

# PMRT

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# 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

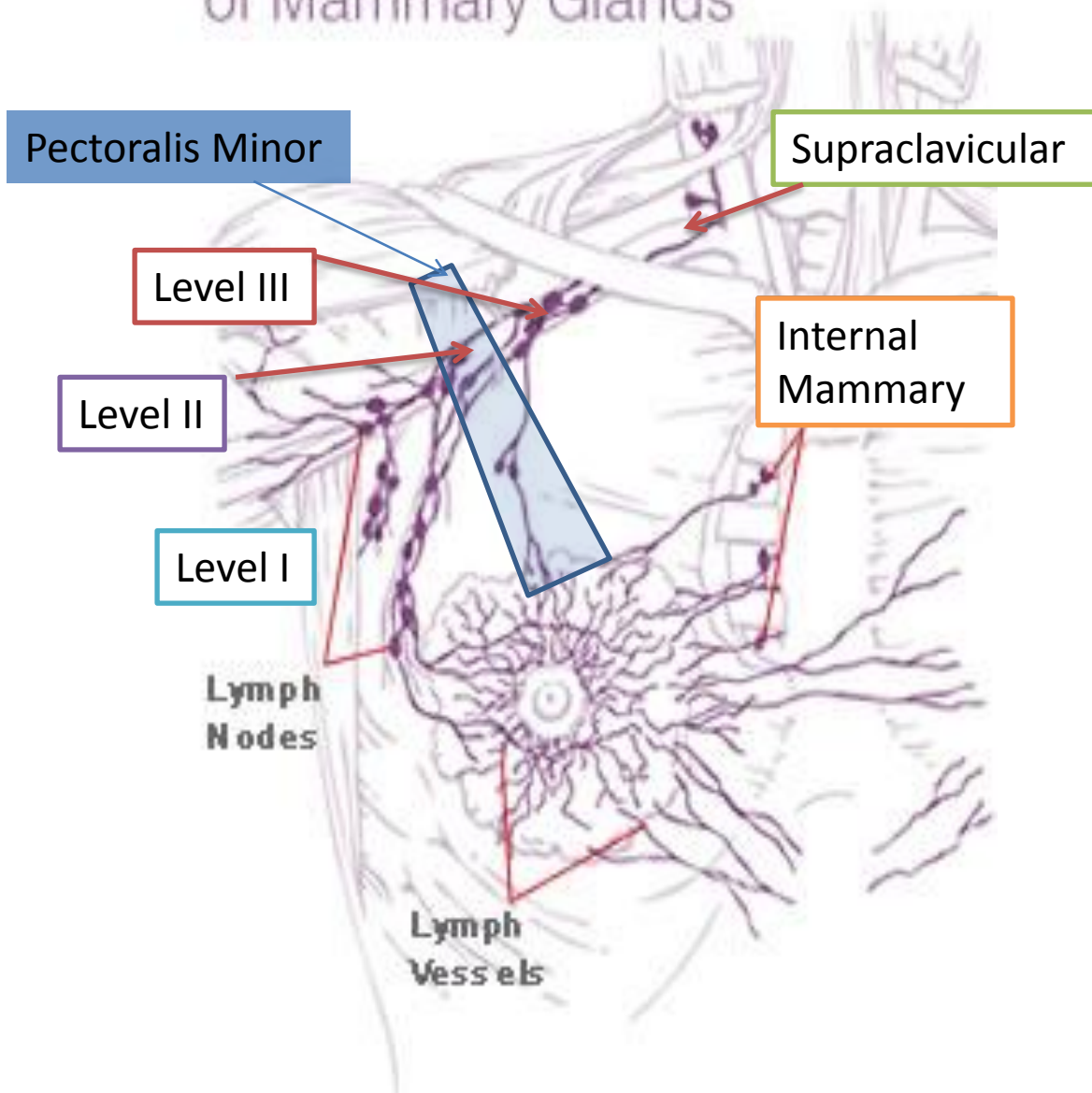
**T4c:** Both T4a and T4b

**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

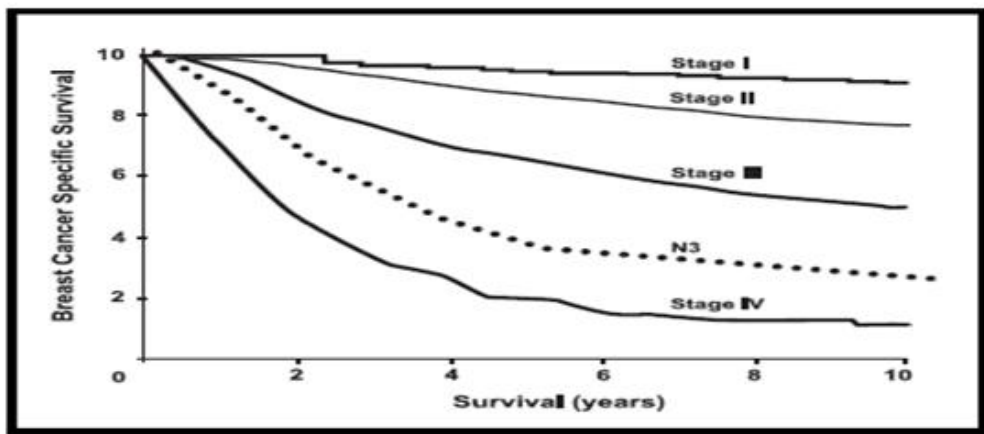
# Lymph Vessels & Nodes of Mammary Glands



# Stage Grouping

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

	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).

