2010 Buschke Lecture:
The Relationship between Local Recurrence and Survival in Breast Cancer

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J. Franz Buschke, M.D.
1902-1983

- Consummate clinician, oncologist, educator, investigator and leader
- Professor and Director of Radiation Oncology at UCSF from 1957 to 1970
- One of the pioneering founders of American Radiation Oncology

The Relationship between Local Recurrence and Survival in Breast Cancer

- 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)

Reasons for Multiplicity of Trials

• In large part, patients’ willingness to participate in clinical trials

• Investigators’ commitment to level I evidence in deciding treatment

• 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
Paradigm Shift! EBCTCG 2005

- EBCTCG meta-analysis of trials of local therapy showed a significant and substantial impact of reduced LR on improved 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 | NSABP B-21 |
| Milan 3    | West Midlands |
| Uppsala-Orebro | CRC UK       |
| St. George's | Swedish      |
| Ontario    | Scottish     |

Refs: EBCTCG, Lancet 366; 2087: 2005
Punglia RS et al. NEJM 356; 2399, 2007

Meta-analysis of Trials of BCS +/- RT

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

Oxford Overview
**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 < 0.3 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)

<table>
<thead>
<tr>
<th>Estimated Mean Cardiac Dose (Gy)</th>
<th>Rate Ratio Cardiac Death for RT/no RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>1.08 (NS)</td>
</tr>
<tr>
<td>5-15</td>
<td>1.32</td>
</tr>
<tr>
<td>&gt;15</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Risk rate per 10 Gy = 1.31, p < 0.0001
Ways to Reduce 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 DFWBCC 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

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 = ER/PR-/HER2+ (32)
- Basal = ER/PR-/HER2- (89)

**Outcome by Biologic Subtype**

<table>
<thead>
<tr>
<th></th>
<th>5-Yr LR</th>
<th>5-Yr DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>0.8%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>1.5%</td>
<td>12%</td>
</tr>
<tr>
<td>HER2</td>
<td>8.4%</td>
<td>19%</td>
</tr>
<tr>
<td>Basal</td>
<td>7.1%</td>
<td>16%</td>
</tr>
</tbody>
</table>

On MVA, subtype was only factor significant for LR

**Similar Results with BCS + RT**

<table>
<thead>
<tr>
<th></th>
<th>5-Yr LR</th>
<th>5-Yr LR*</th>
<th>10-Yr LR^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>0.8%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>1.5%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>HER2</td>
<td>8.4%</td>
<td>13%</td>
<td>17%</td>
</tr>
<tr>
<td>Basal</td>
<td>7.1%</td>
<td>21%</td>
<td>16%</td>
</tr>
</tbody>
</table>

* NSW, Australia: Millar et al. JCO 27: 4701, 2009
^ British Columbia: Voduc et al. JCO 28: 1684, 2010

**Similar Results in Other Settings**

<table>
<thead>
<tr>
<th></th>
<th>5-Yr LR BCS + RT</th>
<th>5-Yr LR Mast + RT*</th>
<th>5-Yr LR Pre-op, BCS+RT^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>0.8%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>1.5%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>HER2</td>
<td>8.4%</td>
<td>13%</td>
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<tr>
<td>Basal</td>
<td>7.1%</td>
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</tr>
</tbody>
</table>

* Danish Trials: Kyndi et al. JCO 26: 1419, 2008
^ MD Anderson (No pCR): Yu et al. SABCS 2009 #957
Outcome by Biologic Subtype

The favorable outcome with Luminal cancers is due to some combination of
• intrinsic low aggressiveness
• positive interaction of RT with hormonal therapy

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)

<table>
<thead>
<tr>
<th>Trial</th>
<th>ER Status</th>
<th>10-Year LR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-13 No Chemo</td>
<td>-</td>
<td>13.3</td>
</tr>
<tr>
<td>B-13 Chemo</td>
<td>-</td>
<td>3.5</td>
</tr>
<tr>
<td>B-14 No Tamoxifen</td>
<td>+</td>
<td>11.0</td>
</tr>
<tr>
<td>B-14 Tamoxifen</td>
<td>+</td>
<td>3.6</td>
</tr>
<tr>
<td>B-19 Chemo</td>
<td>-</td>
<td>6.5</td>
</tr>
<tr>
<td>B-20 Tam +/- Chemo</td>
<td>+</td>
<td>4.7</td>
</tr>
<tr>
<td>B-23 Chemo</td>
<td>-</td>
<td>4.3</td>
</tr>
</tbody>
</table>

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
Use of Breast MRI at Diagnosis

<table>
<thead>
<tr>
<th>Not Established</th>
<th>Established</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Re-excision</td>
<td>Multicentricity Found</td>
</tr>
<tr>
<td>Decreased LR</td>
<td>Increased Delays</td>
</tr>
<tr>
<td>Improved Survival</td>
<td>Increased Biopsies</td>
</tr>
<tr>
<td></td>
<td>Increased Costs</td>
</tr>
<tr>
<td></td>
<td>Increased Mastectomy</td>
</tr>
</tbody>
</table>

