The role of radiotherapy in early and advanced breast cancer

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University of Split, School of medicine

ESO Masterclass,
Šibenik, April 14th 2019.
Impact of breast cancer radiotherapy (RT) was recognized long time ago

NSABP-B06

Started 1976.
FU 20 Years

Local recurrence: 14.3% vs 39.2% (P<0.001)

Cumulative Incidence of a First Recurrence of Cancer in the Ipsilateral Breast during 20 Years of Follow-up among 570 Women Treated with Lumpectomy Alone and 567 Treated with Lumpectomy plus Breast Irradiation.

RT has the relatively long history...
2D treatment planning
3D conformal RT
Intensity modulated RT
Breath adopted RT

Free breathing

Deep inspiration breath hold

Irradiated heart volume 8%

Irradiated heart volume 1%
Respiratory gating

Expiration: Beam OFF

Inspiration: beams ON
Accelerated partial breast irradiation
APBI

- Interstitial brachytherapy
- Intracavitary brachitherapy
- EXRT
- IORT
- Permanent seed
Interstitial Brachytherapy -
Multi-Entry/Multi-Catheter

Arthur and Vicini, 2005
**PBI: MammoSite**

Per RTOG 04-13:
Distance from balloon to skin must be ≥5mm
Intraoperative RT
These developments may:

- improve loco regional control
- improve survival
- reduce acute and late radiation-induced morbidity
- 3D CT planning has improved dose homogeneity both within planning target volume while reducing dosage to critical normal tissues (HEART!)
- breathing-adapted gating techniques have reduced cardiac irradiation
What modern RT can do in our fight against breast cancer
Regional node irradiation:
Meta-analysis of 13,500 women in 14 trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Writing Committee: David Dodwell (presenter), Carolyn Taylor, Paul McGale, Charlotte Coles, Fran Duane, Richard Gray, Thorsten Kühn, Christophe Hennequin, Robert Hills, Sileida Oliveros, Yaochen Wang, Jonas Bergh, Kathy Pritchard, Sandra Swain, Jens Overgaard, Philip Poortmans, Tim Whelan
Regional node radiation therapy (RT)

Axilla

Supraclavicular (SCF)

Internal mammary (IMC)

Same treatment to breast

Dodwell et al. SABCC 2018
Data analysis plan: regional node RT

1. All trials together
2. Separate older & newer trials

Target coverage better in newer trials
Heart dose: Older trials >8 Gy
Newer trials <8 Gy
## Older trials (began 1961-1978)
### Total with data available ≈2,500

<table>
<thead>
<tr>
<th>Year began</th>
<th>Name</th>
<th>Women</th>
<th>RF sites randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>1961</td>
<td>NSABP B-03</td>
<td>1103</td>
<td>IMC, SCF, axilla</td>
</tr>
<tr>
<td>1968</td>
<td>Oslo</td>
<td>542</td>
<td>IMC, SCF, axilla</td>
</tr>
<tr>
<td>1969</td>
<td>Heidelberg</td>
<td>142</td>
<td>IMC, SCF, axilla</td>
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<tr>
<td>1972</td>
<td>WSSA</td>
<td>217</td>
<td>SCF, axilla</td>
</tr>
<tr>
<td>1973</td>
<td>Milan 1</td>
<td>56</td>
<td>IMC, SCF</td>
</tr>
<tr>
<td>1974</td>
<td>Piedmont</td>
<td>160</td>
<td>IMC, SCF</td>
</tr>
<tr>
<td>1974</td>
<td>Mayo</td>
<td>241</td>
<td>IMC, SCF</td>
</tr>
<tr>
<td>1978</td>
<td>Toronto</td>
<td>74</td>
<td>‘regional’</td>
</tr>
</tbody>
</table>

### Median FU (IQR): 9.2 (3.4 – 17.5) years

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Dodwell et al. SABCC 2018
## Newer trials (began 1989 onwards)

**Total with data available ≈11,000**

<table>
<thead>
<tr>
<th>Year began</th>
<th>Name</th>
<th>Women</th>
<th>RT sites randomised</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>Tampere</td>
<td>270</td>
<td>IMC</td>
</tr>
<tr>
<td>1991</td>
<td>French IM*</td>
<td>1407</td>
<td>IMC</td>
</tr>
<tr>
<td>1995</td>
<td>Italian Senology</td>
<td>435</td>
<td>axilla</td>
</tr>
<tr>
<td>1996</td>
<td>EORTC 22922</td>
<td>4004</td>
<td>IMC, SCF</td>
</tr>
<tr>
<td>2000</td>
<td>MA.20</td>
<td>1832</td>
<td>IMC, SCF, axilla</td>
</tr>
<tr>
<td>2003</td>
<td>DBCG-IMN**</td>
<td>3089</td>
<td>IMC</td>
</tr>
</tbody>
</table>