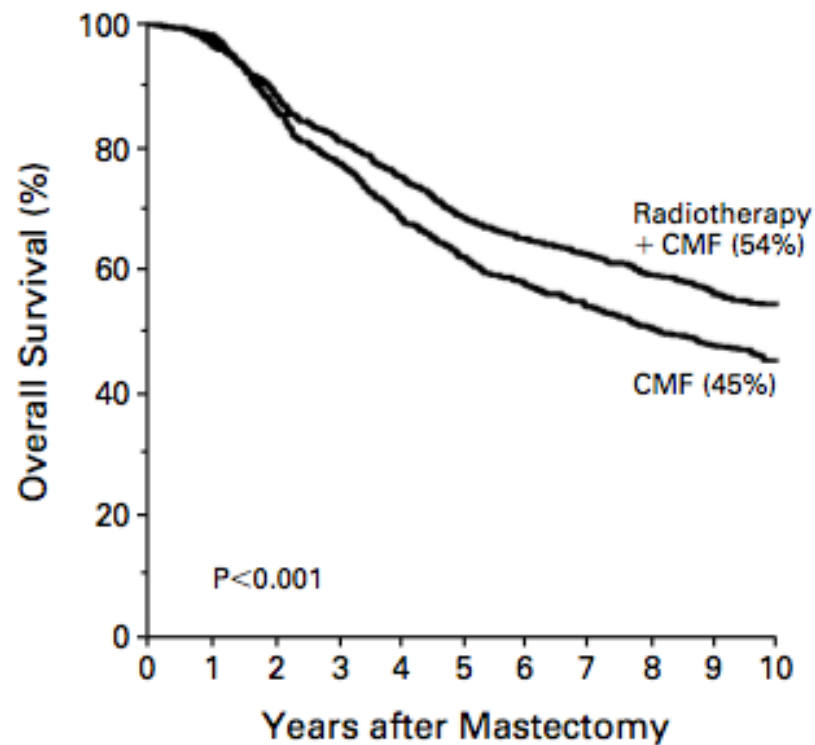
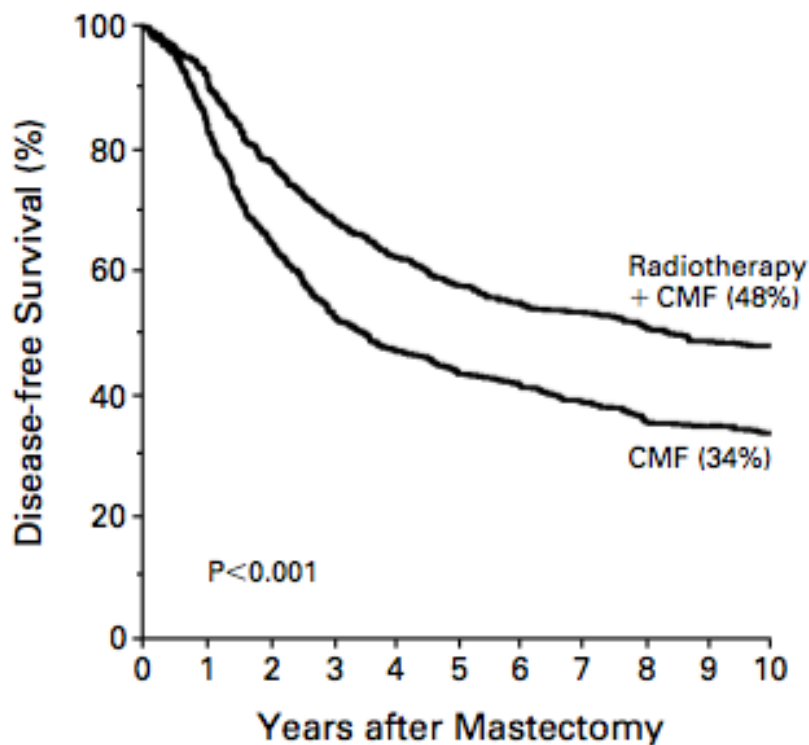
- Surgery consisted of total  
mastectomy + axillary node  
dissection (level I and part of  
level II). Median # of LN removed  
was 7. RT was to chest wall, SCLV  
fossa, infraclavicular LN, and IMN  
in first 4 intercostal spaces. 50 Gy  
in 25 fx (or 48 Gy in 22 fx,  
4days/wk). Recommended use of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