Effect of Systemic Therapy on LR

- Systemic therapy by itself reduces LR in the absence of RT
- This has been evaluated more with hormonal therapy than with chemotherapy
- There has been interest in the use of tamoxifen instead of RT

Can Tamoxifen Substitute for RT?: 5 Published Trials of Tam +/- RT

<table>
<thead>
<tr>
<th># Patients: Selection</th>
<th>FU (med)</th>
<th>Tam</th>
<th>Tam + RT</th>
<th>5-Yr Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-21 1,009: ≤ 1cm, pN0</td>
<td>87 mths</td>
<td>8.4%</td>
<td>1.1%</td>
<td>LR</td>
</tr>
<tr>
<td>Canadian 769: &gt; 50, T1/2, pN0</td>
<td>67 mths</td>
<td>7.7%</td>
<td>13.2%</td>
<td>LR</td>
</tr>
<tr>
<td>Scottish 427: &lt; 70, T1,2, pN0</td>
<td>67 mths</td>
<td>7%</td>
<td>1%</td>
<td>Crude L-RR</td>
</tr>
<tr>
<td>CALGB 636: &gt; 70, T1, c,pN0</td>
<td>95 mths</td>
<td>25.0%</td>
<td>3.1%</td>
<td>L-RR</td>
</tr>
<tr>
<td>Austrian 869: ≤ 3 cm, gr 1,2, pN0, Tam or AI</td>
<td>54 mths</td>
<td>5.1%</td>
<td>0.4%</td>
<td>LR</td>
</tr>
</tbody>
</table>

The results are quite variable and longer FU needed
Can Tamoxifen Substitute for RT?

• Of note, LR increases after 5 years among patients treated with Tam
• In Canadian and NSABP Trials, LR with Tam is higher at 8 yrs than 5 yrs
• Raises question whether Tamoxifen is merely delaying LR

Canadian Trial – Time to LR

8-Year LR Rate in NSABP B-21

Estimating the Effect of Tam Alone

• Estimating is difficult since these trials did not have a no-treatment arm
• If we assume that RT reduced LR by 70%, then 8-Yr LR in B-21 without any treatment would be 9.3%/3 = 31% and the reduction with Tam alone would be 47% and when added to RT, it is 75%
Giving Tamoxifen instead of RT?

Tamoxifen seems appropriate in older patients (aged ≥ 70) with ER+ cancers, particularly if serious co-morbidities are present.

Can Chemotherapy Substitute for RT?

- Few modern studies have administered chemotherapy in absence of breast RT
- A Canadian trial* of CMFVP (36 wks) vs CMVP-AT (12 wks) included 122 women treated with CS alone; with median FU of 54 mths, ~ 50% of patients had LR
- In NSABP B-06^, N+ pts treated with CS and chemotherapy had a 12-year cum incidence of LR of 41%

*Levine et al. BJC 1992 ^Fisher et al. NEJM 1995

10-Year Results of Canadian Trial of Accelerated WB RT

<table>
<thead>
<tr>
<th></th>
<th>LR</th>
<th>Good-Exc Cosmetic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Gy/25</td>
<td>6.7%</td>
<td>71%</td>
</tr>
<tr>
<td>42.5 Gy/16</td>
<td>6.2%</td>
<td>70%</td>
</tr>
</tbody>
</table>

In subset analysis, 50 Gy/25 was better for gr 3 cancers
Ref: Whelan T et al. NEJM 2010

Can WB RT be Given Faster?

- ‘Canadian fractionation’ 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
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 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)

<table>
<thead>
<tr>
<th>ST Used</th>
<th>Isolated LR</th>
<th>B.C. Mortality</th>
<th>Any Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>0.28</td>
<td>0.87</td>
<td>0.88</td>
</tr>
<tr>
<td>No</td>
<td>0.30</td>
<td>0.95</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**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.

**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**

<table>
<thead>
<tr>
<th></th>
<th>5-Year LR Reduction</th>
<th>15-Year Mortality Reduction</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lum A</td>
<td>22-&gt;2%: 20%</td>
<td>11%</td>
<td>~ 2:1</td>
</tr>
<tr>
<td>Lum B</td>
<td>39-&gt;3%: 36%</td>
<td>23%</td>
<td>~ 1.5:1</td>
</tr>
<tr>
<td>HER2</td>
<td>32-&gt;13%: 19%</td>
<td>- 11%</td>
<td>NA</td>
</tr>
<tr>
<td>Basal</td>
<td>30-&gt;21%: 9%</td>
<td>7%</td>
<td>~ 1:1</td>
</tr>
</tbody>
</table>

**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

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

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

• I am confident that Dr. Buschke would be very proud of this progress