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**Global Breast Cancer Conference 2009
with the 7th Biennial Meeting of the
Asian Breast Cancer Society**

Evolution and Future Direction of Local Therapy

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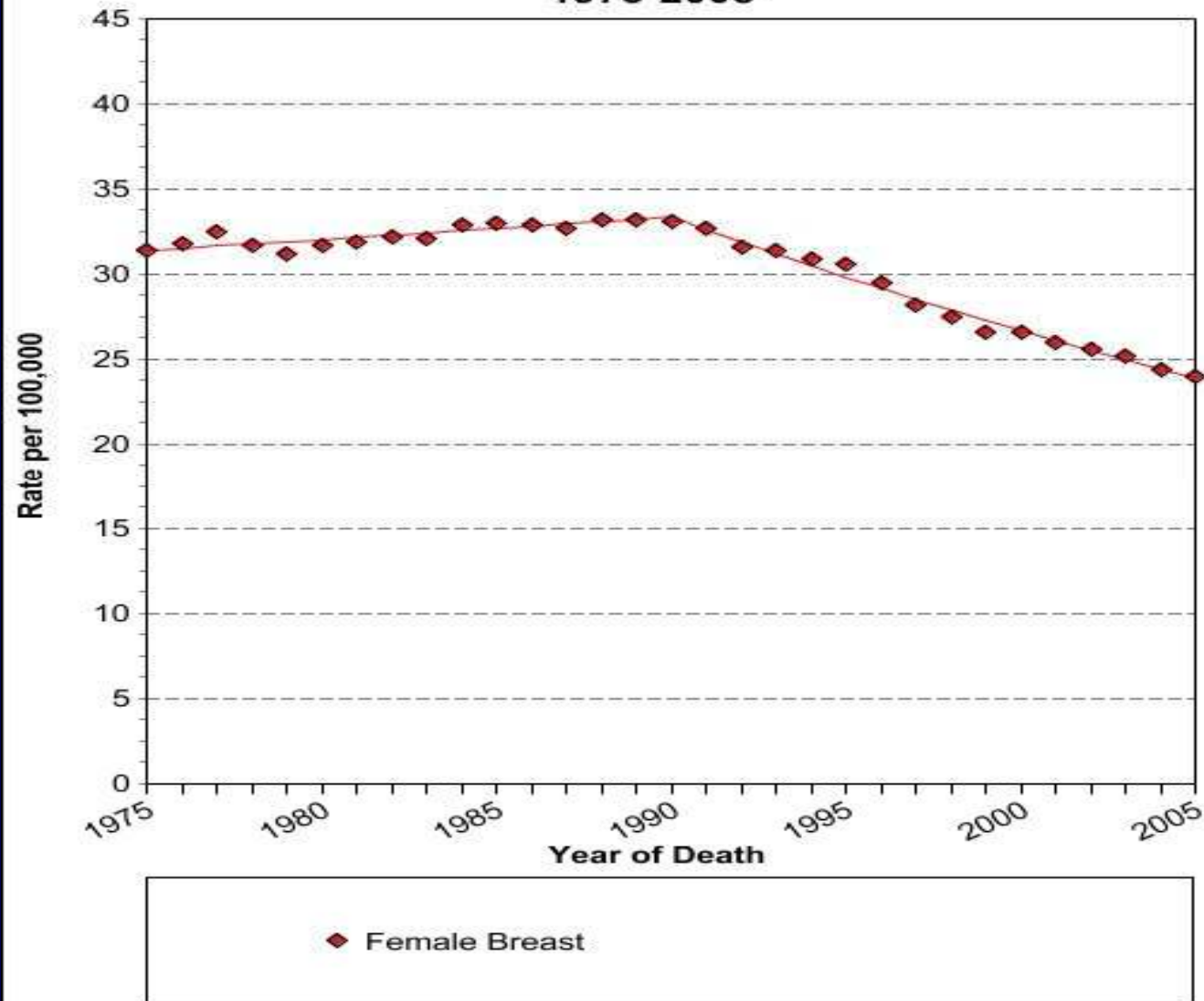
Evolution and Future Direction of Local Therapy

- **State of the Art in 2000**
- **State of the Art today**
- **Gazing forward**

Progress in Breast Cancer: 2000

- By 2000, we had already begun to see a decrease in the mortality rate from breast cancer
- A key factor in this progress has been the availability of many clinical trials, all of which reside in a common repository in Oxford, UK (EBCTCG)

Age-Adjusted U.S. Mortality Rates By Cancer Site For All Ages, All Races, Female 1975-2005



Mortality source: US Mortality Files, National Center for Health Statistics, CDC.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.3, April 2008, National Cancer Institute.

