Radiation Therapy in the Management of Breast Cancer

St. Mary’s 14th Annual Oncology Symposium

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November 8, 2008
2007 Estimated Cancer Cases

Women 678,060

- 26% Breast
- 15% Lung & bronchus
- 11% Colon & rectum
- 6% Uterine corpus
- 4% Non-Hodgkin lymphoma
- 4% Melanoma of skin
- 4% Thyroid
- 3% Ovary
- 3% Kidney
- 3% Leukemia
- 21% All Other Sites

- 178,480 invasive cases
- 62,030 in situ cases
- 2,030 male cases (1%)

Source: American Cancer Society, 2007

1980s: ↑↑use of mammography

2000s: ↓↓use of HRT

Sources: ACS, SEER
2007 Estimated Cancer Deaths

Women 270,100

- 26% Lung & bronchus
- 15% Breast
- 10% Colon & rectum
- 6% Pancreas
- 6% Ovary
- 4% Leukemia
- 3% Non-Hodgkin lymphoma
- 3% Uterine corpus
- 2% Brain/ONS
- 2% Liver & bile duct
- 23% All other sites

Source: American Cancer Society, 2007
Breast Cancer Death Facts

- 40,460 deaths in 2007
- 1990-2004: Death rates decreased by 2.2% annually
  - More screening
  - Better treatments
- Largest decline in women <50
- Race disparities are INCREASING
Strong Risk Factors

- **AGE:**
  - 30-39: 1 in 229
  - 50-59: 1 in 37
  - 80-89: 1 in 8
- Personal history of breast cancer
- Personal history of ADH or LCIS
- 1\textsuperscript{st} degree family history of breast cancer
- Chest irradiation as a child or young adult
- Genetic mutations
Genetic Mutations

- **BRCA-1** (chromosome 17)
  - 65% lifetime risk of breast cancer
  - 40% lifetime risk of ovarian cancer
  - Frequently ER-

- **BRCA-2** (chromosome 13)
  - 45% lifetime risk of breast cancer
  - 10% lifetime risk of ovarian cancer
  - Frequently ER+

- Li-Fraumeni syndrome (p53 mutation)
- Cowden syndrome (PTEN mutation)
- Peutz-Jeghers syndrome (STK11 mutation)

Sources: NCI; Antoniou, *Am J Hum Genet* 2003
ACS Screening Recommendations

- Yearly mammograms starting at age 40
  - 15-20% relative risk reduction in breast cancer death
  - 1% absolute reduction in all-cause mortality

- Clinical breast exam every 3 years for women in their 20s and 30s, and every year for women age 40 and older
BSE is No Longer Recommended: Shanghai BSE Trial

- 266,064 women, ages 33-66
- Randomized to control arm or BSE
- No difference in breast cancer deaths
- No difference in diagnosis of invasive cancer
- More biopsies of benign breast lesions in BSE group (i.e., more harm than good)
- Conclusion: BSE should not be advocated; “breast self awareness” is sufficient

Thomas, JNCI 2002
Radiation Therapy in the Management of DCIS
DCIS: Mastectomy versus Breast Conserving Therapy

- No randomized comparisons available
- 1%-2% local recurrence after mastectomy compares favorably to BCT
- 1%-2% breast cancer mortality regardless of treatment approach
- BCT is preferable to mastectomy unless extent of disease prevents complete excision with acceptable cosmesis
DCIS: Randomized RT Trials

- Four randomized controlled trials, aggregate N>4000
  - NSABP B-17 (Fisher, *Semin Oncol* 1998)
  - EORTC 10853 (Bijker, *JCO* 2006)
  - SweDCIS (Emdin, *Acta Oncol* 2006)

- “no tumor at inked margins” on 3 of the 4 trials
  - 20% positive/unknown margins on SweDCIS