# 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.

# Danish trial 82b (1982-89)



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

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

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

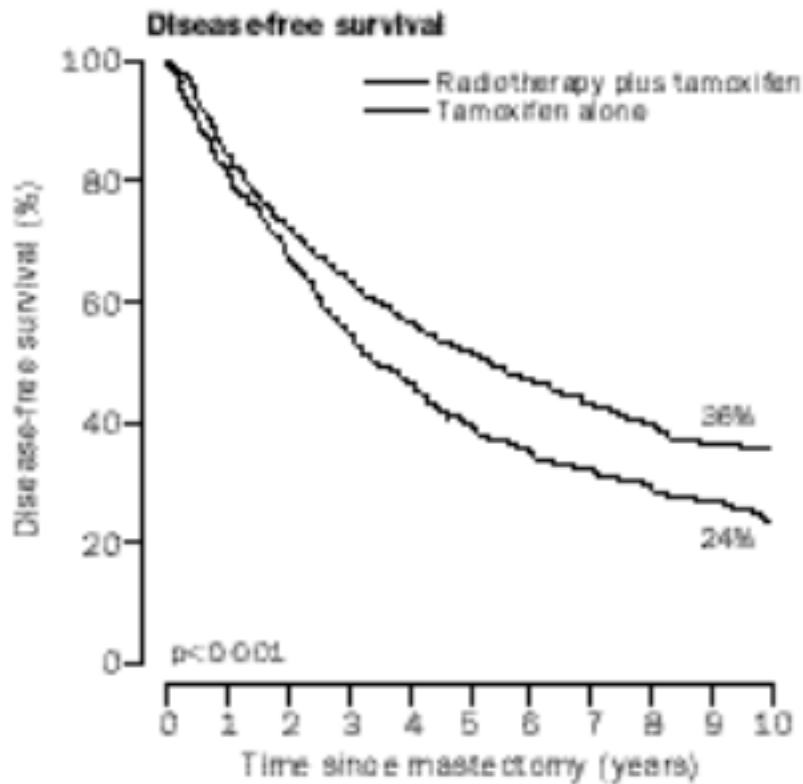
Values in parentheses are disease-free survival at 10 years.

**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.

# Danish trial 82c (1982-90)

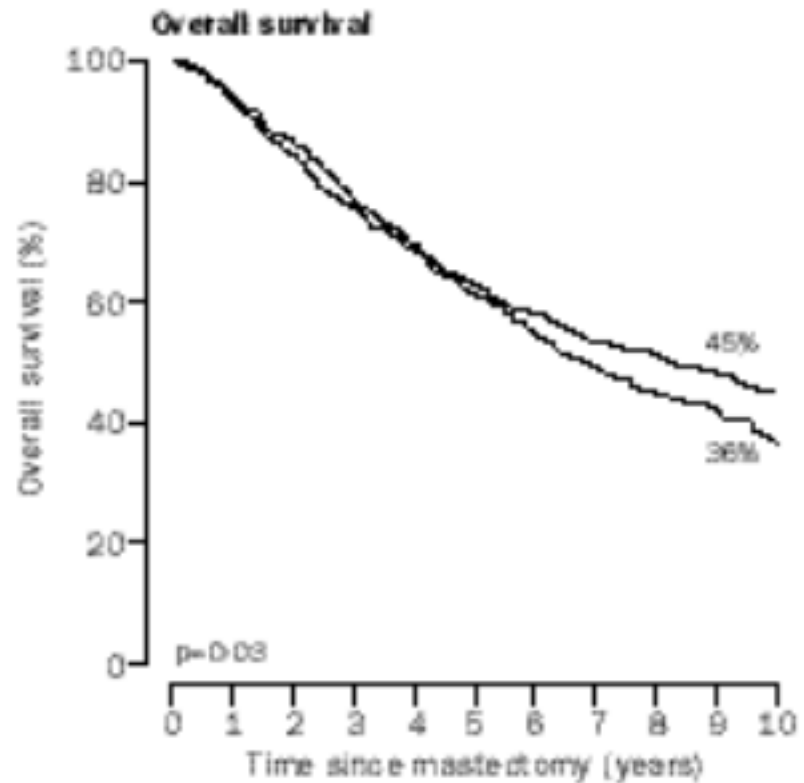
- 1375 pts. Stage II or III
- Postmenopausal high-risk pts. Randomized to post-mastectomy: tamoxifen (for 1 yr), or to tam + RT.
- Median f/u 123 months. LRR 8% (RT) vs 35% (No RT). DFS 36% vs 24%. **10-yr OS 45% vs 36%.**
- The endpoints were first site of recurrence (locoregional recurrence, distant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