Reasons for Multiplicity of Trials

- **In large part, patients' willingness to participate in clinical trials**
- **Investigators' commitment to level I evidence and to cooperation**
- **Early strong commitment of two prominent surgeons to clinical trials**

B. Fisher and U. Veronesi

- **2 surgeons who had the courage in the 1960's to say they didn't 'know the answer' and that RCT's were needed**
- **Bernie Fisher still has the most first author NEJM articles; when he was 75, NEJM gave him a lifetime subscription!**

Status of Local Therapy in 2000

- **Breast-conserving therapy (BCT) provided alternative to mastectomy**
- **Improved breast reconstruction also provided better Quality of Life (QoL)**
- **Sentinel node biopsy begins to replace ALND, also improving QoL**

Status of Local Therapy in 2000

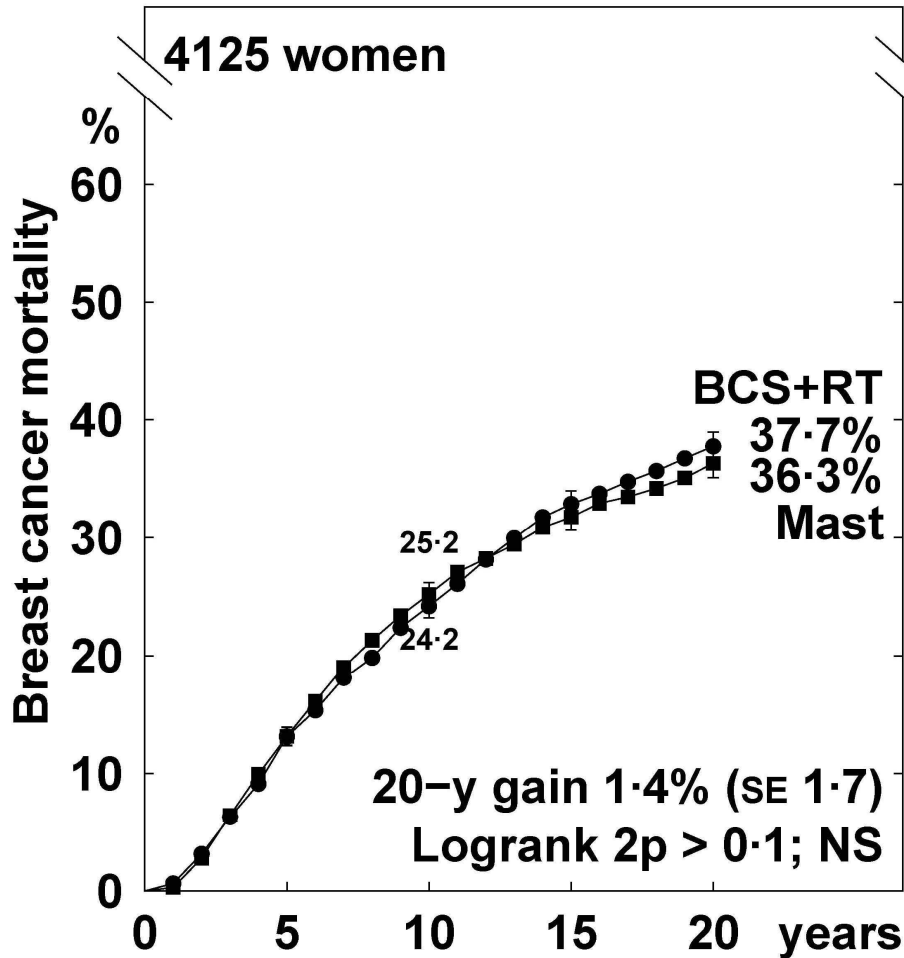
- **It was very widely assumed that local therapy impacted local recurrence, but not survival**
- **Trials testing variations in local therapy (such as NSABP B-04 and B-06) failed to show a survival benefit**

Breast Conserving Therapy (BCT)

(My main area of interest)

- **The development of BCT was based on a partnership between surgeons and radiation oncologists, working with pathologists and breast imagers**
- **Clinical trials have demonstrated survival equivalent to mastectomy**