*Data available only on overall mortality  **RT allocated by tumour laterality

**Median FU (IQR): 9.1 (7.0 – 11.0) years**

Dodwell et al. SABCC 2018
1. All regional node RT trials

Any recurrence

Absolute difference: 2.9%

Breast cancer mortality

Absolute difference: 4%

11,800 women, 3,316 events
15-year gain 2.9% (95% CI 0.4–5.4)  
RR 0.89 (95% CI 0.83–0.96)  
logrank p = 0.002

11,800 women, 2,696 deaths
15-year gain 4.0% (95% CI 1.6–6.4)  
RR 0.88 (95% CI 0.82–0.96)  
logrank p = 0.003

Dodwell et al. SABCC 2018
Data analysis plan: regional node RT

1. All trials together

2. Separate older & newer trials
Any recurrence

Older trials

- 2178 women, 987 events
- 20-year gain 0.2% (95% CI -5.1 to 5.5)
- RR 0.98 (95% CI 0.85 to 1.13)
- logrank p = 0.80

Newer trials

- 9622 women, 2329 events
- 10-year gain 3.2% (95% CI 1.3 to 5.1)
- RR 0.86 (95% CI 0.79 to 0.94)
- logrank p = 0.0005

Absolute difference: 3.2%

Dodwell et al. SABCC 2018
Breast cancer mortality

Older trials
2178 women, 957 deaths
20-year loss 0.5% (95% CI -4.7–5.7)
RR 1.04 (95% CI 0.90–1.20)
logrank p = 0.58

Newer trials
9622 women, 1739 deaths
10-year gain 2.8% (95% CI 1.2–4.4)
RR 0.82 (95% CI 0.75–0.90)
logrank p = 0.00006

Absolute difference: 2.8%
Non-breast-cancer mortality

Older trials

2178 women, 597 deaths
20-year loss 5.8 % (95% CI -1.1–12.7)
RR 1.45 (95% CI 1.21–1.74)
logrank p = 0.00006

Newer trials

9622 women, 438 deaths
10-year gain 0.2 % (95% CI -0.9–1.3)
RR 0.96 (95% CI 0.79–1.16)
logrank p = 0.66

Absolute difference: 5.8%

Dodwell et al. SABCC 2018
**Overall mortality**

**Older trials**

- 2178 women, 1554 deaths
- Absolute difference: 2.8%
- 20-year loss 2.8% (95% CI -2.1–7.7)
- RR 1.18 (95% CI 1.06–1.32)
- logrank p = 0.004

**Newer trials**

- 10956 women, 2713 deaths
- 10-year gain 2.9% (95% CI 1.2–4.6)
- RR 0.87 (95% CI 0.80–0.94)
- logrank p = 0.0003

*Dodwell et al. SABCC 2018*
Newer trials: Breast cancer mortality

pN0

pN1-3

Absolute difference: 1.4%

pN4+

Absolute difference: 2.9%

2150 women, 232 deaths
10-year gain 1.3% (95% CI -1.2–3.8)
RR 0.80 (95% CI 0.62–1.04)
logrank p = 0.10

5135 women, 783 deaths
10-year gain 1.4% (95% CI 0.7–3.5)
RR 0.88 (95% CI 0.77–1.02)
logrank p = 0.08

1873 women, 697 deaths
10-year gain 7.9% (95% CI 3.0–12.8)
RR 0.77 (95% CI 0.66–0.90)
logrank p = 0.0010
Conclusions: regional node irradiation

• Older trials (began 1961-1978)
  – Breast cancer mortality – little effect
  – Overall mortality – significantly increased

• Newer trials (began 1989+)
  – Breast cancer mortality – significantly reduced
  – Overall mortality – significantly reduced
  – Absolute mortality reduction greatest in N4+
### Improvements in systemic therapy vs RT