# Danish trial 82c (1982-90)



**Patients at risk**

	0	1	2	3	4	5	6	7	8	9	10
Radiotherapy plus tamoxifen	688	485	373	296	194	82					
Tamoxifen only	689	465	307	226	150	39					



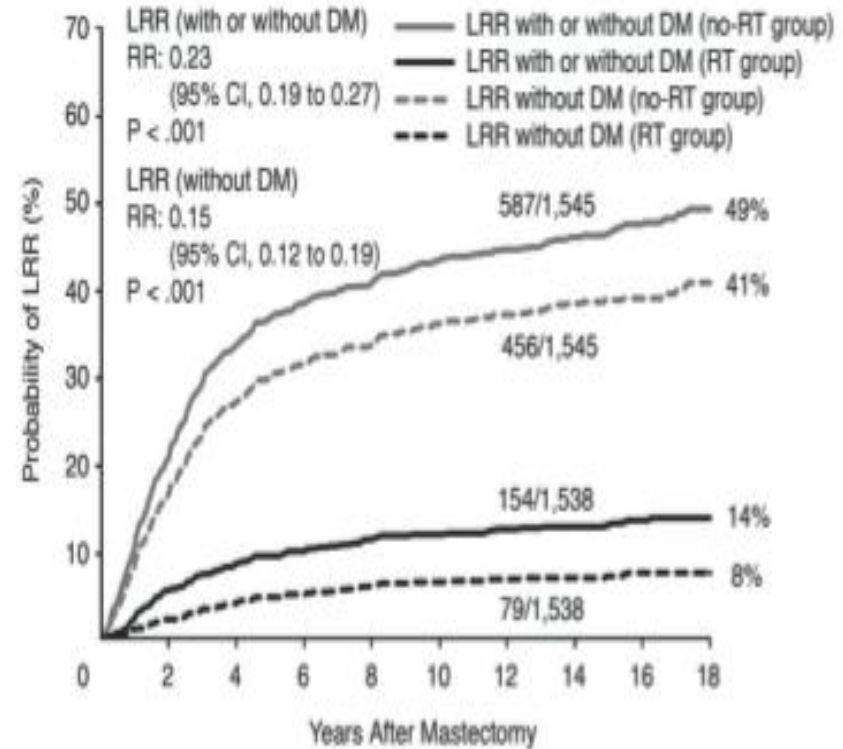
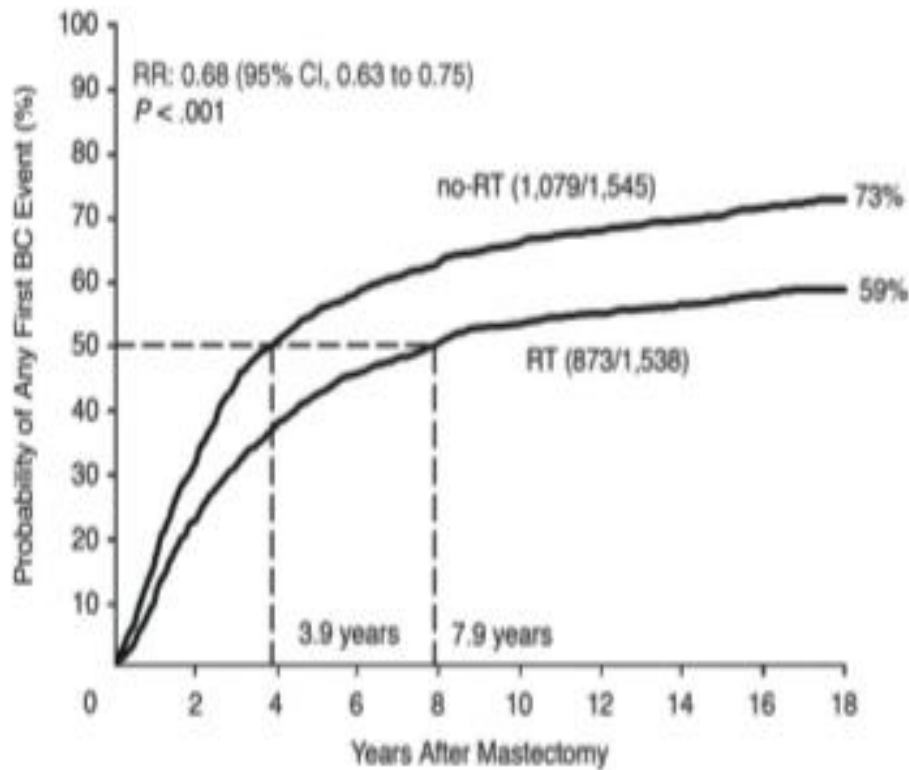
**Patients at risk**