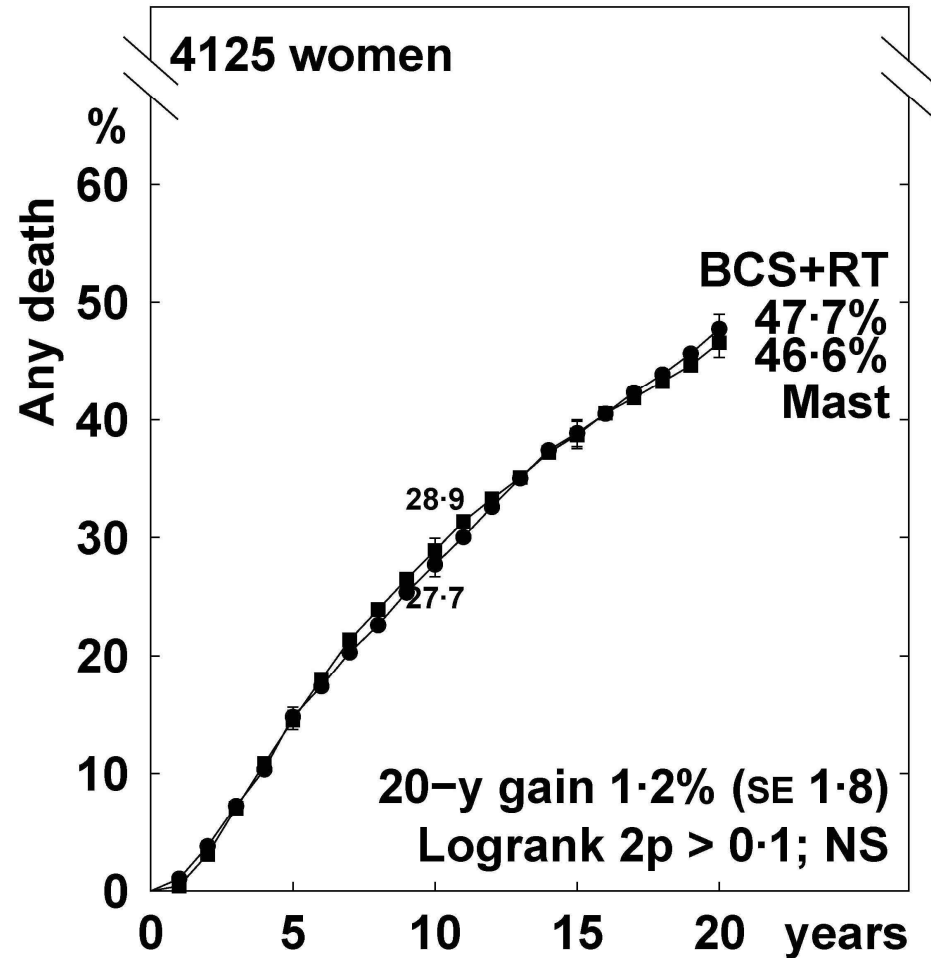
Mastectomy vs BCS + RT, both with AC BREAST CANCER MORTALITY



After-recurrence or possible-breast-cancer death rates (% / year) and logrank analyses

	Years 0 - 9	Years 10 - 19	Year 20+
Mast	2.84 (479 / 16842)	1.64 (154 / 9386)	1.15 (17 / 1473)
BCS+RT	2.77 (483 / 17437)	2.09 (209 / 10010)	1.99 (32 / 1612)
Rate ratio, from (O-E) / V	1.05 SE 0.07 10.7 / 227.9	0.80 SE 0.10 -19.2 / 85.8	0.63 SE 0.24 -5.3 / 11.5

Mastectomy vs BCS + RT, both with AC ANY DEATH



Death rates (% / year) and logrank analyses

	Years 0 - 9	Years 10 - 19	Year 20+
Mast	3.33 (561 / 16842)	2.90 (272 / 9386)	2.85 (42 / 1473)
BCS+RT	3.22 (562 / 17437)	3.25 (325 / 10010)	3.97 (64 / 1612)
Rate ratio, from (O-E) / V	1.05 SE 0.06 12.3 / 267.5	0.88 SE 0.08 -17.8 / 142.6	0.68 SE 0.17 -9.7 / 25.0

Paradigm Shift!

