Overview of Partial breast Radiotherapy (PBRT)

Prof John Yarnold (Professor of clinical oncology at the Institute of Cancer Research & Royal Marsden NHS Foundation Trust)
Breast cancer mortality falling, despite rising incidence
Why is Breast Mortality Falling?

• Earlier presentation
• Better organisation of health services
• More effective treatment
  - Imaging & pathology
  - Surgery, drugs & radiation
Themes Relating to PBRT

- Benefits of whole breast (WB)RT
- Case for PBRT
- Case against PBRT
- Trials testing PBRT
Medial Tangential Field to Left Breast
Tangential Beams to Whole Breast

Courtesy of Dr A Kirby, Royal Marsden
Whole Breast RT After Tumour Excision in pN+ Cancer (N= 1050)

![Graphs showing recurrence and breast cancer death rates](image)

- **Any first recurrence**
  - BCS: 63.7%
  - BCS+RT: 53.7%
  - 10-year gain: 21.2% (SE 3.4)
  - RR: 0.53 (95% CI 0.44-0.64)
  - Log-rank 2p<0.00001

- **Breast cancer death**
  - BCS: 51.3%
  - BCS+RT: 42.6%
  - 15-year gain: 8.5% (SE 3.4)
  - RR: 0.79 (95% CI 0.65-0.95)
  - Log-rank 2p=0.01

EBCTCG Lancet, 2011, 378, 1707-1716
Whole Breast RT After Tumour Excision in pN0- Cancer (N= 7287)

Women with pN0 disease (n=7287)

Any first recurrence

- 10-year gain 15.4% (SE 1.1)
- RR 0.49 (95% CI 0.45–0.55)
- Log-rank 2p<0.00001

Breast cancer death

- 15-year gain 3.3% (SE 1.3)
- RR 0.83 (95% CI 0.73–0.95)
- Log-rank 2p=0.005

EBCTCG Lancet, 2011, 378, 1707-1716
Themes Relating to PBRT

- Benefits of whole breast (WB)RT
- Case for PBRT
- Case against PBRT
- Trials testing PBRT
The Case For Partial Breast RT (PBRT)

- PBRT targets 75% of local relapse risk
- **WBRT** does not reduce the other 25% relapse risk
  - other quadrant new primary tumours
- PBRT reduces complications
  - less damage to healthy breast, ribs, muscle, lung, heart
Ipsilateral Breast Relapse after Breast Cons. Surgery (BCS) +/- RT

2,544 patients treated by BCS at NCI, Milan 1970 - 89

<table>
<thead>
<tr>
<th>Location of relapse</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2cm from scar</td>
<td>142 (74)</td>
</tr>
<tr>
<td>Other quadrant</td>
<td>43 (23)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

Salvadori, BJS, 1999, 86, 84-87
Patterns of Breast Relapse after Quadrantectomy + WBRT (n=1232)

Veronesi, Ann Surg, 1990, 211; 250-9
Late Adverse Effects of WBRT

No change

Marked change

Pre-RT

5yr post-RT
Causes of Excess Non-Breast Cancer Mortality (N=23,500)

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No. events</th>
<th>Ratio events</th>
<th>2p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>1106</td>
<td>1.27</td>
<td>0.0001</td>
</tr>
<tr>
<td>Lung Ca</td>
<td>156</td>
<td>1.78</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

EBCTCG, Lancet 2005; 366, 2087-2106
The Case Against Partial Breast RT

• Foci of invasive cancer outside PBRT volume are common
• WBRT reduces ipsilateral new primary tumour rate after all
• Perhaps no RT is needed!
Topographic Schema of Whole Breast, Frontal Projection, 5 mm slice

Holland R, Cancer, 56; 979-90, 1985
40% pT1 tumours have DCIS &/or invasive foci >2cm beyond tumour edge

Holland R, Cancer, 56: 979-90, 1985
Multiple Foci in Different Ducts
EORTC Boost Trial (N=5318): Spatial Pattern of Local Relapse

443 (8%) local relapses @ 10yr
57% in tumour bed/scar
43% outside tumour bed/diffuse

Bartelink, JCO, 2007, 25; 3259-65
Patterns of Breast Relapse after Quadrantectomy + WBRT (n=1232)

Veronesi, Ann Surg, 1990, 211; 250-9
Patterns of Relapse after Quadrantectomy + WBI (N=1232)

Contralateral primary

HR≈0.5

Ipsilat. new primary ‘elsewhere’

Whole Breast RT Reduces Local Relapse Risk in Years 5-9

5-y gain 18.6% (SE 0.9)

Yr 5-9 HR=0.4

Themes Relating to PBRT

• Benefits of whole breast (WB)RT
• Case for PBRT
• Case against PBRT
• Trials testing PBRT
Evidence so Far....