	0	1	2	3	4	5	6	7	8	9	10
Radiotherapy plus tamoxifen	688	580	469	398	285	175					
Tamoxifen only	689	598	479	378	251	136					

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

# 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.



- **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.

# 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+.

# 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

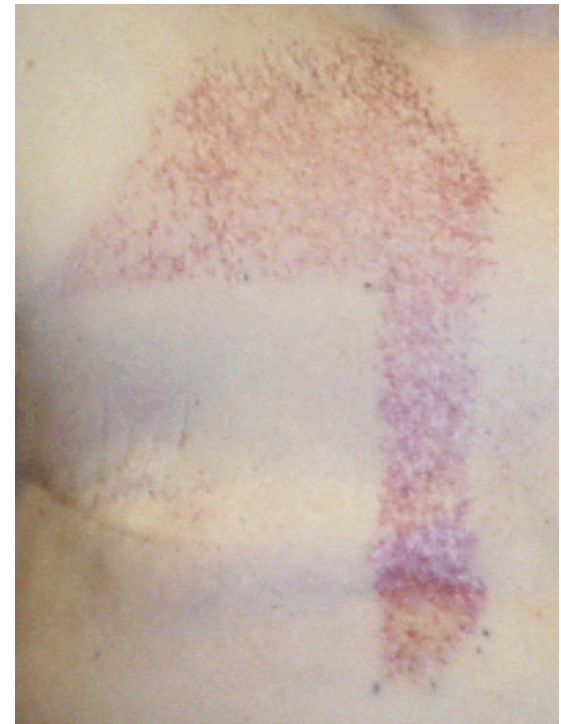


# British Columbia Trial

- 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.