EBCTCG 2005

- **EBCTCG meta-analysis of trials of local therapy showed a significant and substantial impact of reduced LR on long-term survival**
- **This survival benefit was achieved either by better surgery or adding RT**

Ref: EBCTCG, *Lancet* 366; 2087: 2005

EBCTCG Meta-analysis of Trials of BCS +/- RT

NSABP B-06

Milan 3

Uppsala-Orebro

St. George's

Ontario

NSABP B-21

West Midlands

CRC UK

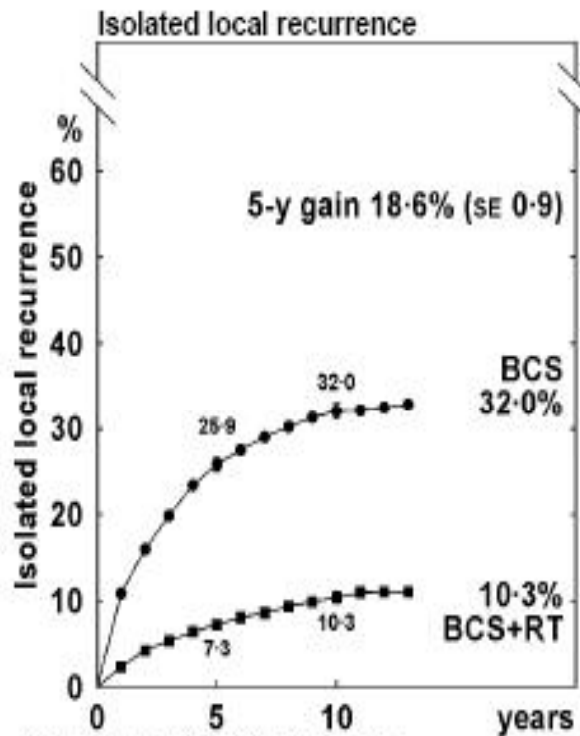
Swedish

Scottish

Refs: EBCTCG, *Lancet* 366; 2087: 2005

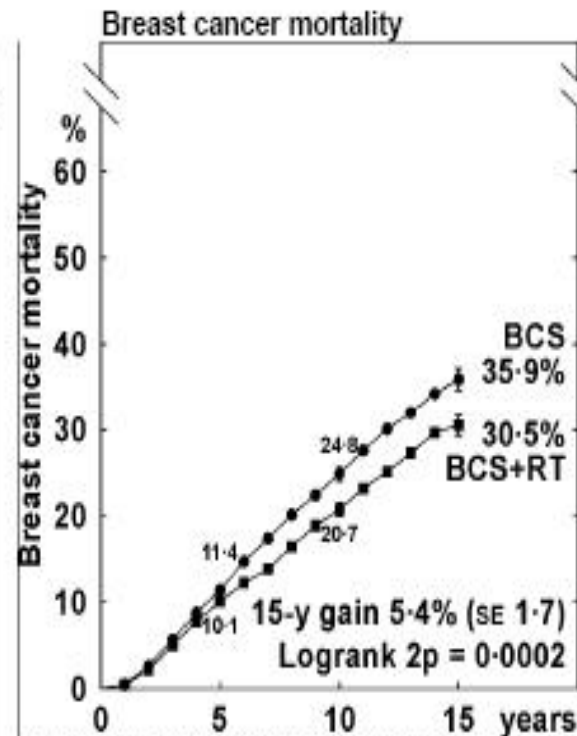
Punglia RS et al. *NEJM* 356; 2399, 2007

Meta-analysis of Trials of BCS +/- RT



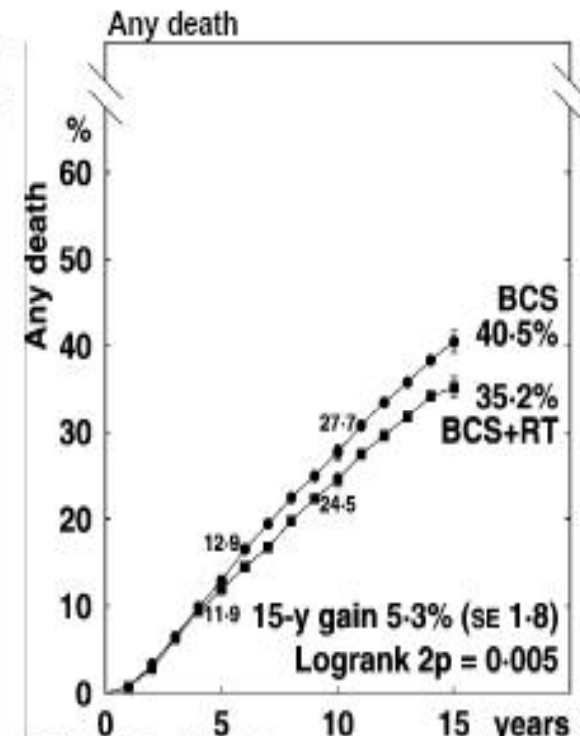
Isolated local recurrence rates (% / year) and logrank analyses

