Radiation Therapy following BCS: More, Less or Not at All

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In early-stage breast cancer, Radical Mastectomy was common until mid-1970s. Today, Breast Conserving Surgery is most common.
Early Breast Cancer Trialists’ Collaborative Group

(17 randomized trials of BCS +/- RT; 1976-1999; 10,801 women)

Conclusion: RT, generally to the whole breast, after Breast Conserving Surgery reduced recurrences and improved survival
Radiation Therapy following BCS: More, Less or Not at All

Pauline Truong: Treat the nodes too?
Tanya Berrang: Just treat part of the breast?
Sally Smith: Women who don’t need RT?
More? Nodal RT after BCS

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Radiation Oncologist, BCCA, Vancouver Island
Clinical Professor, UBC
RT volume vs Level I/II AxD

RT to Breast alone
(possible inclusion of part of level I/II axilla)

RT to Breast + Nodes
(axilla, supraclavicular, internal mammary nodes)
<table>
<thead>
<tr>
<th>RT Risk Benefit Ratio: Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short term</strong></td>
</tr>
<tr>
<td>• inconvenience</td>
</tr>
<tr>
<td>• fatigue</td>
</tr>
<tr>
<td>• breast pain</td>
</tr>
<tr>
<td>• skin reaction</td>
</tr>
<tr>
<td><strong>Long term</strong></td>
</tr>
<tr>
<td>• lymphedema</td>
</tr>
<tr>
<td>• pneumonitis</td>
</tr>
<tr>
<td>• cardiac injury</td>
</tr>
<tr>
<td>• brachial plexopathy</td>
</tr>
<tr>
<td>• rib fracture</td>
</tr>
<tr>
<td>• poor cosmesis</td>
</tr>
<tr>
<td>• secondary malignancies</td>
</tr>
</tbody>
</table>
Why consider adding nodal RT?

Oxford Overview: 25 Trials, 8505 women, N+, Mastectomy
Chest wall + nodal RT improves local control + survival

LRR

\[ \downarrow \] BrCa death

\[ \downarrow \] 5%

\[ \downarrow \] 20%

Mastectomy

Mastectomy + RT

EBCTCG Lancet 2005
Why consider adding nodal RT?

ASTRO, ASCO and Canadian Guidelines:

• Recommended postmastectomy chest wall + nodal RT for:
  * advanced primary tumors (T > 5 cm or invasion of skin, pectoral muscle or chest wall)
  * high volume nodal burden: ≥4 +ve nodes; large, matted nodes; extranodal extension

• Recognized controversy and need for further study among women with 1-3 +ve nodes and/or women treated with BCS

ASTRO: Harris IJROBP 2001
ASCO: Recht JCO 2003
Canadian CPG: Truong CMAJ 2004
Trial Data Impacts Practice in BC

NCIC MA20 study opens in British Columbia

Publication of randomised post-mastectomy radiotherapy trials

Wai E et al. Radiother Oncol 2010
NCIC MA20 Trial

1832 Node-positive or High-risk N0 after BCS + AxD

All had chemo and/or hormones

RT to Breast alone

RT to Breast + Nodes

Whelan, Olivotto et al. Proc ASCO 2011; abs LB1
MA20 Baseline Characteristics: well balanced

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Br alone RT (N=916)</th>
<th>Br+ Nodal RT (N=916)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean yrs)</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Axillary nodes removed (mean)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Node –ve</td>
<td>89 (10)</td>
<td>89 (10)</td>
</tr>
<tr>
<td>Nodes 1-3 +ve</td>
<td>780 (85)</td>
<td>776 (85)</td>
</tr>
<tr>
<td>Tumor size &gt; 2 cm</td>
<td>416 (45)</td>
<td>457 (50)</td>
</tr>
<tr>
<td>Grade III</td>
<td>387 (42)</td>
<td>390 (43)</td>
</tr>
<tr>
<td>ER –ve</td>
<td>235 (26)</td>
<td>232 (25)</td>
</tr>
<tr>
<td>Adj chemotherapy</td>
<td>829 (91)</td>
<td>830 (91)</td>
</tr>
<tr>
<td>Adj endocrine therapy</td>
<td>705 (77)</td>
<td>700 (76)</td>
</tr>
<tr>
<td>Boost RT</td>
<td>221 (24)</td>
<td>206 (22)</td>
</tr>
</tbody>
</table>
Actuarial 5-year rates: 94.5% vs. 96.8%
$p = 0.02; HR = 0.58$