# 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”.

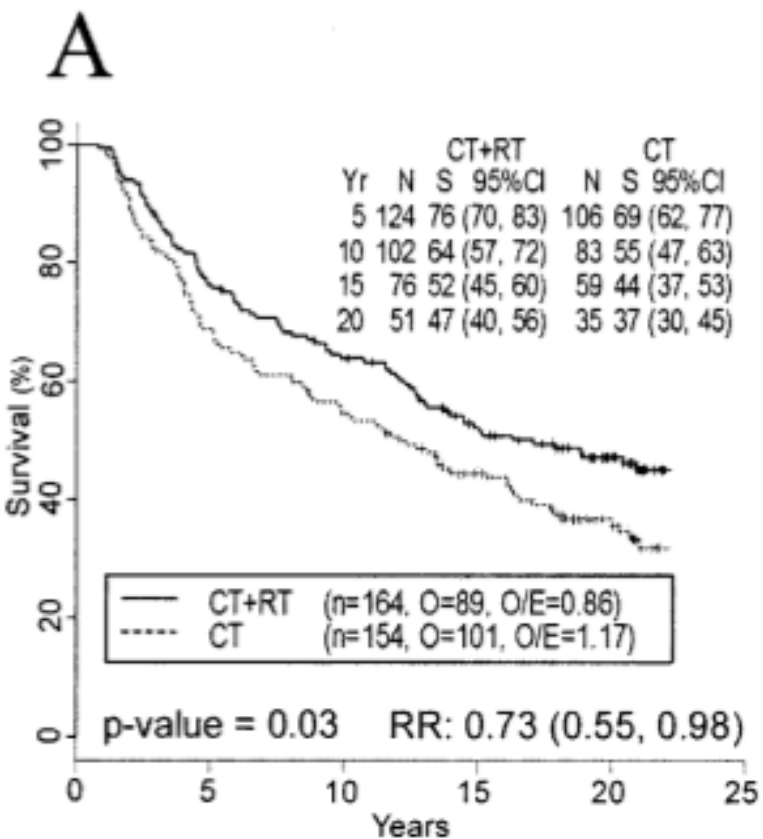


# British Columbia Trial

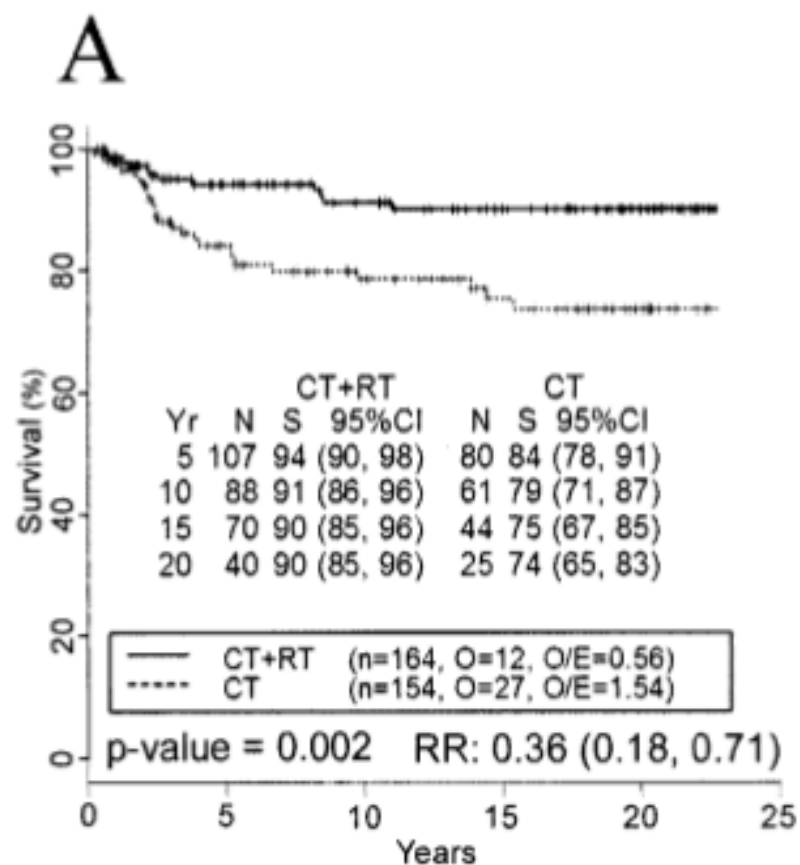
- LRR: 26% vs 10%(RT)
- **OS: 37% vs 47%(RT) SS**
- Similar results for 1-3 LN and >4 LN
- Arm edema in 3.2% vs 9.1%(RT).

# British Columbia Trial

Overall Survival



Recurrence free survival



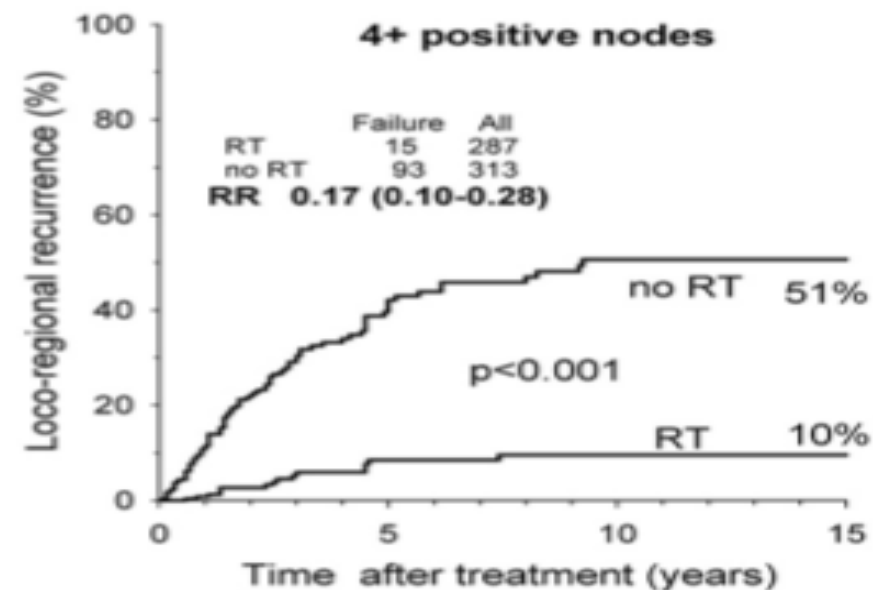
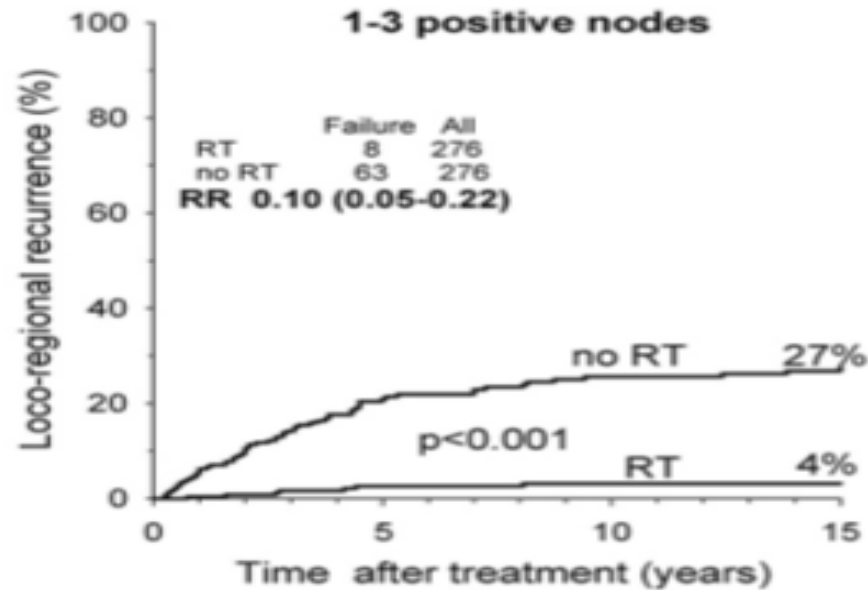
# British Columbia Trial