- Tamoxifen allowed on 1/4 trials
  - UK/ANZ – complicated multi-arm schema

- RT dose 50 Gy to whole breast
  - No boost on any of the trials
## DCIS Randomized RT Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Time (years)</th>
<th>Overall Breast Recurrences</th>
<th>Invasive Breast Recurrences</th>
<th>DCIS Breast Recurrences</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-17</td>
<td>12</td>
<td>No RT: 31.4%</td>
<td>RT: 15.7%</td>
<td>p&lt;0.000005</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No RT: 16.8%</td>
<td>RT: 7.7%</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No RT: 14.6%</td>
<td>RT: 8.0%</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>EORTC 10853</td>
<td>10</td>
<td>Overall: 26%</td>
<td>RT: 15%</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive: 13%</td>
<td>RT: 8%</td>
<td>p=0.0065</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCIS: 14%</td>
<td>RT: 7%</td>
<td>p=0.0011</td>
<td></td>
</tr>
<tr>
<td>SweDCIS</td>
<td>5</td>
<td>Overall: 22%</td>
<td>RT: 8%</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive: 9%</td>
<td>RT: 4%</td>
<td>p=sig</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCIS: 13%</td>
<td>RT: 4%</td>
<td>p=sig</td>
<td></td>
</tr>
<tr>
<td>UK/ANZ</td>
<td>5</td>
<td>Overall: 14%</td>
<td>RT: 6%</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive: 6%</td>
<td>RT: 3%</td>
<td>p=0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCIS: 7%</td>
<td>RT: 3%</td>
<td>p=0.0004</td>
<td></td>
</tr>
</tbody>
</table>
In 4 randomized trials, no subset has been identified that does not benefit from RT

However, risk of recurrence may vary based on:

- Tumor grade (EORTC)
- Tumor size (B-24)
- Margin status (B-17, EORTC, SweDCIS)
- Comedonecrosis (B-17, B-24)
- Multifocality (B-24)
- Symptomatically detected lesions (EORTC)
- Age ≤ 40 (EORTC)
BCS +/-RT for Favorable DCIS: RTOG 98-04

- MMG detected
- Grade 1-2
- \( \leq 2.5 \) cm
- Inked margins \( \geq 3 \) mm

- RT: 42.5-50 Gy, no boost
- Observation

- Closed in 2006 due to poor accrual (<1/2 of target enrollment)
- Analysis pending but results will be limited
# Modified Van Nuys Prognostic Index

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (cm)</td>
<td>≤1.5</td>
<td>1.6 - 4.0</td>
<td>≥ 4.1</td>
</tr>
<tr>
<td>“Group”</td>
<td>- necrosis</td>
<td>+ necrosis</td>
<td>G3</td>
</tr>
<tr>
<td>Margins (mm)</td>
<td>&gt;10</td>
<td>1 - 9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;60</td>
<td>40-60</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

**Total Score**

- 4 - 6: lumpectomy alone
- 7 - 9: lumpectomy + XRT
- 10 - 12: mastectomy

**Problems**

- Not validated on external datasets
- Model revisions have likely resulted in over-fitting on the training dataset
- Only a small minority of all DCIS patients fall at either extreme

Silverstein, *Breast* 2003
Non-Randomized DCIS Trials: Harvard Observational Study

- Wide excision alone for “favorable” DCIS
  - Mammographic size \( \leq 2.5 \) cm
  - Margins \( \geq 1 \) cm
  - Predominantly nuclear G1 or G2
    - 6% of cases contained G3 disease
  - Comedonecrosis allowed (present in 39%)

- Tamoxifen not permitted
Non-Randomized DCIS Trials: Harvard Observational Study

- Closed early when local recurrence rate met predetermined stopping rules
- 158 patients accrued
- Median follow-up 40 months
- Local recurrence rate: 2.4% per patient-year
- Projected 5-year recurrence rate: 12%

Wong, JCO 2006
Non-Randomized DCIS Trials: ECOG 5194 Observational Study

- Wide excision alone for “favorable” DCIS
  - Grade 1-2, size <2.5 cm
  - Grade 3, size <1 cm
  - Margins ≥3 mm
  - Negative postoperative mammogram

- Tamoxifen allowed

Hughes, SABCS 2006
### Non-Randomized DCIS Trials: ECOG 5194 Observational Study

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>580 patients</td>
<td>102 patients</td>
</tr>
<tr>
<td>Median tumor size 6mm</td>
<td>Median tumor size 7mm</td>
</tr>
<tr>
<td>Median margin 5-10mm</td>
<td>Median margin 5-10mm</td>
</tr>
<tr>
<td>31% declared intention to take tamoxifen</td>
<td>30% declared intention to take tamoxifen</td>
</tr>
<tr>
<td>5-yr local failure rate 6.8%</td>
<td>5-yr local failure rate 13.7%</td>
</tr>
</tbody>
</table>

Hughes, SABCS 2006
Benefit Seen in Elderly Patients

- SEER-Medicare analysis of 3409 women age ≥66
- Stratified by presence of any high-risk features:
  - Tumor >2.5 cm, high grade, comedo histology, age 66-69

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr Breast Recurrence</td>
<td>5-yr Breast Recurrence</td>
</tr>
<tr>
<td><strong>No RT</strong></td>
<td><strong>No RT</strong></td>
</tr>
<tr>
<td>8.2%</td>
<td>13.6%</td>
</tr>
<tr>
<td>p-value</td>
<td>p-value</td>
</tr>
</tbody>
</table>