Equal # local recurrence events: 25 in each arm
# regional recurrence events: 23 vs 4
Distant Disease-Free Survival

Actuarial 5 year rates: 87.0% vs. 92.4%

\[ \Delta 5yr = 5.4\% \]

\[ p = 0.002 \]

\[ HR = 0.64 \]
Overall Survival

Actuarial 5-year rates: 90.7% vs. 92.3%

\[ \Delta 5\text{yr} = 1.6\% \text{ and growing} \]

\[ p = 0.07 \]

\[ HR = 0.76 \]
# Adverse Events

*(NCI – Common toxicity criteria v2.0, 1998)*

<table>
<thead>
<tr>
<th></th>
<th>Br alone RT (n=927)</th>
<th>Br+ Nodal RT (n=893)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4/5</td>
</tr>
<tr>
<td><strong>Acute</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT dermatitis</td>
<td>349</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Delayed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphedema</td>
<td>34</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Δ5yr = 1.1%**

**Δ5yr = 3.2%**

*Patients and Assessors were not blinded to treatment allocation*
MA20: Implications on Practice

- 85% of subjects were 1-3 N+ve
- Nodal RT added to Breast RT improved 5-yr
  - Loco-Regional RFS
  - Distant RFS
- Trend to improved Overall survival
- Nodal RT conferred small increased adverse effects, including pneumonitis (1%) and lymphedema (3%)
Can Ax Dissection be Omitted in Selected Pts with 1-2 +ve SLN?

- Randomized 891 pts with cT1-2 tumor with H&E-positive SLNs to AxD vs no further axillary surgery
- 40% had micrometastasis or isolated tumor cells
- In AxD group, 27% had additional metastasis
- All pts received whole breast RT (possible inclusion of level I/II axilla)
- Trial closed early before reaching targeted 1900 pts
- At 6 years: no Δ in axillary recurrence, LRR, DFS and OS

Giuliano JAMA 2011
ACOSOG Z0011 has changed practice in BC

- AxD no longer routinely performed in pts who meet all criteria of:
  - T1-2 tumors
  - 1-2 positive SLNs without extranodal ext
  - acceptance of adjuvant RT

- Cases in which Z0011 results are not directly applicable (eg. T3 tumors, >2 positive SLN, extranodal disease, mastectomy) are discussed at multidisciplinary conference
What about ‘high risk N0’?

Defined in MA20 as:

– $T \geq 5$ cm, or

– $T \geq 2$ cm and $< 10$ nodes removed

with Gr 3 or LVI+ or ER –ve
Population-based outcomes in women with MA20-defined high-risk N0 breast cancer

- BCCA Breast Cancer Outcomes Unit:
  - identified 11,865 women diagnosed 1989-2005, with pT1-3, 0-3 positive nodes, M0
  - All had BCS + adjuvant breast RT
  - Of 9201 pN0 cases, 550 (6%) met MA20-defined high-risk N0 criteria.

Truong  CARO 2012
Results

- Nodal RT use
  - 1% in ‘non high risk N0’,
  - 5% in ‘MA20-defined high risk N0’
  - 44% in 1-3 N+

- Systemic therapy: 51%, 79% and 95% of the three cohorts (p<0.001)

- Multivariable analysis of N0 subjects: significantly increased regional and distant relapse with:
  - T>2cm
  - Grade 3
  - LVI
10-year outcomes in ‘high risk N0’ similar to 1-3N+

LRR

Dist mets

Survival
What strategies to spare heart & lung?

9-Beam IMRT reduced heart V30Gy, Lung V20 and mean dose to Healthy Tissue

Colorwash shows volume receiving >80% of prescribed dose
IMRT increased volume of heart and other healthy tissues receiving 2-5Gy

Colorwash shows volume receiving >10% of prescribed dose
Deep Inspiration Breath Hold

Varian RPM Gating System

Wai et al. IJROBP 2008
Free Breathing

Deep Inspiration
Breath Hold
Summary
When to consider nodal RT after BCS?

• All women with node +ve disease should be offered the option of Nodal RT after BCS, especially if no AxD after positive SLNB.