	Years 0-4	Years 5-9	Year 10+
BCS+RT	1.62 (202 / 10526)	0.79 (75 / 9338)	0.23 (9 / 3541)
BCS	0.39 (55 / 1383)	1.00 (127 / 1267)	0.29 (5 / 1554)
Rate ratio, from	0.29 vs 0.95	0.49 vs 0.99	1.14 vs 4.1
(95% CI) / V	-0.16 / 204.2	-46.7 / 69.1	8.4 / 3.1



Death rates (% / year; total rate - rate in women without recurrence) & logrank analyses

	Years 0-4	Years 5-9	Years 10-14	Year 15+
BCS+RT	2.08 (252 / 10258)	2.47 (272 / 10971)	2.74 (30 / 1081)	2.88 (29 / 1007)
BCS	2.08 (295 / 10644)	3.98 (356 / 10530)	5.04 (113 / 2061)	2.54 (24 / 951)
Rate ratio, from	1.48 vs 0.97	0.75 vs 0.47	0.62 vs 0.12	1.19 vs 0.33
(95% CI) / V	-23.1 / 174.1	-42.6 / 149.8	-9.2 / 49.6	2.1 / 12.6



Death rates (% / year) and logrank analyses

	Years 0-4	Years 5-9	Years 10-14	Year 15+
BCS+RT	3.51 (423 / 10858)	3.10 (343 / 11071)	3.32 (150 / 3618)	4.17 (42 / 1007)
BCS	2.70 (448 / 10644)	3.70 (388 / 10591)	3.93 (133 / 3061)	3.33 (32 / 961)
Rate ratio, from	0.92 vs 0.97	0.92 vs 0.97	0.49 vs 0.12	1.25 vs 0.27
(95% CI) / V	-17.4 / 204.2	-36.1 / 173.7	-12.0 / 98.6	3.8 / 17.8

Oxford Overview

- **This study provided strong evidence that improved local control (surgery or RT) → improved survival**
- **The individual trials were not large enough (“had sufficient power”) to rule out a 5% survival benefit**

Oxford Overview

- Reduction in 5-year LR → Reduction in 15-year (not 5-year) mortality
- No increase in non-breast mortality
- Similar benefit with post-mastectomy RT and with more surgery
- A 20% reduction in 5-year LR → a 5% reduction in 15-year mortality (“4:1”)

This Linkage is Strengthened by:

- **Proportionality of the effect: The greater the reduction in 5-year LR, the greater the reduction in 15-year mortality (with a 4:1 ratio)**
- **Time course: With $> 10\%$ reductions in 5-year LR, the mortality benefit only emerges after 5 years**

Possible Explanation

- **A hallmark of cancer is genomic instability**
- **A recurrent tumor likely has more genetic alterations than the primary**
- **For some patients (? 1 in 4), the recurrent tumor has the capacity for metastasis that the primary did not**

Clinical Implication: Local Therapy is Important!

- **We can no longer be cavalier in our concern about local recurrence**
- **Every reasonable measure should be taken to reduce local recurrence**
- **We are still trying to determine all the clinical implications of this finding**

Calculating the Survival Benefit

- **A: Estimate the 5-year risk of LR without RT**
- **B: Multiply A by ≥ 0.7 to get the risk of 5-year risk of LR with RT**
- **C: $A - B =$ absolute reduction in LR divided by 4 = estimated reduction in 15-year mortality**

Status of Local Therapy Today

- **Local recurrence following BCT has continued to decrease**
- **Sentinel node biopsy is very widely used**
- **Reconstruction techniques and options have continued to improve**

Status of Local Therapy Today

- **Data from the EBCTCG and other sources have clearly shown harmful effects if the heart is irradiated**
- **RT techniques are available after BCS and after mastectomy to reduce or eliminate cardiac irradiation**

Cardiac Deaths related to Dose

(Ref: EBCTCG, Courtesy Sarah Darby)

Estimated Cardiac Dose (Gy)	Rate Ratio Cardiac Death for RT/no RT
< 5	1.08 (NS)
5-15	1.32
>15	1.63

Risk rate per 10 Gy = 1.31, $p < 0.0001$

Ways to Eliminate Cardiac Dose

- **Come off midline**
- **Cardiac block**
- **Prone technique**
- **Breath-hold technique**
- **Use of separate IMN field (left side)**

