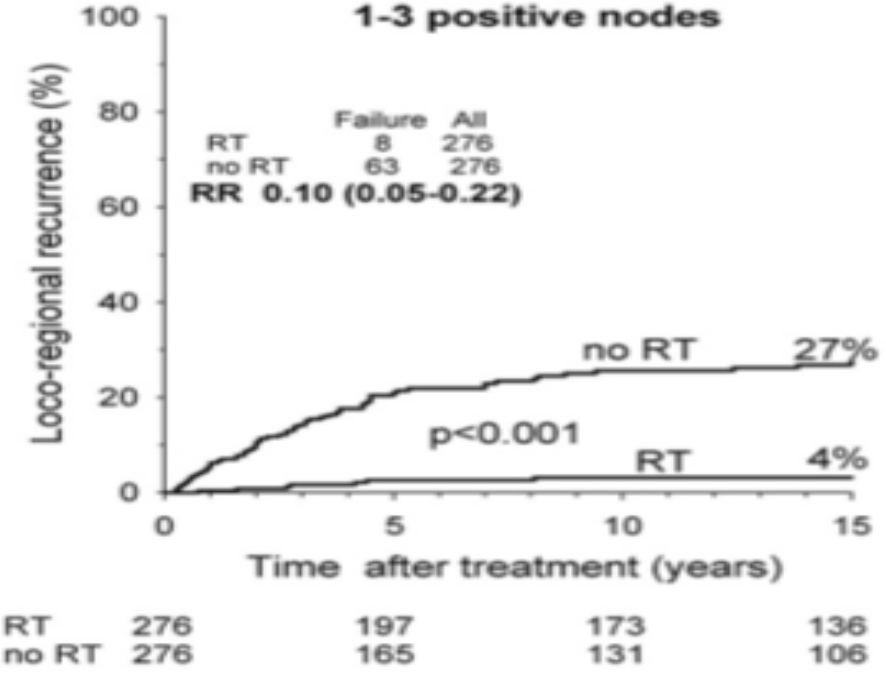
Outcome	Chemotherapy-alone arm		Chemotherapy and radiation therapy arm		RR (95% CI)	P†
	Survival, %‡	No. of events/ No. of patients	Survival, %‡	No. of events/ No. of patients		
			All 318 patients			
Event-free survival	25	116/154	35	105/164	0.70 (0.54 to 0.92)	.009
Breast cancer–free survival	30	107/154	48	84/164	0.63 (0.47 to 0.83)	.001
Survival free of isolated locoregional disease	74	27/154	90	12/164	0.36 (0.18 to 0.71)	.002
Systemic breast cancer–free survival	31	104/154	48	84/164	0.66 (0.49 to 0.88)	.004
Breast cancer–specific survival	38	95/154	53	75/164	0.67 (0.49 to 0.90)	.008
Overall survival	37	101/154	47	89/164	0.73 (0.55 to 0.98)	.03

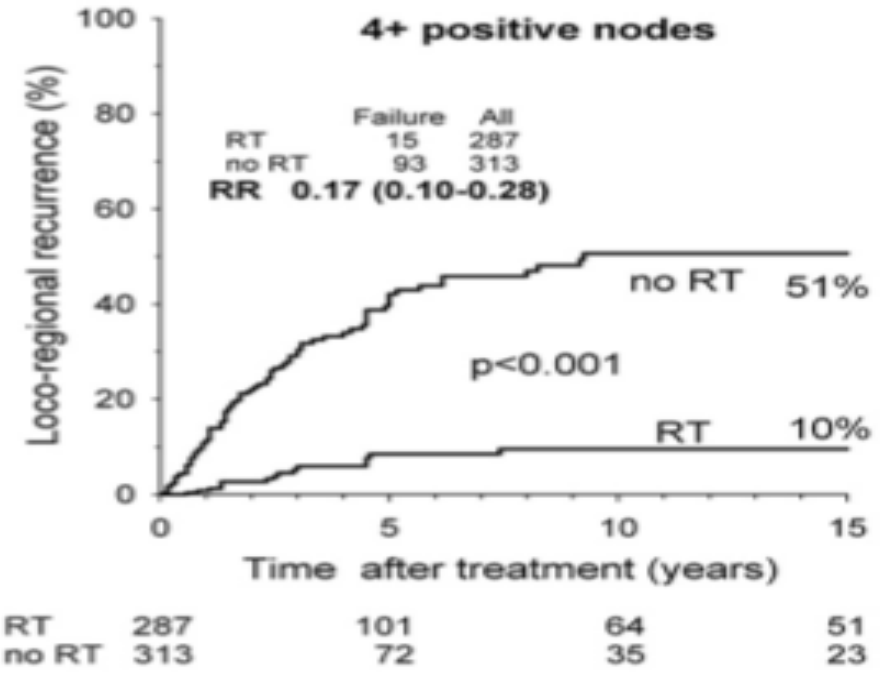
Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended by international consensus reports?