• Women with node –ve disease meeting high risk criteria of T>5cm or T>2cm, <10 nodes removed, with grade 3, or LVI, or ER-ve disease are a small minority of N0 patients who warrant similar RT consideration as women with 1-3N+
Summary
When to consider nodal RT after BCS?

- Patients should be informed of the potential benefits and be willing to accept potential toxicities with added nodal RT.

- Care team should apply careful RT planning to ensure adequate coverage of regions at risk and to minimize normal tissue exposure, esp cardiac/pulmonary structures.
‘Less’ radiation post breast conserving surgery?

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Clinical Assistant Professor, UBC
Goals of Breast Conservation

• Don’t compromise outcome

• Optimize cosmetics

• Optimize patient convenience/QOL
Partial Breast Irradiation (PBI)

- RT to smaller volume of breast
- Higher dose per day
- Shorter time/ more convenient
Low Risk Women Post BCS

- age >40
- \( \leq 3 \text{cm} \) tumours
- margin negative
- node negative
- LVI negative
What do we need to worry about?

1. Where is the risk of recurrence?

2. Normal tissue tolerance to RT
Local Recurrence post BCS

- 70 - 80% close to the primary tumour bed or ‘seroma’
- Do we need to treat the whole breast?
Cancer Control

• High dose/fraction

Normal Tissue Toxicity

• Low dose/fraction
Whole Breast RT

25+ fractions

16 fractions
Whole Breast RT

25+ fractions 😊

16 fractions 😊

<16 fractions 😞
Whole Breast RT

25+ fractions

16 fractions

<16 fractions

Partial Breast <16 fractions?
Whole Breast RT

25+ fractions

16 fractions

<16 fractions

Partial Breast <16 fractions?

(10 fractions in 5 days)
What is the target for PBI?

Pre-op tumour location
What is the target for PBI?

‘Ideal’ Target
What is the target for PBI?

Seroma + Clips
What is the target for PBI?

‘Actual’ Target
Various Techniques for PBI

Mammosite

Intra-op 50Kv, (Targit)

Intra-op electrons (Milan)

HDR Brachytherapy

Permanent Seed Brachytherapy

3D Conformal Photons
3D conformal Partial Breast
Most commonly used because techniques and resources are available in most RT departments

4 beam PBI
Dose localized
Whole vs. Partial Breast RT

- 3.5 to 5+ weeks
- 42.5-50 Gy
- Once daily treatment
- 2 beams
- Target = whole breast

- 5 to 8 days
- 38.5 Gy
- Twice a day
- 3-5 beams
- Target = seroma + margin
Canadian Pilot Study

• 120 women prospectively accrued (2005-2006)

• Low risk
  – Node negative
  – Invasive or DCIS ≤ 3cm
  – Negative margins

• 5 Canadian centres

• External Beam PBI (3-5 fields)
104 women treated with PBI
3 year follow-up

- 97% DFS

- toxicity data (84% of patients)
  - Most toxicities were Grade 1

- Cosmesis was good to excellent in 86% at baseline and 82% at 3 years

Berrang et al. IJROBP 81(5) 1220:2011
PBI Trial Eligibility

**RAPID**
- Age $\geq 40\ y$
- $T \leq 3\ cm$
- $pN0$
- not lobular histology

*Completed accrual: 2135*

**NSABP B39**
- Age $\geq 18\ y$
- $T \leq 3\ cm$
- $pN0$ and 1-3N+
- ductal and lobular

*Target accrual: 4300*
Rapid Canadian RCT

April/06 to July/11

Eligible:
>40 years, pN0, not lobular, T<3cm, margins clear, not BRCA1-2+
PBRT is technically possible

Randomize (n = 2135)

Standard Whole Br RT

Experimental Partial Br RT

Outcomes: LR, Cosmesis, Toxicity
Challenges of PBI
Agreeing on how to contour the Seroma

Guidelines and Training reduced inter-observer variation.