Current Results with BCT

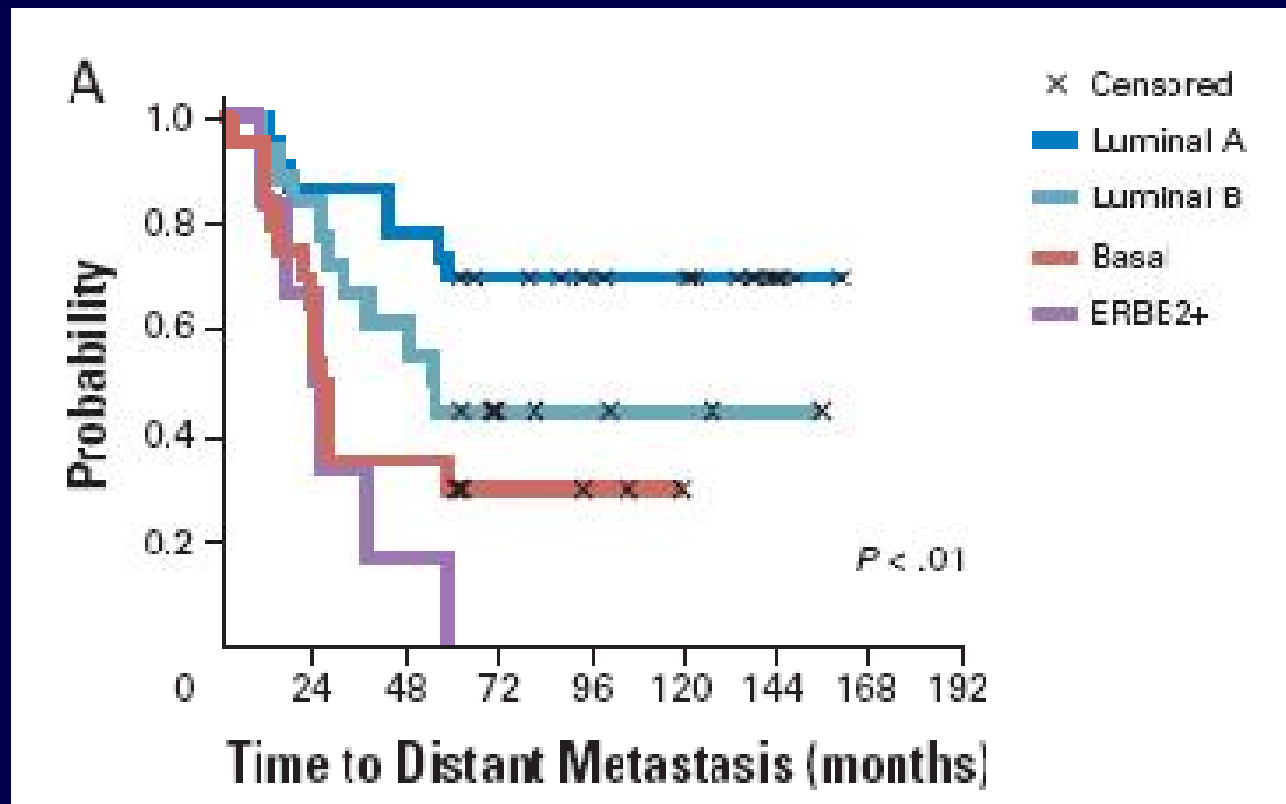
- **Our results from DFBWCC and MGH are illustrative of the current excellent results seen with BCT**
- **These results also illustrate the growing importance of considering biologic subtypes**

Our Recent Experience

- 793 BCT patients treated 7/98 – 12/01
- T1 80%, N0 71%
- Margins: Negative 84%, close 13%
- ST used in 90% (No Herceptin)
- Median FU = 70 months
- 5-year LR = 1.8%!

(Ref: Nguyen P et al, JCO 26: 2373, 2008)

Subtype is Prognostic for DM



Luminal A
Favorable

Luminal B
Intermediate

Basal and
HER2
Unfavorable

Ref: Sorlie, et al PNAS 2003:100, 8418

Is Subtype also Prognostic for LR?