- Recurrence rates without RT are comparable to ECOG 5194
- Proportional benefit of RT is comparable to NSABP B-17

Smith, *JNCI* 2006
Tamoxifen for DCIS: NSABP B-24

- n=1804
- Stratified by age and method of detection (MMG or PE)

Lumpectomy + RT (50 Gy, no boost)

Lumpectomy + RT (50 Gy, no boost) + Tamoxifen x5 yrs

5-year Results

- All breast events reduced from 13.4% to 8.2%
- Benefit in both ipsilateral and contralateral events
- Benefit greatest for women <50 (38% RRR vs 22% RRR)
- Toxicities greater in women >50 (TE events, GYN cancer)

Fisher, Lancet, 1999
Summary of DCIS Management

- Mastectomy or breast conserving therapy

- Give RT after BCS for most patients
  - Reduces local event risk by about one-half
  - Standard dose is 50 Gy
  - No evidence for boost, but reasonable for high risk (large, G3)

- Consider observation after BCS for select patients
  - <1 cm size, pure G1-2, with 5-10 mm negative margins, age>60

- Consider Tam for all patients, especially
  - ER+
  - Age <50 years old
Management of Early Stage Breast Cancer
Mastectomy vs BCT: Randomized Trials

- Seven randomized trials
- In aggregate 4100 patients with 3.3-20 years follow up
- Equivalent disease-specific and OS
- Local-regional control
  - Was not an endpoint for most trials
  - In-breast recurrences frequently censored
Local Control for Mastectomy vs BCT: Meta-Analysis

- *Indirect* 10-year comparisons suggest that BCT is equivalent to mastectomy for early stage disease:

<table>
<thead>
<tr>
<th></th>
<th>Node Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>8.0%</td>
</tr>
<tr>
<td>BCS+RT</td>
<td>10.0%</td>
</tr>
</tbody>
</table>
## BCS vs BCS+RT: Randomized Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Yrs</th>
<th>IBTR (%)</th>
<th>IBTR (%)</th>
<th>IBTR event</th>
<th>N stage</th>
<th>CT/HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B06</td>
<td>1137</td>
<td>20</td>
<td>39.2</td>
<td>14.3</td>
<td>1st</td>
<td>N0-1</td>
<td>CT</td>
</tr>
<tr>
<td>Britain</td>
<td>400</td>
<td>20</td>
<td>49.8</td>
<td>28.6</td>
<td>any</td>
<td>N0-1</td>
<td>both</td>
</tr>
<tr>
<td>Ontario</td>
<td>837</td>
<td>10</td>
<td>40</td>
<td>18</td>
<td>1st</td>
<td>N0</td>
<td>none</td>
</tr>
<tr>
<td>Milan III</td>
<td>579</td>
<td>10</td>
<td>23.5</td>
<td>5.8</td>
<td>any</td>
<td>N0-1</td>
<td>both</td>
</tr>
<tr>
<td>Uppsala</td>
<td>381</td>
<td>10</td>
<td>24</td>
<td>8.5</td>
<td>any</td>
<td>N0</td>
<td>none</td>
</tr>
<tr>
<td>NSABP B21</td>
<td>673</td>
<td>8</td>
<td>16.5</td>
<td>2.8</td>
<td>1st</td>
<td>N0</td>
<td>HT</td>
</tr>
<tr>
<td>Scotland</td>
<td>585</td>
<td>5.7</td>
<td>24.5</td>
<td>5.8</td>
<td>any</td>
<td>N0-1</td>
<td>both</td>
</tr>
</tbody>
</table>
Local Control with BCS vs BCS+RT: Meta-Analysis

Node Negative Patients

10 yr difference:
19% absolute
66% relative

Node Positive Patients

10 yr difference:
33% absolute
72% relative

EBCTCG, Lancet 2005
Breast Cancer Survival with BCS vs BCS+RT: Meta-Analysis

Node Negative Patients

Breast cancer mortality, %

15 year difference:

5.1% absolute
16.3% relative

Node Positive Patients

Breast cancer mortality, %

15 year difference:

7.1% absolute
12.9% relative

EBCTCG, Lancet 2005
Radiation after BCS Summary

- Improves local control by 20-30%
  - Two-thirds relative risk reduction

- Improves breast cancer survival by 5-7%
  - 15% relative risk reduction

Local control gains lead to survival gains!
Omission of RT for Widely Negative Margins: Milan III

Tumor ≤2.5 cm

Quadrantectomy + ALND

Quadrantectomy + ALND + RT (50 Gy + 10Gy boost)