<table>
<thead>
<tr>
<th>Chemotherapy¹</th>
<th>CMF vs. no chemo</th>
<th>Anthracycline vs. CMF</th>
<th>Taxane + anthracycline vs. anthracycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in recurrence rate after 5 years</td>
<td>+9.9%</td>
<td>+3.2%</td>
<td>+3.6%</td>
</tr>
<tr>
<td>After 10 years</td>
<td>RR = 0.70</td>
<td>RR = 0.89</td>
<td>RR = 0.84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endocrine therapy²³</th>
<th>Tam 5 years vs. no tam</th>
<th>AI 5 years vs. tam 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in recurrence rate after 5 years</td>
<td>+11.4%</td>
<td>+1.1–3.1%</td>
</tr>
<tr>
<td>After 5 years</td>
<td>RR = 0.50</td>
<td>RR = 0.80–0.90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-HER2 therapy⁴⁻⁶</th>
<th>Trastuzumab vs. observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS benefit after 5 years</td>
<td>+5.9–9.0%</td>
</tr>
<tr>
<td>After 10/11 years</td>
<td>(HR = 0.72–0.77)</td>
</tr>
</tbody>
</table>

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Much worse results in CEE region than in western countries – unmet need for improvement

Survival

Survival rate in Western Europe is up to 40% higher than in Eastern Europe (depending on the type of cancer)\(^5\)

### Extremely unfavourable mortality/incidence ratio

<table>
<thead>
<tr>
<th>Region</th>
<th>Male (%)</th>
<th>Female (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE Europe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>58%</td>
<td>48%</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>65%</td>
<td>50%</td>
</tr>
<tr>
<td>Serbia</td>
<td>62%</td>
<td>47%</td>
</tr>
<tr>
<td>Romania</td>
<td>65%</td>
<td>49%</td>
</tr>
<tr>
<td>Poland</td>
<td>62%</td>
<td>47%</td>
</tr>
<tr>
<td>Montenegro</td>
<td>65%</td>
<td>49%</td>
</tr>
<tr>
<td>FYR Macedonia</td>
<td>69%</td>
<td>48%</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>70%</td>
<td>48%</td>
</tr>
<tr>
<td>Albania</td>
<td>71%</td>
<td>55%</td>
</tr>
<tr>
<td>Median (%)</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Neighbouring WE countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>38%</td>
<td>33%</td>
</tr>
<tr>
<td>Italy</td>
<td>41%</td>
<td>32%</td>
</tr>
<tr>
<td>Austria</td>
<td>44%</td>
<td>37%</td>
</tr>
<tr>
<td>Median (%)</td>
<td>41%</td>
<td>33%</td>
</tr>
<tr>
<td>Other WE countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>France</td>
<td>38%</td>
<td>31%</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>41%</td>
<td>31%</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>42%</td>
<td>35%</td>
</tr>
<tr>
<td>Median (%)</td>
<td>40%</td>
<td>31%</td>
</tr>
<tr>
<td>Scandinavian countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>31%</td>
<td>32%</td>
</tr>
<tr>
<td>Finland</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>Norway</td>
<td>36%</td>
<td>31%</td>
</tr>
<tr>
<td>Sweden</td>
<td>40%</td>
<td>34%</td>
</tr>
<tr>
<td>Median (%)</td>
<td>35%</td>
<td>33%</td>
</tr>
</tbody>
</table>

**Note:**

Reasons for worse treatment outcome

Genetic factors

Environmental factors

Lifestyle

Lack of multidisciplinarity

Problems with health care organization

Insufficient investment in oncology (equipment, doctors, nurses, education, ...)

Lack of national strategy

Lancet Oncology Global Radiotherapy Commission

• Worse oncology care – local?
  – 50% of patients with cancer would benefit from radiotherapy
  – Worldwide access to radiotherapy is low, especially in low- or medium-income countries

Number of linear accelerators: Per 1 million inhabitants

Radiotherapy capacity in Europe

Most European countries do not have the quantity or quality of radiotherapy facilities required to provide an adequate service to their populations, while some have more than enough, according to an analysis published in *The Lancet Oncology* in 2013.