Subtype approximated by markers:

Luminal A = ER or PR+/ HER2- (595)

Luminal B = ER or PR+/ HER2+ (77)

HER2 = ERPR-/ HER2+ (32)

Basal = ER/PR-/HER2- (89)

Outcome by Biologic Subtype

	5-Yr LR	5-Yr DM
Luminal A	0.8%	3.3%
Luminal B	1.5%	12%
HER2	8.4%	19%
Basal	7.1%	16%

On MVA, subtype was only factor significant for LR

Similar Results in Danish Trials

	5-Yr LR BCS + RT	5-Yr LR Mast + RT*
Luminal A	0.8%	2%
Luminal B	1.5%	3%
HER2	8.4%	13%
Basal	7.1%	21%

* Ref: Kyndi M et al. JCO 26: 1419, 2008

Reasons for Excellent Outcomes

- **Better imaging with mammography (not MRI); use of MRI controversial**
- **Better evaluation of the resected breast specimens, especially margins**
- **Use of systemic therapy (ST), which greatly improves results of RT**

10-Year LR in Recent NSABP Trials

(Ref: Wapnir I et al. Proc ASCO 2005)

Trial	ER Status	10-Year LR (%)
B-13 No Chemo	-	13.3
B-13 Chemo	-	3.5
B-14 No Tamoxifen	+	11.0
B-14 Tamoxifen	+	3.6
B-19 Chemo	-	6.5
B-20 Tam +/- Chemo	+	4.7
B-23 Chemo	-	4.3

Current Controversies

- **Use of breast MRI at diagnosis**
- **Preferential use of mastectomy**
- **Use of tamoxifen instead of RT**
- **Use of Accelerated Whole Breast RT**
- **Use of Accelerated Partial Breast RT**
- **Local therapy with preoperative ST**

10-Year Results of Canadian Trial of Accelerated WB RT

	LR	Good-Exc Cosmetic Results
50 Gy/25	6.7%	71%
42.5 Gy/16	6.2%	70%

In subset analysis, 50 Gy/25 was better for gr 3 cancers

Ref: Whelan T et al. Proc. San Antonio 2007

Can WB RT be Given Faster?

- **Faster treatment seems appropriate in older patients (aged ≥ 60) with grade 1, 2 cancers (where a boost has limited value)**
- **This has emerged as an alternative to tamoxifen alone**

APBI: Arguments for WB RT

- **Safe and effective with very long FU**
- **Breast MRI's frequently show multicentric cancer, but 10-year LR is low**
- **Uncertainty about long-term results with APBI; large fractions/volumes**
- **Learning curve for APBI is inevitable; Our first BCT cohort had high LR rate**

Gazing Forward

- The major focus for progress is further improvements in systemic therapy
- Local treatment plays a role both in QoL (BCT) and in contributing to the survival rate by decreasing LR
- Q: What is the role of local treatment with improving systemic therapy?

Local Treatment with Improving ST?

- **BCT results will likely get even better with improved ST**
- **We can now only speculate how improved ST will affect the (4:1) ratio**
- **4:1 was based on the ends of curves derived from older trials without ST**

Local Treatment with Improving ST?

- **We are just beginning to obtain data on this question**
- **We have some data on this from a subset analysis from the Oxford Overview and from the recent retrospective review from the Danish Trial**

Subset Analysis of PMRT by ST (N+ Patients)

ST Used	Isolated LR	B.C. Mortality	Any Death
Yes	0.28	0.87	0.88
No	0.30	0.95	0.98

Ref: EBCTCG, *Lancet* 366; 2087: 2005 (website)

Likely Explanation

- **In N+ patients treated with mastectomy and without ST, the correlation of residual local disease and the presence of micro-metastatic disease is very high**
- **In such patients, reduction of LR is unlikely to improve long-term survival in the absence of ST**

New Danish Trials Results

- **2 separate PMRT trials: for premenopausal patients, CMF vs CMF + RT and for postmenopausal patients, Tam x 1 year vs Tam + RT**
- **Findings in the subset of 1241 patients with ER, PR, HER2 results**

Ref: Kyndi M et al. JCO 26: 1419, 2008

Danish Trial Results

	5-Year LR Reduction	15-Year Mortality Reduction	Ratio
Lum A	22->2%: 20%	11%	~ 2:1
Lum B	39->3%: 36%	23%	~ 1.5:1
HER2	32->13%: 19%	- 11%	NA
Basal	30->21%: 9%	7%	~ 1:1