10-year Results

- IBTR 23.5% without RT, versus 5.8% with RT (p<.001)

Veronesi, *Annals Oncol* 2001
Systemic Therapy vs RT for Favorable Disease: NSABP B-21

Tumor ≤1cm Node negative BCS+ALND

Tamoxifen x 5 years
RT (50 Gy +/-boost)
RT + Tam

Primary endpoint: ipsilateral breast tumor recurrence (IBTR)

Fisher, JCO 2002
Systemic Therapy vs RT for Favorable Disease: NSABP B-21

8-yr IBTRs:

Tam: 16.5%
RT: 9.3%
RT+Tam: 2.8%

RT benefited all age groups

Fig 1. Cumulative incidence of IBTR after treatment with TAM, XRT and placebo, or XRT and TAM. Pairwise comparisons: TAM v XRT + placebo: P = .006; TAM v XRT + TAM: P < .0001; XRT + placebo v XRT + TAM: P = .01.

Fisher, JCO 2002
PBI Rationale

- 20-40% of patients do not receive RT after breast-conserving surgery
  - proximity of RT facility
  - duration of standard therapy

- >70% of in-breast recurrences are at/near the tumor bed (Veronesi, *NEJM* 2002; Liljegren *JCO* 1999)

- Partial breast irradiation has the potential to
  - Control the tumor
  - Increase treatment compliance
  - Minimize side effects
PBI versus WBI: RTOG 04-13

DCIS or invasive cancer
Tumor ≤3cm
0-3 positive nodes
Breast-conserving surgery

Dec 2006: closed to low risk patients (ER+, node-, age>50)

- 1° endpoint: Local control
- 2° endpoints: DF, OS, cosmesis, side effects

Whole breast irradiation (45-50Gy in 1.8-2.0Gy fx, +/-boost)

Partial breast irradiation (physician chooses technique)

Multi-catheter brachytherapy (34Gy in 3.4Gy fx BID)

MammoSite (34Gy in 3.4Gy fx BID)

3D conformal external beam RT (38.5Gy in 3.85Gy fx BID)
PBI: Multicatheter Brachytherapy

Per RTOG 04-13:
Implant may be single plane or multi-plane
PBI: MammoSite

Per RTOG 04-13:
Distance from balloon to skin must be $\geq 5$mm
Per RTOG 04-13:
Electrons not allowed
Beams may not be directed toward critical structures
RTOG 04-13: 3D Conformal EBRT
Target Volume Construction

GTV = Seroma + clips

CTV = GTV + 15mm – skin, pec

PTV = CTV + 10mm

PTV_eval = PTV – skin, pec
Most Data Still Short-Term

- Multicatheter brachytherapy:
  - Long-term Phase I/II data

- MammoSite:
  - Short-term registry data
  - Short-term Phase II data for DCIS

- 3D-conformal EBRT:
  - Short-term Phase I/II data
Long-term Data on PBI: Multicatheter Brachytherapy

- William Beaumont Hospital
- Phase I/II trial
- N=199
- Tumor ≤3 cm, N0-1 (82% T1 N0)
- Generous volume treated (tumor bed +2cm)
- 10-yr actuarial breast recurrence rate 3.8%
- 10-yr actuarial regional nodal failure rate 1.6%

Vicini, IJROBP 2007
PBI Summary

- PBI may prove to be an important advance in the treatment of early breast cancer

- However, it is still unproven against a highly effective and minimally toxic gold standard (whole breast irradiation)

- Therefore, it is best administered in the context of a rigorous clinical trial

- Physician support of RTOG 04-13 is crucial to generate high-quality evidence on PBI
PBI Off Protocol

- Follow the American Brachytherapy Society’s eligibility guidelines!
  - Age ≥50
  - Infiltrating ductal carcinoma histology
  - Tumor ≤3 cm, unicentric and unifocal
  - No EIC
  - Pathologically node negative

ABS Breast Brachytherapy Task Group, 2007
# Accelerated Whole Breast RT

## Canadian Trial
- **Whelan, SABCS 2007**
- T1-T2 N0
- Mostly T1 and age >50
- 50 Gy/25 fractions versus 42.5 Gy/16 fractions
- No boost given
- 12-yr results:
  - Identical local control
  - Identical overall survival
  - Identical cosmesis

## UK Start-B Trial
- **Dewar, ASCO 2007**
- T1-T3 N0-N1
- Tumor size, age NA
- 50 Gy/25 fractions versus 40 Gy/15 fractions
- Stratified by +/-boost
- 5-yr results:
  - Identical local control
  - Better cosmesis with 40 Gy/15 fractions