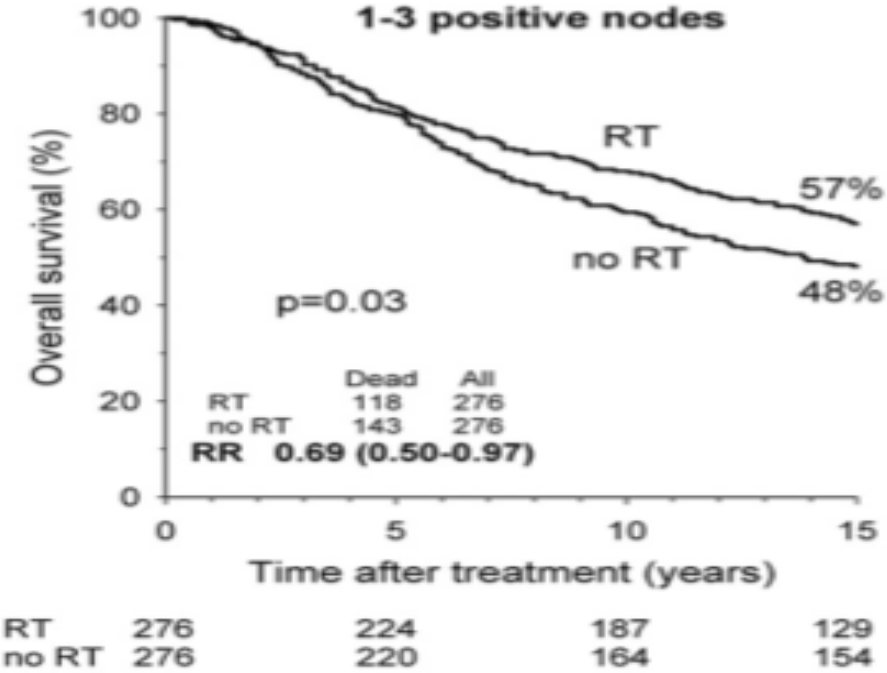
A subgroup analysis of the DBCG 82 b & c randomized trials.

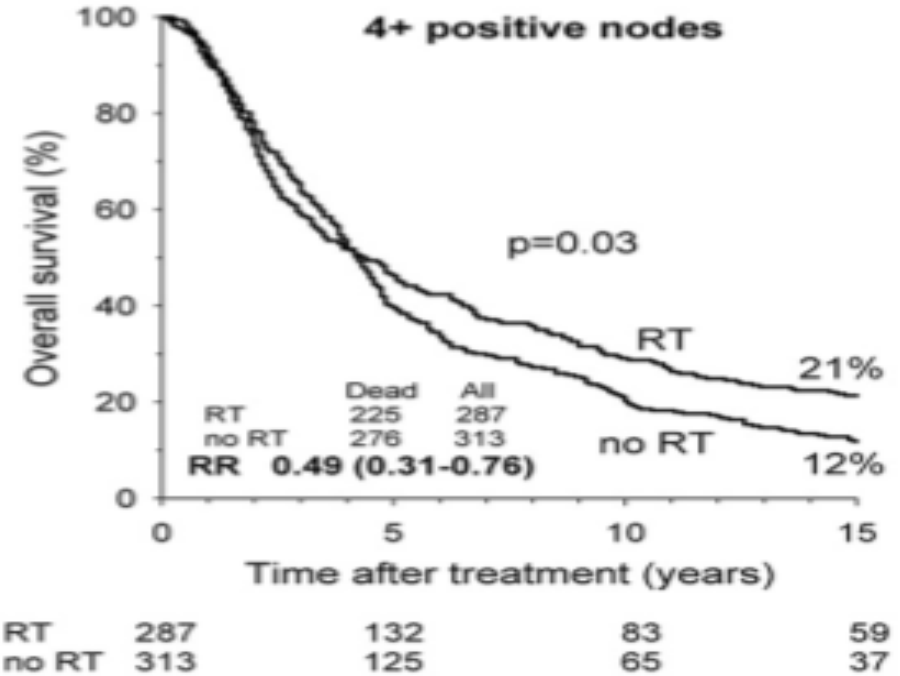
- Analysis of pts with 8 or more nodes
- 1152 patients