• Encouraging long-term results of non-randomised series
• Randomised trials maturing
## Phase III Trials of PBRT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target accrual</th>
<th>Accrual complete</th>
<th>Reported</th>
<th>Med FU (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polgar</td>
<td>258</td>
<td>**</td>
<td>**</td>
<td>6.8</td>
</tr>
<tr>
<td>TARGIT-A</td>
<td>3500</td>
<td>**</td>
<td>**</td>
<td>4.0</td>
</tr>
<tr>
<td>ELIOT</td>
<td>1305</td>
<td>**</td>
<td>**</td>
<td>6.0</td>
</tr>
<tr>
<td>IMPORT Low</td>
<td>2015</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEC-ESTRO</td>
<td>1170</td>
<td></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>NSABP-39</td>
<td>9000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAPID</td>
<td>2000</td>
<td></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>IRMA</td>
<td>3300</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intrabeam (50 kV Xrays)

Volume $\geq 10$ Gy

10cc
Intra-Operative Electron Therapy

Volume ≥20 Gy
100cc

Mammosite: $^{192}$Iridium $\gamma$-rays

- Catheter inserted at/after surgery
- $^{192}$Iridium $\gamma$-ray source inserted twice daily
- 38.5Gy in 10F over 5 days

High dose volume $\geq 100cc$
IMPORT Low trial: 6MV x-rays (linear accelerator)

High dose volume ≥100cc

Dr C Coles, Addenbrooke’s Hosp
## PBRT Trials: How to Generalise?

<table>
<thead>
<tr>
<th>Time of RT post-surg.</th>
<th>RT Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \sqrt{10\text{cc}} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minutes</th>
<th>*IORT 50kV XR</th>
<th>IORT 8MV e-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>-</td>
<td>- Iridium implant</td>
</tr>
<tr>
<td>Weeks</td>
<td>-</td>
<td>External beam RT</td>
</tr>
</tbody>
</table>

*IORT = Intra-Operative RT*
TARGIT-A Trial (n=2232)

Patients: 40% ≥65yr
Stage: 86% pT≤2cm, 82% pN0, 90% ER+
Surgery: Local excision (LE)

Randomisation

* IORT

*20% needed mastectomy or WBRT

Vaidya, Lancet, 2010, 376; 91-102
Ipsilateral Local Relapse & Mortality (n=3451)

Blue = TARGIT
Red = EBRT

San Antonio Breast Cancer Symposium – December 4-8, 2012

Ipsilateral Breast Recurrence
34 events

HR 2.05 (1.01-4.25)
Logrank p=0.042

Number at risk
TARGIT 1679
EBRT 1696
0 1 2 3 4 5 years

Death
88 events

HR 0.70 (0.46-1.07)
Logrank p=0.099

Number at risk
TARGIT 1721
EBRT 1730
0 1 2 3 4 5 years

Difference 2.01%
(0.32-3.7)

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Vaidya (with permission), SABC, Dec 2012
Mortality

Blue = TARGIT
Red = EBRT

San Antonio Breast Cancer Symposium – December 4-8, 2012

All Deaths
88 events

HR 0.70
Logrank p=0.099

Number at risk
TARGIT 1721
EBRT 1730

Breast Cancer Deaths
36 events

HR 0.94
Logrank p=0.56

Non-Breast Cancer Deaths
52 events

HR 0.47
Logrank p=0.009

Vaidya (with permission), SABC, Dec 2012
Non-Breast-Cancer deaths

5-year risk = 1.4% vs. 3.5%
HR 0.47 (0.26 – 0.84)
Log rank $p = 0.009$

Vaidya (with permission), SABC, Dec 2012
ELIOT Trial (n=1305)