Correlations of health expenditures per capita and mortality-to-incidence ratio: All cancers/male (N=25)

Overall Spearman’s $\rho = -0.90$
WP and Scandinavia, $\rho = -0.17$
CE Europe, $\rho = -0.91$

TREATMENT BY STAGE
RT in DCIS

• After breast conserving surgery
• After mastectomy, only with close/positive margins
• Dosing schedule 4256cGy/16x
• Boost should be individualised
• Van Nuys Prognostic Index (VNPI) score may helpful in treatment guide

Adjuvant RT significantly reduces both IBTR and DCIS after BCS

- All trials: BCS +/- RT

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>N of pts</th>
<th>FU/years</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-17</td>
<td>818</td>
<td>15</td>
<td>RR of all local recurrences (35% vs 19.8%), with a 52% reduction in IBTR (19.6% vs 10.7%; ( P &lt; .001 )) and a 47% reduction in DCIS IBTR (15.4% vs 9.0%; ( P &lt; .001 )).</td>
</tr>
<tr>
<td>EORTC 10853</td>
<td>1010</td>
<td>15</td>
<td>Local recurrence (31% vs 18%; ( P &lt; .001 )), with similar findings noted for IBTR (16% vs 10%; ( P = .007 )) and DCIS recurrences (16% vs 8%; ( P = .003 ))</td>
</tr>
<tr>
<td>SweDCIS</td>
<td>1046</td>
<td>4.4</td>
<td>Reduction in local recurrence 27% vs 12% ( p &lt; 0.0001 )</td>
</tr>
<tr>
<td>UKCCCR</td>
<td>1701</td>
<td>12.7</td>
<td>Reduced the incidence of IBTRs ( (P &lt; .0001) ) and DCIS IBTRs ( (P &lt; .0001) ) as well as all new breast events ( (P &lt; .0001) )</td>
</tr>
</tbody>
</table>

IBRT= invasive breast recurrence tumor

Meta-analysis, 4 trials, 10-year cumulative risks of any ipsilateral breast event (recurrent DCIS or invasive)

- 5-yr gain 10.5% (SE 1.2)
- 10-yr gain 15.2% (SE 1.6)
- logrank 2P < 0.00001

Absolute benefit: 15.2%
# Van Nuys Prognostic Index

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of tumour (mm)</td>
<td>≤ 15</td>
<td>16–40</td>
<td>&gt;40</td>
<td></td>
</tr>
<tr>
<td>Margin width (mm)</td>
<td>&gt;10</td>
<td>1–10</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Grade</td>
<td>Non high grade, no comedo necrosis</td>
<td>Non high grade with comedo necrosis</td>
<td>High grade with or without comedo necrosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>3-4</th>
<th>98% local control without RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-7</td>
<td>32% failed without RT, 16% with RT</td>
<td></td>
</tr>
<tr>
<td>8-9</td>
<td>100% failure without RT, 60% with RT</td>
<td></td>
</tr>
</tbody>
</table>

RT in early breast cancer
Effect of RT after BCS on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials - EBCTCG

1. RT to the conserved breast halves the rate at which the disease recurs
2. RT reduces the breast cancer death rate by about a sixth
3. One breast cancer death was avoided for every four recurrences avoided

EBCTCG, Lancet Oncol 2011.
Mastectomy vs BCS + RT: similar outcomes

<table>
<thead>
<tr>
<th>Institute</th>
<th>IGR</th>
<th>Milan</th>
<th>NSABP B-06</th>
<th>NCI</th>
<th>EORTC</th>
<th>Danish</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>1</td>
<td>1</td>
<td>1,2</td>
<td>1,2</td>
<td>1,2</td>
<td>1,2,3</td>
</tr>
<tr>
<td>Surgery</td>
<td>2cm gross margin</td>
<td>Quadrantectomy</td>
<td>Lumpectomy</td>
<td>Gross excision</td>
<td>1 cm gross margin</td>
<td>Wide excision</td>
</tr>
<tr>
<td>Follow-up(y)</td>
<td>15</td>
<td>20</td>
<td>22</td>
<td>18</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>OS: BCS+RT(%)</td>
<td>73</td>
<td>42</td>
<td>46</td>
<td>59</td>
<td>65</td>
<td>79</td>
</tr>
<tr>
<td>M(%)</td>
<td>65</td>
<td>41</td>
<td>47</td>
<td>58</td>
<td>66</td>
<td>82</td>
</tr>
<tr>
<td>LR: BCS+RT(%)</td>
<td>9</td>
<td>9</td>
<td>14</td>
<td>22</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>M(%)</td>
<td>14</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Boost to tumor bed

RATIONALE:
• higher microscopic tumor burden in proximity to the site of lumpectomy
• clinical observation of the local pattern of failure close to the primary tumor location

INDICATIONS:
• age less than 50 years
• + margins, and the patient is either unable or unwilling to have further surgery
• Pt over 50 years with high pathological features, consider the benefit of boost

EORTC boost trial

- 5,000 patients
- 20-year breast tumor recurrence rate of 16.4% in the no-boost group vs 12.0% in the boost group (P<0.0001)
- The boost significantly reduced the risk of a recurrence for young patients or those with an EIC or a grade 3 tumor.
- For patients with grade 3, ER-negative tumors, the boost reduced the risk of a breast tumor recurrence from 31% to 5% (P=0.01)

Cochrane review: boost vs no boost

- Improved local control, no effect on OS

Shorter course of RT?