Overgaard M et al. Radiother Oncol 82:247-253, 2007


1-3 positive nodes
Loco-regional recurrence (%)
Failure All
RT 8 276
no RT 63 276
RR 0.10 (0.05-0.22)
no RT 27%
p<0.001
RT 4%
Time after treatment (years)
RT 276 197 173 136
no RT 276 165 131 106


4+ positive nodes
Loco-regional recurrence (%)
Failure All
RT 15 287
no RT 93 313
RR 0.17 (0.10-0.28)
no RT 51%
p<0.001
RT 10%
Time after treatment (years)
RT 287 101 64 51
no RT 313 72 35 23


1-3 positive nodes
Overall survival (%)
RT
57%
no RT
48%
p=0.03
Dead All
RT 118 276
no RT 143 276
RR 0.69 (0.50-0.97)
Time after treatment (years)
RT 276 224 187 129
no RT 276 220 164 154


4+ positive nodes
Overall survival (%)
p=0.03
RT
21%
no RT
12%
Dead All
RT 225 287
no RT 276 313
RR 0.49 (0.31-0.76)
Time after treatment (years)
RT 287 132 83 59
no RT 313 125 65 37

DBCG 82 b & c randomized trials

Subanalysis of pts with ≥ 8 LN's

Table 2
The Bottom line estimate

Parameter	1–3 pos. nodes	4+ pos. nodes
Endpoint: loco-regional recurrence		
Relative risk reduction	87%	82%
Absolute risk reduction	20%	24%
Number of patients needed to treat to avoid an LRR	5	4
Endpoint: death		
Relative risk reduction	17%	11%
Absolute risk reduction	9%	10%
Number of patients needed to treat to avoid a death	11	10

Relative and absolute risk reduction and number of patients needed to treat to achieve benefit of postmastectomy radiotherapy as a function of number of positive lymph nodes. Estimates are calculated for the benefit of avoiding an isolated first loco-regional recurrence or death.

Overgaard M et al. Radiother Oncol 82:247-253, 2007

DBCG 82 b & c randomized trials

Subanalysis of pts with ≥ 8 LN's

Conclusion:

- The survival benefit after postmastectomy RT was substantial and similar in patients with 1–3 and 4+ positive lymph nodes.
- The indication for RT seems therefore to be at least equally beneficial in patients with 1–3 positive nodes

Overgaard M et al. Radiother Oncol 82:247-253, 2007

Neoadjuvant chemo

MDACC – Retrospective review 1977-2000

- 542 patients treated on six consecutive institutional prospective trials with neoadjuvant chemotherapy, mastectomy, and PMRT
- compared to 134 patients who received similar treatment in these same trials but without radiation
- Median follow up – 10 yr
- RT - CW+LN's 50 Gy + 10 Gy CW boost.

Huang EH et al. J Clin Oncol. 2004 Dec 1;22(23):4691-9

Neoadjuvant chemo

Table 1. Neoadjuvant Chemotherapy Regimens

Protocol	Years of the Study	Neoadjuvant Chemotherapy Regimen	No. of Cycles	No. of Patients		
				CT + M	CT + M + RT	Total Study Population*
Advanced Primary	1974-1985	FAC	3	33	91	191
85-01	1985-1989	VACP	3	19	141	200
89-007	1989-1991	FAC	4	11	104	203
91-015	1991-1994	FAC or dose-escalated FAC	4	11	101	202
94-002	1994-1998	FAC or paclitaxel	4	60	41	174
97-099	1998-2000	AT	6	0	64	88
Total	1974-2000			134	542	1,058

Abbreviations: FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; VACP, vincristine, doxorubicin, cyclophosphamide, and prednisone; AT, doxorubicin, docetaxel; CT, chemotherapy; M, mastectomy; RT, radiation.

*The total study population includes other patients who were not analyzed in this report, such as those receiving breast-conserving surgery with or without radiation.