Eligibility: Age>48yr; T<25mm
Surgery: Local excision (LE)

Randomisation

- **IORT**
  - 21Gy/1F

- **WBRT**
  - 50Gy/25F WB
  - 10Gy/5F boost
### ELIOT Ipsilateral breast relapse

#### Tumour bed \( (p=0.0002) \)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB RT</td>
<td>-</td>
<td>0.0</td>
<td>0.2</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>ELIOT</td>
<td>-</td>
<td>0.7</td>
<td>2.2</td>
<td>3.9</td>
<td>6.4</td>
<td>9.2</td>
</tr>
</tbody>
</table>

#### Elsewhere \( (p=0.0001) \)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB RT</td>
<td>-</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ELIOT</td>
<td>-</td>
<td>0.4</td>
<td>1.9</td>
<td>2.8</td>
<td>3.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

#### Total ipsilateral \( (p=0.0001) \)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>WB RT</td>
<td>-</td>
<td>0.0</td>
<td>0.2</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>ELIOT</td>
<td>-</td>
<td>1.1</td>
<td>4.1</td>
<td>6.7</td>
<td>9.9</td>
<td>12.7</td>
</tr>
</tbody>
</table>
The Case Against Partial Breast RT

- Foci of invasive cancer outside PBRT volume are common
- Patients censored at time of first local relapse can bias estimates of relapse risk in other quadrants
- WBRT may reduce ipsilateral new primary tumour rate after all
- Perhaps no RT is needed!
Local Relapse (LR) Rates are Falling: Breast Conservation Surgery +/- RT

<table>
<thead>
<tr>
<th>Trial</th>
<th>5-yr LR (%) BCS+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-06 (1976-1984)</td>
<td>14.3</td>
</tr>
<tr>
<td>CRC, UK (1981-1990)</td>
<td>19.7</td>
</tr>
<tr>
<td>Ontario COG (1984-1989)</td>
<td>11</td>
</tr>
<tr>
<td>SCTBG (1985-1991)</td>
<td>5.8</td>
</tr>
<tr>
<td>INT Milan 3 (1987-1989)</td>
<td>5.8</td>
</tr>
<tr>
<td>NSABP B-21 (1989-1998)</td>
<td>2.8</td>
</tr>
<tr>
<td>Swedish BCG 91-RT (1991-1997)</td>
<td>4.0</td>
</tr>
<tr>
<td>Holli et al. (1990-1995)</td>
<td>6.3</td>
</tr>
<tr>
<td>Fyles et al. (1992-2000)</td>
<td>0.6</td>
</tr>
<tr>
<td>CALGB C9343 study (1994-1999)</td>
<td>1.0</td>
</tr>
<tr>
<td>BASO II (1992-2000)</td>
<td>0.4 pa</td>
</tr>
<tr>
<td>ABCSG study 8 (1996-2004)</td>
<td>0.4</td>
</tr>
</tbody>
</table>
### Adjuvant Endocrine Therapy Reduces Local Relapse

<table>
<thead>
<tr>
<th>Systemic therapy</th>
<th>RR for local relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen <em>vs</em> nil (EBCTCG)</td>
<td>0.47</td>
</tr>
<tr>
<td>Exemestane + tamoxifen <em>vs</em> tamoxifen (IES)</td>
<td>0.72</td>
</tr>
<tr>
<td>Anastrozole <em>vs</em> tamoxifen (ATAC)</td>
<td>0.83</td>
</tr>
<tr>
<td>Letrozole <em>vs</em> tamoxifen (BIG 1-98)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

*EBCTCG, IES, ATAC, BIG 1-98*
Future Stratification?
Total doses in 2.0Gy fractions (α/β=3Gy)

Ipsilateral Breast Relapse Risk

- <5%
- 5-10%
- >10%

No RT? 5 Fractions?
In Conclusion: Evidence and Future

- On historically required levels of evidence, PBI should not yet be offered as a standard of care.
- PBI likely to find a worthwhile niche in future, either as IORT or as 5F of external beam RT.
My treatment center does not have access to a High Dose Rate (HDR) Afterloader. How do I get one?

Click here to be contacted by a representative who can help you.