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		
<i>All 318 patients</i>						
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?

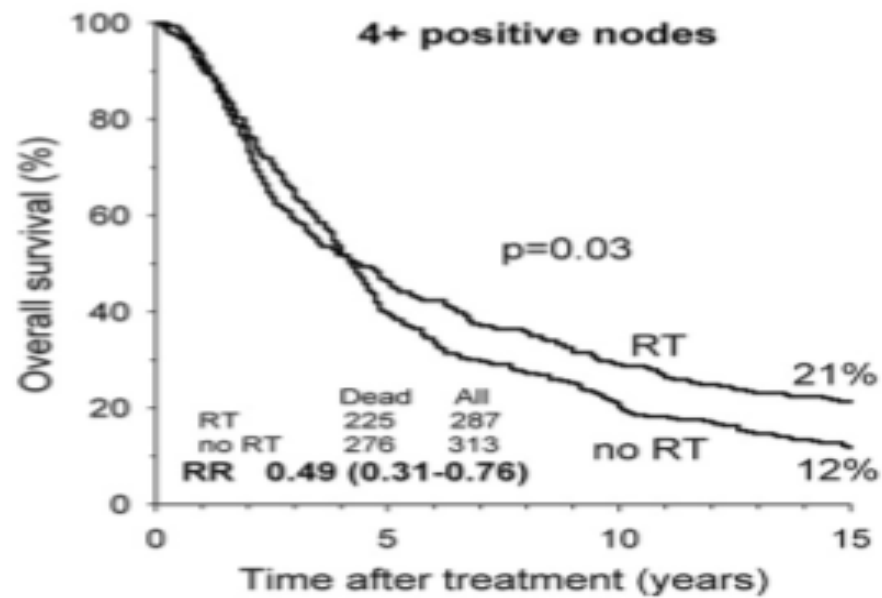
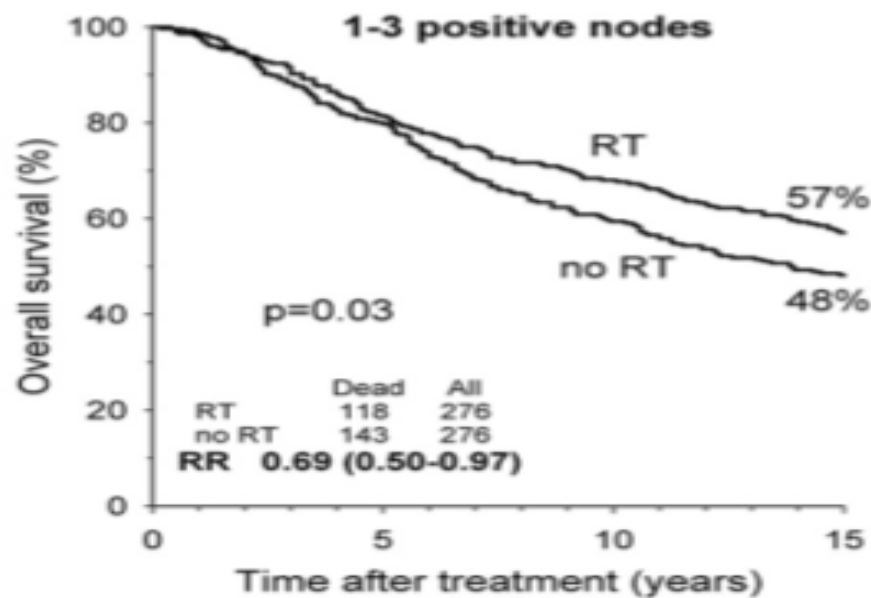
A subgroup analysis of the DBCG 82 b & c randomized trials.