Huang EH et al. J Clin Oncol. 2004 Dec 1;22(23):4691-9

Neoadjuvant chemo

Outcomes:

- LRR 11%(RT) vs. 22% (SS)
- Clinical stage LRR:
  - I-IIA no benefit for PMRT.
  - Stage IIB+ 11%(RT) vs. 26% (SS)
  - cT3-T4 8%(RT) vs. 22% (SS)
  - cN2-3 12%(RT) vs. 40%.
- Pathologic stage LRR:
  - ypT2+ 14%(RT) vs. 59% (SS)
  - Stage II with 1-3 LN+ no benefit for PMRT (but few pts)
  - pN0 4%(RT) vs. 11% (SS)
  - $\geq$ 4 LN+ 16%(RT) vs. 59% (SS)

Survival benefit:

- CSS
  - cStage IIIB+ 22%(RT) vs. 44% (SS)
  - cT4 24%(RT) vs. 45% (SS)
  - cN2-3 27%(RT) vs. 49% (SS)
  - $\geq$ 4 LN+ 18%(RT) vs. 44%
  - *No inflammatory breast ca included

Neoadjuvant chemo

Predictors for LRR:

- no PMRT, >20% LN+, no tamoxifen, cStage IIIB+, no response to neoadjuvant chemo

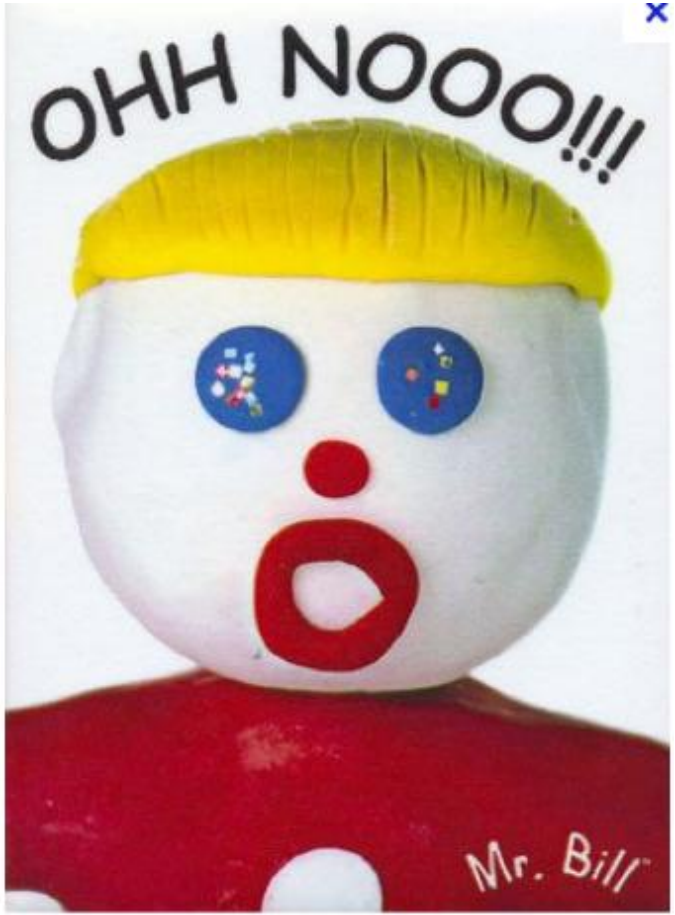
Neoadjuvant chemo

Conclusion:

- PMRT should be considered for clinical T3, clinical Stage III-IV and patients with ≥ 4 LN+ at surgery, regardless of response to chemotherapy

T3N0

Ohh no! What do you do??



LOW LOCAL RECURRENCE RATE WITHOUT POSTMASTECTOMY RADIATION IN NODE-NEGATIVE BREAST CANCER PATIENTS WITH TUMORS 5 cm AND LARGER

SCOTT R. FLOYD, M.D., PH.D.,*§ THOMAS A. BUCHHOLZ, M.D.,† BRUCE G. HAFFTY, M.D.,‡
SAVELI GOLDBERG, PH.D.,* ANDRZEJ NIEMIERKO, PH.D.,* RITA ABI RAAD, M.D.,*
MARY J. OSWALD, B.S.,† TIMOTHY SULLIVAN, B.S.,* ERIC A. STROM, M.D.,†
SIMON N. POWELL, M.D., PH.D.,* ANGELA KATZ, M.D.,* AND ALPHONSE G. TAGHIAN, M.D., PH.D.*