## Conclusions:
- 42.5 Gy/16 fractions is safe & effective for T1 N0 and age >50
- Decision to boost is independent of whole breast fx schedule
Timing Comparisons

- Standard 5 weeks of daily XRT (+/--boost)
- Canadian fractionation 4240 cGy in 3 wks
  - >50yo with T1N0
- RTOG Partial Breast Irradiation in 1 week
Radiation in the Management of Elderly Patients
Omission of RT for Elderly Patients: CALGB C9343

- Age ≥70
- Tumor ≤2cm
- Clinically node negative
- ER+ or unknown
- BCS, no ALND

- Tamoxifen x 5 years
- Tam + RT (breast and low axilla, 45Gy + 14Gy boost)

Endpoints: LRR, mastectomy, DM, survival

Hughes, NEJM 2004
Omission of RT for Elderly Patients: CALGB C9343

Trend toward increased mastectomies with Tam only (p=.07)

No difference in DM, breast cancer-specific survival, or OS

Hughes, NEJM 2004; SABCS 2006
Omission of RT in Elderly Patients: SEER-Medicare

- 8724 women age ≥70
- CALGB C9343 eligible
- IBTR rates similar to CALGB

However:
- Higher risk of subsequent mastectomy without RT (p<.001)
- RT most beneficial for women 70-79 with minimal comorbidity (8 yr IBTR 16% vs 3%)

<table>
<thead>
<tr>
<th></th>
<th>5yr IBTR</th>
<th>8yr IBTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No RT</td>
<td>5.1%</td>
<td>8.0%</td>
</tr>
<tr>
<td>RT</td>
<td>1.1%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Smith, *JNCI* 2006
### Life Expectancy for the Elderly

<table>
<thead>
<tr>
<th>Current Age</th>
<th>Life Expectancy (years)</th>
<th>Expected Age at Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>23.53</td>
<td>84</td>
</tr>
<tr>
<td>70</td>
<td>15.72</td>
<td>86</td>
</tr>
<tr>
<td>75</td>
<td>12.29</td>
<td>87</td>
</tr>
<tr>
<td>80</td>
<td>9.22</td>
<td>89</td>
</tr>
<tr>
<td>83</td>
<td>7.59</td>
<td>90</td>
</tr>
<tr>
<td>84</td>
<td>6.88</td>
<td>91</td>
</tr>
<tr>
<td>85</td>
<td>6.42</td>
<td>91</td>
</tr>
</tbody>
</table>

- Healthy elderly women are likely to live long enough to risk increased relapse of breast cancer

Source: Social Security Administration
Discuss RT with all patients after BCS

*Consider* omitting RT for
- $\geq 70$ with T1 N0, ER+ tumors
- Fit for and willing to take endocrine therapy x5 years

Omission of RT is probably best reserved for
- women age 70-79 with multiple comorbidities
- women age $>80$ (LE <8 years)

For some women, RT may be preferable to HT
Management of Intermediate Stage Breast Cancer
Main Difference is Nodal Risk

- Axillary involvement of 1-3 LNs predicts for:
  - Involvement of other regional nodes
  - Increasing risk of distant failure and death

- Tumor size and location may increase the regional nodal risk in node-negative patients

- Lymph nodes at risk include axillary, SCV, ICF, IMN
Nodal RT For Intermediate Dz

SCV RT
- NCCN and ASCO:
  - Category 2B recommendation for 1-3 +nodes
  - Insufficient evidence to make any recommendation in T3 N0 patients

IMN RT
- NCCN:
  - Category 3 recommendation for high-risk patients
- ASCO:
  - Insufficient evidence to make any recommendation for any patients
Nodal RT for Intermediate Disease: EORTC 22922

Axillary node+ or central/medial tumor
BCS or mastectomy

RT to breast/CW only

RT to breast/CW + SCV + IM

1° endpoint: Overall Survival
Closed to accrual; results pending
Nodal RT for Intermediate Disease: NCIC MA-20

BCS only
N+ or
T3 N0 or
T2 N0 and high risk (ER-, Gr3, LVSI)

# of nodes +
chemotherapy
hormonal therapy
institution

1° endpoint: Overall Survival
Closed to accrual; results pending

RT to breast
RT to breast+
axilla+
SCV+IM
Target Delineation: SCV Nodes

- Conventional prescriptions using 6 MV photons miss the target in 80% of obese patients.
- For all BMI classes, CT-delineated targets and individually optimized treatment planning achieves the best coverage.