Wong E et al. IJROBP 2006:66:372-6
Small Breast
Limiting RT to Normal Tissues

- Heart
- Contralateral Breast
- Lung
PBI Summary

- Low risk women post BCS
- Larger fraction size to part of the breast
- Complete RT in ≤ 1 week

↑ convenience

cosmesis, toxicity & recurrence?
Status of PBI in BC

• Awaiting results of RAPID

• Not generally available in BC off study

• Current pilot study
Current BCCA Study

• 2012
• Permanent seed brachy for PBI
  – CSI 3/5 patients
  – VIC 3/5 patients
  – Feasibility and resource allocation
Not At All?
Identification of Patients at Very Low Risk of Local Recurrence after Breast Conserving Surgery

Sally Smith BSc MD FRCP
Radiation Oncologist, BCCA, Vancouver Island Centre
Clinical Assistant Professor, UBC
Background

- Breast conserving surgery (BCS) + whole breast RT is current standard of care for women with early breast ca
- Consistent 2/3 reduction in local recurrence (LR) with RT
- Absolute risk reduction varies according to clinical-pathologic characteristics
- RT is inconvenient, costly, and has acute and late adverse effects, some impacting QOL (breast pain, fatigue, fibrosis, cosmesis) and some life threatening (lung/heart injury, RT-induced malignancy)
• Could some women safely avoid RT?

• Can we identify them?
RCT Data

**Toronto/BC**
769 women aged ≥50, pT1-2, N0 breast ca randomized to tamoxifen alone versus tamoxifen + breast RT.

5 year LR **7.7%** with tam alone vs **0.6%** with tam + RT (p=0.001)
10 year LR **13.8%** with tam alone vs **5%** with tam + RT (p=0.001)

**CALGB 9343**
603 women aged ≥70, pT1 (<2cm), ER+ breast ca randomized to tamoxifen alone versus tamoxifen + breast RT.

5 year LR **4%** with tam alone vs **1%** with tam + RT (p<0.001)
10 year LR **8%** with tam alone vs. **2%** with tam + RT (p<0.015)

Fyles et al.  NEJM 2004
Hughes et al. NEJM 2004
Meta analysis of RT post BCS: 10,801 women in 17 randomized trials

5 yr risk of local or distant recurrence: absolute reduction with addition of breast RT after BCS in node negative women

<table>
<thead>
<tr>
<th>T1 (1-20mm) tumours</th>
<th>Low grade</th>
<th>Intermediate grade</th>
<th>High grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;40</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Lumpectomy, ER+ tam-</td>
<td>17</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Lumpectomy, ER-poor</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>&gt;Lumpectomy, ER+ tam- or ER-poor*</td>
<td>6</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Lumpectomy, ER+ tam+</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
Why ask the question again?

New information on intrinsic subtypes

Voduc et al.
- 1271 pts treated with BCS + RT
- Identified intrinsic subtype; luminal A (ER or PR positive, Her 2 negative, Ki67 <14%) best prognosis

Ontario/BC – retrospective analysis of a prospective trial

<table>
<thead>
<tr>
<th></th>
<th>10yr LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tam</td>
</tr>
<tr>
<td>Luminal A (n=95)</td>
<td>6.9%</td>
</tr>
<tr>
<td>Luminal A ≥60</td>
<td>5.4%</td>
</tr>
<tr>
<td>Luminal B (n=74)</td>
<td>24%</td>
</tr>
<tr>
<td>Her 2+ (n=24)</td>
<td>44%</td>
</tr>
</tbody>
</table>

Voduc JCO 2010
Fyles Cancer Res 2011
Hypothesis

- it is possible to identify groups of patients with LR risk <5% without adjuvant whole breast RT or <1.5% with RT at 5 years
Methods

• Prospective cohort study thought to be best way to identify such a population

• Who to include??
BCOUU Project Objectives

• to evaluate LR and LRR risks in women aged ≥50 years with stage I breast cancer treated with BCS +/- RT

• to determine clinical/pathologic factors associated with ‘very low’ 5-year LR risk:
  <5% without breast RT
  or
  <1.5% with breast RT
Methods

• BCCA BCOU identified women aged ≥50 yrs, referred 1989-2006, pathologic stage I (T≤2 cm, pN0) invasive breast ca

• All women had BCS +/- whole breast RT

• 5- and 10-year LR and LRR with and without RT examined using Kaplan-Meier methods