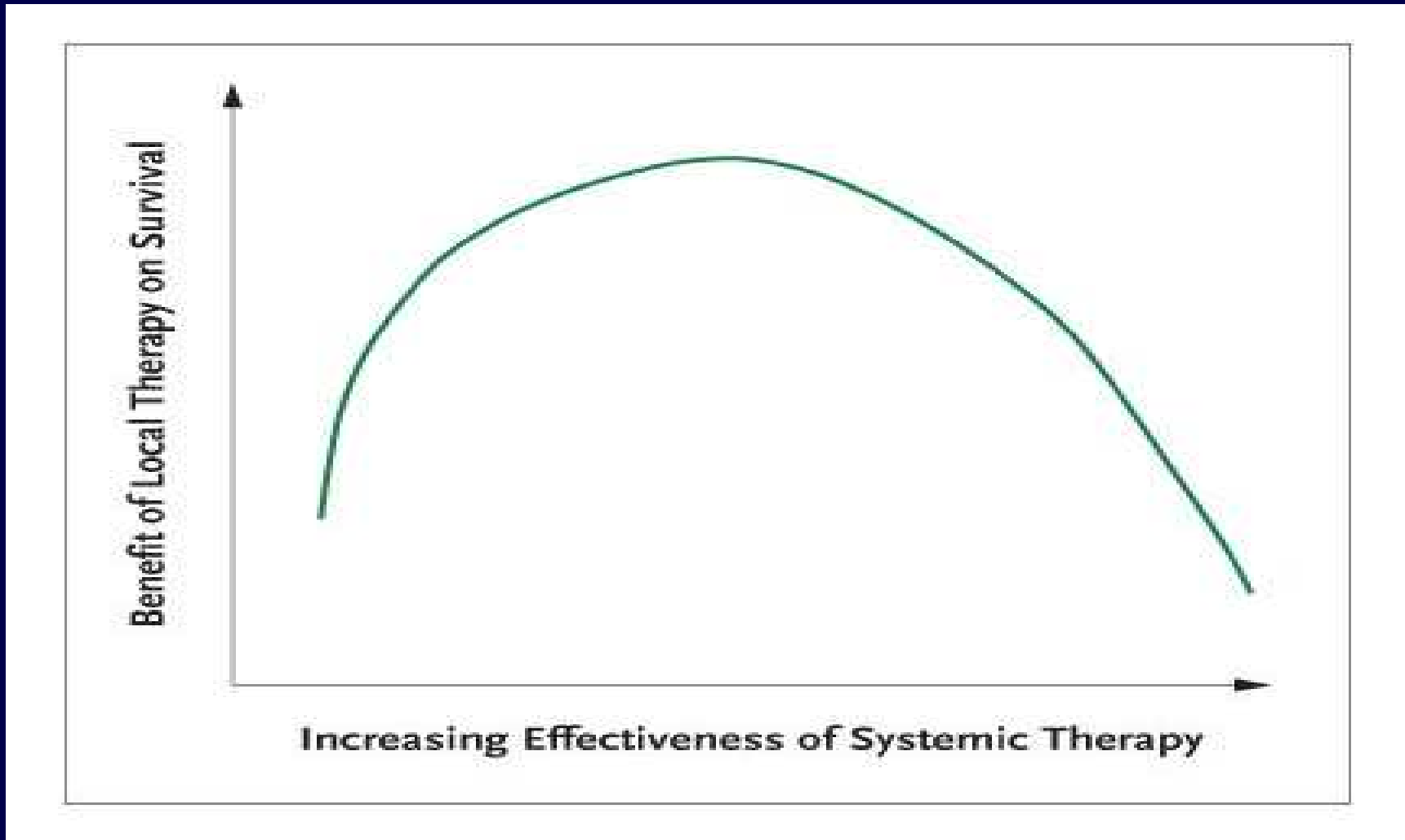
Danish Trial Results

- Limited by retrospective design, small numbers in subgroups, outdated systemic therapy and merging of 2 separate trials
- Results suggest that Ratio is less than 4:1 with adjuvant therapy and that it varies with subtype/therapy

Will the Ratio Stay at 4:1?

- **We don't have enough data to know the answer with certainty**
- **The current data suggests that with increasingly effective systemic therapy, the risk of LR will be less, but the ratio will also be less**

Local Therapy with Improving ST



Ref: Punglia R et al. N Engl J Med 356:2399, 2007

Conclusions

- **Local treatment is important both for QoL (BCT) and for maximizing long-term survival by reducing LR**
- **The current estimate is for every 4 LR's avoided at 5 years, there is 1 additional 15-year survivor**
- **BCT results have improved, largely due to the interaction of ST and RT**

Conclusions

- **As ST improves, BCT results will likely get even better**
- **As ST improves near term, local treatment will likely become even more important in maximizing survival**
- **Eventually, ST will become so good, the role of local treatment will diminish**

Progress in Breast Cancer over My Career

**It has been a privilege to be involved
in the breast cancer effort over the
past 3 decades**