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



RT	276	197	173	136
no RT	276	165	131	106

RT	287	101	64	51
no RT	313	72	35	23



RT	276	224	187	129
no RT	276	220	164	154

RT	287	132	83	59
no RT	313	125	65	37

# DBCG 82 b & c randomized trials

## Subanalysis of pts with $\geq 8$ LN's

Table 2  
The Bottom line estimate

Parameter	1–3 pos. nodes	4+ pos. nodes
<i>Endpoint: loco-regional recurrence</i>		
Relative risk reduction	87%	82%
Absolute risk reduction	20%	24%
Number of patients needed to treat to avoid an LRR	5	4
<i>Endpoint: death</i>		
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.



# DBCG 82 b & c randomized trials

Subanalysis of pts with  $\geq 8$  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

# 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.

# Neoadjuvant chemo

**Table 1.** Neoadjuvant Chemotherapy Regimens

Protocol	Years of the Study	Neoadjuvant Chemotherapy Regimen	No. of Cycles	No. of Patients		Total Study Population*
				CT + M	CT + M + RT	
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
<b>Total</b>	<b>1974-2000</b>			<b>134</b>	<b>542</b>	<b>1,058</b>

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.

# 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  $\geq 4$  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

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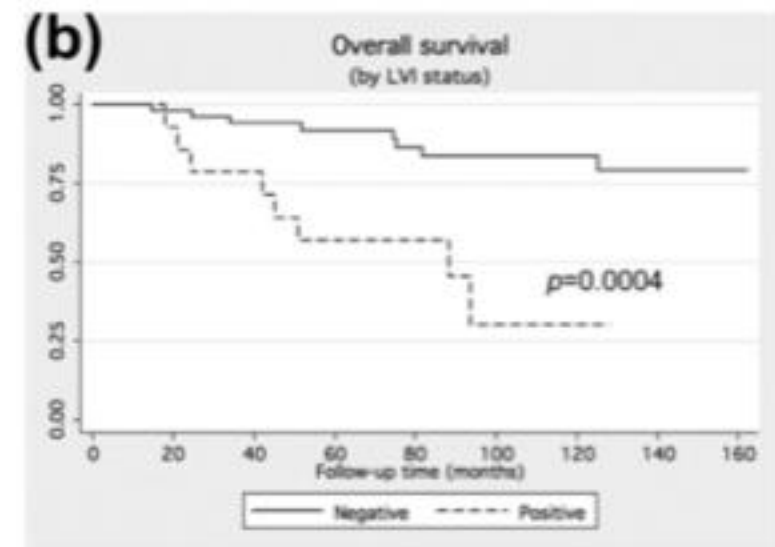
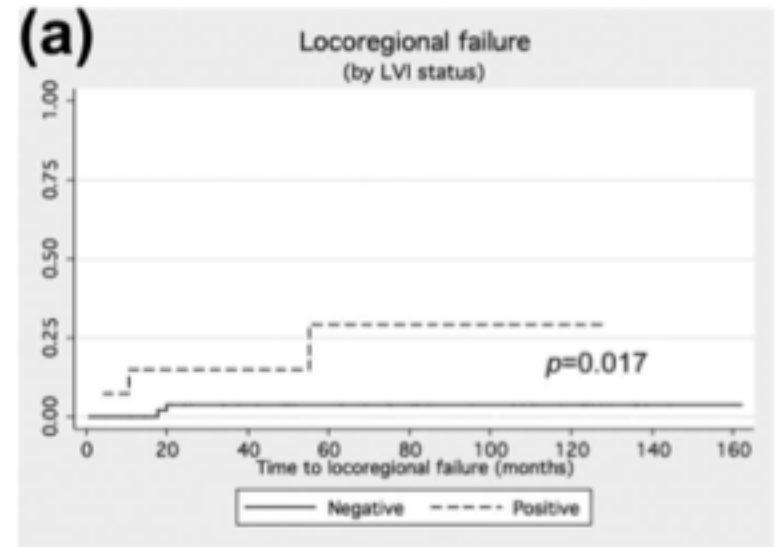
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- MGH/MDACC/Yale - Between 1981 and 2002
- Review of multi-institutional database (Floyd, IJROBP 2006)
- 70 pts
- T3N0
- s/p mastectomy+chemo
  - no PMRT. No neoadj. Median FU 7y.



# T3N0

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



# T3N0

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

# 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%

# 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

# 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.