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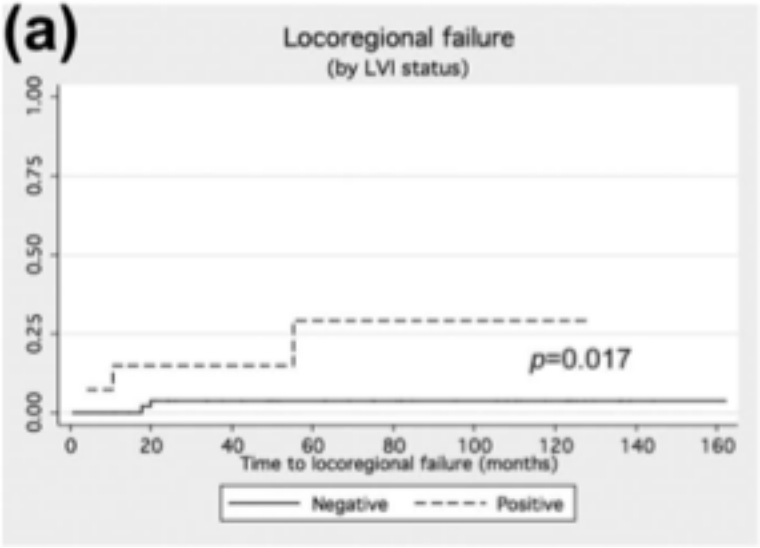
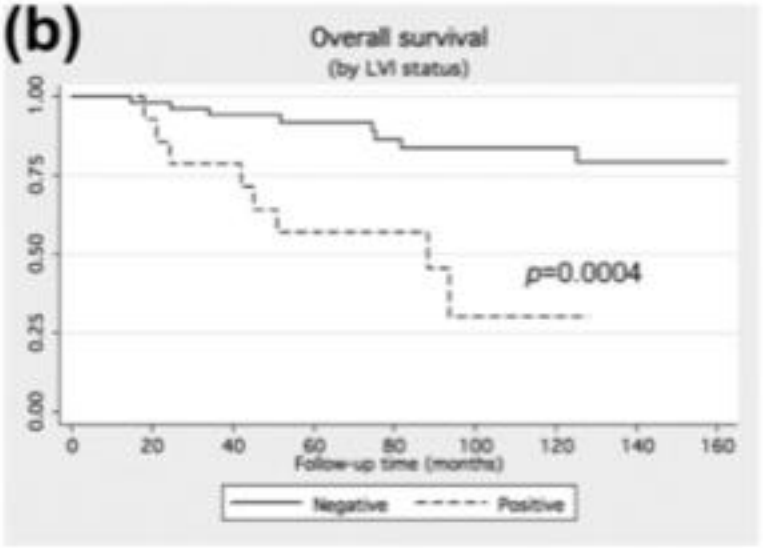
- MGH/MDACC/Yale - Between 1981 and 2002
- Review of multi-institutional database (Floyd, IJROBP 2006)
- 70 pts
- T3N0
- s/p mastectomy+chemo
  - no PMRT. No neoadj. Median FU 7y.

Floyd S. Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 2, pp. 358 –364, 2006

T3N0

- 5y LRF 7.6%, mostly in CW (4/5)
- **LVSI significant prognostic factor**
- DFS 83%, OS 86%





Floyd S. Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 2, pp. 358 –364, 2006

T3N0

- Conclusion: No need for PMRT in T3N0, consider if LVSI present

Floyd S. Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 2, pp. 358 –364, 2006

Review of NSABP postmastectomy chemo trials

B-13, B-14, B-19, B-20, and B-23 node-negative trials

- 313 pts, T3N0 treated with MRM +/- chemo, no PMRT, on NSABP trials
  - Therapy included adjuvant chemotherapy in 34.2% of pts; tamoxifen in 21.1%; chemotherapy plus tamoxifen in 19.2%; and no systemic therapy in 25.5%

Taghian AG, J Clin Oncol. 2006 Aug 20;24(24):3927-

Review of NSABP postmastectomy chemo trials

B-13, B-14, B-19, B-20, and B-23 node-negative trials

- Median Fu 15.1y.
- 10y isolated LRF 7.1% and LRF +/- DM 10%, mostly at the **CW**.
- No significant prognostic factors

- Conclusion: Routine use of PMRT in this group is not warranted

Taghian AG, J Clin Oncol. 2006 Aug 20;24(24):3927-

Who needs PMRT?

- All women with > 3 positive nodes.
- All women with any positive node and a tumor larger than 5 cm.
- ?? Women with positive margins: *With other risk factors like size, young age, LVSI or high grade*.
- ? Women with T3N0: *Probably not, especially in older women*.
- ? Women with 1-3 positive nodes and T1/T2: *Generally yes and especially in women < 45.*
- ?After neoadjuvant chemo*: If Stage III/IV at diagnosis, if node positive after chemo, if node positive prior to chemo with other high risk features.*

Why not PMRT?

- Greater risk for lymphedema of breast and arm
- Increased amount of lung that is fibrosed by radiation, primarily from treatment of either the supraclavicular nodes or internal mammary nodes. EBCTCG also showed increase risk of lung cancer, RR=1.78 but no increase in respiratory disease.
- May expose contralateral breast to radiation.
- Decrease in the quality of the cosmetic outcome following reconstruction, especially with implants.