Liengsawangwong, *IJROBP* 2007
IMN XRT Technique

- Tumor bed
- IMN
- Lateral Tangents
- Medial Electrons
Alternative Technique

IM Nodes

Tumor Bed
Management of Breast Cancer in the Setting of Neoadjuvant Chemotherapy
**Oxford Overview: Adjuvant CTX**

### Local Recurrence
- **LN- Disease**: 8% vs. 3%
- **LN+ Disease**: 29% vs. 8%

- 2/3 reduction w/ RT

### Breast Ca Survival
- **LN- Disease**: none
- **LN+ Disease**: 5% for LN+ pts

- 60% vs. 55%

---

1428 women treated with mastectomy, AC chemotherapy +/- RT
Historical Guidelines for XRT

- Upfront surgery provided pathology
- Pathology was the gold standard
- ECOG, MDACC, NSABP
  - tumor size over 5 cm (T3)
  - 4 or more lymph nodes (N2)
Defining LRR Risk after NCT + Mastectomy

150 patients, 1974-1998 at MDACC

- treated on prospective clinical trials
- neoadjuvant chemotherapy
- modified radical mastectomy
- no radiation therapy

Buchholz et al., JCO, 2002
Factors Associated with LRR

Clinical Factors
- clinical stage
- T stage
- N stage

Treatment Factors
- tamoxifen use

Residual Cancer Burden (RCB)
- number of +LN
- primary tumor size
## Multivariate Analysis

<table>
<thead>
<tr>
<th>Factors</th>
<th>$p$ value</th>
<th>hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>clinical IIIB/C</td>
<td>&lt;0.001</td>
<td>4.5</td>
</tr>
<tr>
<td>4 or more + LN (ypN2)</td>
<td>0.008</td>
<td>2.7</td>
</tr>
<tr>
<td>no tamoxifen use</td>
<td>0.027</td>
<td>3.9</td>
</tr>
</tbody>
</table>
LRR According to Response

5-yr LRR by Path Response

- path CR (n=18) 19%
- residual disease (n=132) 28%

p=0.413

4/18 failures - Stages: T3N0, T2N2, T4N2, T4Nx
Recurrences in Clinical Stage I/II

Garg et al., Int J Radiat Oncol Biol Phys, 2004
Recurrences by Axillary RCB

- $n = 6$
- $n = 84$ (LRR 6%)
- $n = 42$ (LRR 8%)
- $\geq 4+ LN$ (LRR 67%)

$P = < 0.0001$
B-18 Study
1230 women with operable breast cancer were randomized to preop vs postop ACx4
- mastectomy patients did not receive radiation
- 87% of pts in the trial had T1, T2 tumors
- total population of NCT + mastectomy – 239 pts

Mamounas, SABCS, 2003
LRR According to Response

10-yr LRR by Path Response (B-18)

- breast CR w/ LN- or LN+ (n=13) 0%
- residual breast disease w/ LN- 10.5%
- residual breast disease w/ LN+ 20.3%

Not much different between 1-3+LN or ≥4 +LN
Is PMRT Necessary after a Favorable Response to Neoadjuvant Chemotherapy?
MDACC trials +/- PMRT

713 patients
Neoadjuvant
Doxorubicin-based chemotherapy

Mastectomy

136 patients
No XRT

579 patients
+ XRT

XRT: Non-randomized
6 consecutive prospective MDACC trials
1974-1998

Huang et al., JCO, 2005
Caveats

• Radiation use was not randomized

• Selection of who received radiation

• Excluded recurrences < 2 months of Rx
  – 11% of no XRT group excluded
  – 3% of XRT group excluded
Chemotherapy Phase II and III Trials

- All treated with doxorubicin
- Mastectomy: median LN = 15 removed
- Radiation to chest wall and LNs
  - median dose 50 Gy
  - boost to 60Gy
Comparisons Between Groups

Irradiated patients had **significantly worse disease:**

- Clinical T3-4
  - RT: 56%
  - No RT: 85%
- Clinical N2-3
  - RT: 44%
  - No RT: 20%
- Minimal response
  - RT: 24%
  - No RT: 11%
- 4 or more pos. nodes
  - RT: 39%
  - No RT: 22%
- Close/pos. margins
  - RT: 12%
  - No RT: 3%