• Recursive Partitioning Analysis (RPA): to identify patients with LR risk <5% without RT or <1.5% with RT at 5 years
## Clinico-pathologic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RT (N=5974)</th>
<th>No RT (N=431)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (yrs)</td>
<td>63 (50 – 91)</td>
<td>70 (50 – 89)</td>
<td></td>
</tr>
<tr>
<td>Median T Size (cm)</td>
<td>1.2</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>LVI</td>
<td>10%</td>
<td>7%</td>
<td>ns</td>
</tr>
<tr>
<td>Grade III</td>
<td>20%</td>
<td>17%</td>
<td>ns</td>
</tr>
<tr>
<td>Ductal Histology</td>
<td>92%</td>
<td>93%</td>
<td>ns</td>
</tr>
<tr>
<td>Margin Positive or close</td>
<td>7%</td>
<td>7%</td>
<td>ns</td>
</tr>
<tr>
<td>ER Positive</td>
<td>78%</td>
<td>81%</td>
<td>0.003</td>
</tr>
<tr>
<td>Endocrine Therapy</td>
<td>47%</td>
<td>44%</td>
<td>ns</td>
</tr>
</tbody>
</table>
5-year LRR
No RT: 9.5% (n=253; 95% CI 6.5-12.5)
RT: 2.1% (n=4573; 95% CI 1.7-2.5)

10-year LRR
No RT: 13.8% (n=133; 95% CI 9.7-17.7)
RT: 4.4% (n=2275; 95% CI 3.8-5.1)
RPA of Entire Cohort

* Denotes groups with LR risk <1.5% with RT at 5 years

- All Patients
  - Breast RT
    - Grade 1
      - Negative margins
        - n=821
    - Grade 2, 3, unknown
      - n=1792
  - No Breast RT
    - Grade 1
    - Grade 2 and 3
      - Positive/close/unknown margins
RPA of LR – pts treated with endocrine tx

**Endocrine Tx**
- **n=3018**
  - **RT**
    - **n=2830**
  - **No RT**
    - **n=188**

* Denotes groups with LR risk <1.5% with RT at 5 years

**Grade 1**
- **n=1038**

**Grade 2, 3**
- **≥ 60 yo**
  - **Grade 2**
    - **n=872**
  - **Grade 3**
- **<60 yo**
  - **ER positive**
  - **ER negative**
In patients treated with endocrine tx, subsets with LR ≤1.5% with RT:

- **Grade 1** (n=1038)
  LR 0.2% (95% CI 0.0-0.5) at 5 yrs
  LR 0.8% (95% CI 0.1-1.6) at 10 yrs

- **Over 60 plus grade 2** (n=843)
  LR 0.5% (95% CI 0-1.1) at 5 yrs
  LR 0.9% (95% CI 0.2-1.6) at 10 yrs
RPA of LR – pts treated without endocrine tx

* Denotes groups with LR risk <1.5% with RT at 5 years
In patients treated without endocrine tx, subsets with LR ≤1.5% with RT:

- Grade 1 histology plus clear margins (n=821)
  LR 0.6% (95% CI 0.1-1.2) at 5 yrs
  LR 2.2% (95% CI 1.0-3.4) at 10 yrs
Conclusions

• Grade, age, margin status can be used to identify stage I patients with very low LR risk after BCS + RT

• Considering consistent two-thirds LR reduction with RT, findings suggest that patients with 5-year LR risk <5% without RT are:

  ≥50 yo, stage 1, grade 1, treated with endocrine tx
  ≥60 yo, stage 1, grade 2, treated with endocrine tx
  ≥50 yo, stage 1, grade 1, clear margins, no endocrine tx
Prospective study is critical to evaluate safety of RT omission
Lum A, No RT cohort study (Ontario/BC)

- women aged ≥60 years, treated with BCS
- unifocal pT1 pN0 invasive ductal ca
- grade 1 or 2, no LVI, clear margins
- ER and PR positive, Her 2 negative

- accepts endocrine therapy
- accessible for follow up

- send tissue block for Ki67 testing
- women with Luminal A disease (Ki67<14%) will be followed prospectively for LR risk without RT
Key Messages

• MORE? High to intermediate risk (all N+, high-risk N0): consider adding nodal to breast RT

• LESS? Non-high risk N0: whole breast RT is standard of care; partial breast RT remains investigational pending long-term follow-up

• NOT AT ALL? Very low risk N0: prospective study of no RT approach in patients with luminal A subtype who accept endocrine therapy