*P < .01 for all factors*
Local-Regional Recurrence

\[ P < .0001 \]
Local-Regional Recurrence By Extent of Disease

<table>
<thead>
<tr>
<th>Factor</th>
<th>No Radiation (%)</th>
<th>Radiation (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical T-stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0</td>
<td>8</td>
<td>.535</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
<td>7</td>
<td>.408</td>
</tr>
<tr>
<td>T3</td>
<td>22</td>
<td>8</td>
<td>.002</td>
</tr>
<tr>
<td>T4</td>
<td>46</td>
<td>15</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Clinical N-stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>23</td>
<td>10</td>
<td>.014</td>
</tr>
<tr>
<td>N1</td>
<td>14</td>
<td>9</td>
<td>.062</td>
</tr>
<tr>
<td>N2-3</td>
<td>40</td>
<td>12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Pathological tumor size, cm</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>13</td>
<td>8</td>
<td>.051</td>
</tr>
<tr>
<td>2.1-5.0</td>
<td>31</td>
<td>14</td>
<td>.002</td>
</tr>
<tr>
<td>≥ 5.0</td>
<td>52</td>
<td>13</td>
<td>.001</td>
</tr>
<tr>
<td><strong>No. of positive nodes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>11</td>
<td>4</td>
<td>.010</td>
</tr>
<tr>
<td>1-3</td>
<td>13</td>
<td>11</td>
<td>.636</td>
</tr>
<tr>
<td>≥ 4</td>
<td>59</td>
<td>16</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Local-Regional Recurrence

Clinical Stage I-II

9% vs 5%
P = 0.82

Clinical Stage III

20% vs 9%
P = 0.009
## Local-Regional Recurrence

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>Hazard</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No radiation</td>
<td>4.1</td>
<td>.0001</td>
</tr>
<tr>
<td>≥20% pos. nodes</td>
<td>2.9</td>
<td>.0001</td>
</tr>
<tr>
<td>Stage ≥ IIIB</td>
<td>2.3</td>
<td>.001</td>
</tr>
<tr>
<td>Nodes sampled &lt; 10</td>
<td>2.0</td>
<td>.005</td>
</tr>
<tr>
<td>No tamoxifen</td>
<td>1.9</td>
<td>.034</td>
</tr>
<tr>
<td>ER negative</td>
<td>1.8</td>
<td>.014</td>
</tr>
<tr>
<td>Path size &gt;2cm</td>
<td>1.7</td>
<td>.026</td>
</tr>
</tbody>
</table>
Cause Specific Survival

Univariate Analysis by Stage & Lymph Node Status:
RT improved CSS ~20%

Clinical T4

≥ 4 nodes

Stage IIIB/C

P=.011
39%

P=.002
22%

P=.015
44%

P=.002
24%
### Cause-specific Survival

<table>
<thead>
<tr>
<th>Univariate subset analysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>• clinical stage IIIB/C</td>
<td>0.002</td>
</tr>
<tr>
<td>• clinical T4 tumors</td>
<td>0.015</td>
</tr>
<tr>
<td>• 4 or more positive nodes</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Radiation improved CSS ~ 20%
## Cause-specific Survival

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>Hazard</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage (\geq) IIIB</td>
<td>2.4</td>
<td>.0001</td>
</tr>
<tr>
<td>Path. tumor size (&gt;0) cm</td>
<td>2.3</td>
<td>.001</td>
</tr>
<tr>
<td>(\geq) 4 positive nodes</td>
<td>2.1</td>
<td>.0001</td>
</tr>
<tr>
<td>No radiation</td>
<td>1.8</td>
<td>.001</td>
</tr>
<tr>
<td>Nodes sampled (&lt;10)</td>
<td>1.5</td>
<td>.004</td>
</tr>
<tr>
<td>ER negative</td>
<td>1.5</td>
<td>.003</td>
</tr>
</tbody>
</table>
LRR in Stage III Patients after a pCR

McGuire et al., Int J Radiat Oncol Biol Phys,
DM-Free and OS in Stage II Patients after a pCR
Radiotherapy Techniques to Decrease Skin Toxicity
CT Simulation For Breast Radiotherapy

- Optimizes target delineation
  - Tumor bed
  - Regional nodes

- Facilitates patient tailored 3D-conformality
  - Better coverage of target volumes
  - Reduces cardiac and pulmonary exposure
  - Reduces acute effects
  - May improve cosmetic outcome
Traditional Physical Wedges

- Wedge acts as a tissue compensator for smaller separation at nipple region, thereby reducing anterior hot spots
Intensity Modulated Breast Radiation

- Usually involves standard tangent beam arrangement
- Forward or inverse planned MLC segments
- Less contralateral breast dose than physical wedging
- Better dose homogeneity than dynamic wedging
- Reduces acute effects, which should improve QOL and cosmesis
**IMRT Field in Field Treatment Technique**

- Forward-planned intensity modulation

- Open tangents + 2-8 static MLC-reduced fields
  - All fields share same beam orientation
  - MLC-reduced fields block regions with >100% of dose
Field in Field: 1st MLC Reduction

Highest dose hot spot is blocked on medial field

Relative weighting of blocked field is increased until hot spot disappears
Field in Field: 2nd MLC Reduction

Next highest dose hot spot is blocked on lateral field

Relative weighting of blocked field is increased until hot spot disappears
Field in Field Technique

- Process is repeated until an optimally homogenous treatment plan is generated
- No extra work for physicians (no organ contouring)
- Labor-intensive for dosimetrists/physicists
Inverse Planned IMRT

- Standard tangents or multi-beam
- Breast and normal structures are contoured
- Cost functions applied to critical structures
- Reduces dose to heart
  - if multiple beams are used, low dose is spread to more normal tissues
- Labor intensive for physicians

Chiu, Med Phys 2002; Krueger, Semin Rad Oncol 2002
IMRT versus Wedging: Canadian Phase III Trial

Breast-only RT
Stratified by breast size and use of boost

IMRT 50 Gy +/-16 Gy boost
Wedging 50 Gy +/-16 Gy boost

1° Endpoints: Grade 3-4 acute skin reactions
Grade 2-4 moist desquamation

Pignol, ASTRO 2006
IMRT versus Wedging: Canadian Phase III Trial

- **IMRT arm:**
  - Tangent beams with segment modulation
  - Most (78%) inverse planned

- **Wedge compensation arm:**
  - Most treated with dynamic wedging

- **Skin toxicity assessed by a blinded researcher**
  - Weekly during treatment
  - Until 6 weeks post-treatment

Pignol, ASTRO 2006
Phase III Trial of IMRT vs Wedging: Results

- IMRT reduced moist desquamation:

<table>
<thead>
<tr>
<th>Moist desquamation</th>
<th>WC</th>
<th>IMRT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inframammary fold</td>
<td>43%</td>
<td>26%</td>
<td>.0012</td>
</tr>
<tr>
<td>All quadrants</td>
<td>48%</td>
<td>31%</td>
<td>.0019</td>
</tr>
</tbody>
</table>

- IMRT reduced any acute skin reaction in the inframammary fold (OR .262)

Pignol, ASTRO 2006
Prone Positioning Technique
Prone Dosimetry
Prone Breast Irradiation: Outcomes

- MSKCC: prone standard fractionation WBI
  - 245 patients treated between 1992-2004
  - Median follow-up 4.9 years
  - 5-yr IBTR rate 6.1%
  - Acute grade 3 skin reactions 4%
  - Chronic grade 2 skin toxicity 4.4%
  - Chronic grade 2 subcutaneous toxicity 13.7%

Stegman et al, IJROBP 2007
Radiotherapy Techniques to Decrease Cardiac Toxicity
Respiratory Gating for Cardiac Protection in Breast Radiotherapy

- Best technique is deep inspiration breath hold
- Displaces heart from tangent field edge
- Useful in select left breast cancer patients
- Varian RPM system used at MDACC is well tolerated by patients and only modestly increases simulation and daily treatment time
Cardiac Shape & Location Change
Image Guidance in Treatment Delivery: Respiratory Gating

Reflective marker

Infrared tracking camera
DIBH Reduces Cardiac Exposure

Free Breathing  Deep Inspiration Breath Hold
Among early stage left breast cancer patients receiving tangential breast RT:

<table>
<thead>
<tr>
<th></th>
<th>Heart V50 (mean)</th>
<th>Left ventricle V50 (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FB</td>
<td>3.9%</td>
<td>12.7-14.6%</td>
</tr>
<tr>
<td>DIBH</td>
<td>0.7%</td>
<td>1.5-2.7%</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Krauss, *IJROBP* 2005
DIBH and Cardiac Protection

Among advanced stage left breast cancer patients receiving comprehensive RT via a 3-field technique (deep tangents + AP SCV field):

<table>
<thead>
<tr>
<th></th>
<th>Heart V50 (median)</th>
<th>LAD V50 (median)</th>
<th>NTCP: cardiac mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>FB</td>
<td>19.2%</td>
<td>88.9%</td>
<td>4.8%</td>
</tr>
<tr>
<td>DIBH</td>
<td>1.9%</td>
<td>3.6%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Korreman SS et al, Radiother Oncol 2005; IJROBP 2006
Summary

- RT confers LC benefit in node- disease and a survival benefit in node+ disease

- After neoadjuvant chemotherapy, PMRT for Stage II should consider RCB
Summary

- Patients with Stage III require PMRT even after achieving a pCR

- Modern technology and imaging permit safe delivery with minimal toxicity
Acknowledgements

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