“Hypofractionated radiation therapy offers patients a more convenient and lower cost option for their treatment without compromising the likelihood that their cancer will return or increasing their risk of side effects,” Reshma Jagsi
Hypofractionated WBRT: new standard in early breast cancer after BCS

• effective and safe
• improves patient convenience and quality of life
• reducing overall cost

• **Recommended dose:** 4000cGy/15x or 4250cGy/16x

BCS: breast conserving surgery  
WBRT: whole breast RT

### Randomized trials evaluating hypofractionated vs conventional WBRT—efficacy outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Fractionation Scheme(^a)</th>
<th>Number of Patients</th>
<th>Stage</th>
<th>Median Follow-up</th>
<th>LRR(^b)</th>
<th>OS(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMH/GOC [5,6] 1986–1998</td>
<td>50/25/2.0 (35) 42.9/13/3.3 (35) 39/13/3.0 (35)</td>
<td>470 466 474</td>
<td>T1-3 N0-1</td>
<td>9.7 yr</td>
<td>12% 10% 15%</td>
<td>NR</td>
</tr>
<tr>
<td>Canadian [3,4] 1993–1996</td>
<td>50/25/2.0 (35) 42.5/16/2.66 (22)</td>
<td>512 622</td>
<td>pT1-2 pN0</td>
<td>12 yr</td>
<td>8% 7% 84%</td>
<td>85%</td>
</tr>
<tr>
<td>START A [7,9] 1998–2002</td>
<td>50/25/2.0 (35) 41.6/13/3.2 (35) 39/13/3.0 (35)</td>
<td>749 750 737</td>
<td>pT1-3a pN0-1</td>
<td>9.3 yr</td>
<td>7% 6% 9%</td>
<td>80% 82% 80%</td>
</tr>
<tr>
<td>START B [8,9] 1999–2001</td>
<td>50/25/2.0 (35) 40/15/2.67 (21)</td>
<td>1105 1110</td>
<td>pT1-3a pN0-1</td>
<td>9.9 yr</td>
<td>6% 4%</td>
<td>81% 84%</td>
</tr>
</tbody>
</table>

Long-Term Results of Hypofractionated RT for Breast Cancer – Whelan, NEJM 2010.

1234 patients
T1 and T2, N0 patients, BCS and ALND
Primary endpoint: Local recurrence (LR)
Other endpoints: Toxicity, cosmetic results, overall survival (OS)

LR
P < 0.001, for non-inferiority

OS
P = 0.79
“The decision to offer hypofractionated therapy should be independent of the following factors: tumor grade; whether the tumor is in the left or right breast; prior chemotherapy; prior or concurrent trastuzumab or endocrine therapy; and breast size, provided that homogenous dosing can be achieved. It may be independent of the following factors: hormone receptor status; HER2 receptor status; margin status following surgical resection; and age.”
Dose escalated simultaneous integrated boost (SIB) RT for early breast cancer: IMPORT HIGH trial, fIII

- trial to test whether dose escalated, IMRT after BCS for early breast cancer could reduce RT side effects, whilst maintaining or increasing cancer cure, in women with higher than average local recurrence risk.
- tests effects of simultaneous RT escalation to boost volume & reducing RT to low risk breast volumes & RT completed in 3 weeks

Coles CE; SABCC 2018
TRIAL DESIGN: Dose Escalated IMRT

Sequential boost

Concomitant boost

Concomitant boost

40Gy/15Fr

56Gy/23Fr*
Sequential dose escalation

23 (15+8) fractions

36Gy/15Fr

40Gy/15Fr
48Gy/15Fr
Concomitant dose escalation

15 fractions

36Gy/15Fr

40Gy/15Fr
53Gy/15Fr
Concomitant dose escalation

15 fractions

*56 Gy/23Fr: represents 40 Gy/15 Fr to whole breast plus 16 Gy/8 Fr sequential photon boost.

Coles CE; SABCC 2018
ENDPOINTS: CRO: *breast induration* at 3 years

Proportion ‘quite a bit’/‘very much’:

- 40Gy + 16Gy
- 48Gy/15F (3.2Gy/F)
- 53Gy/15F (3.5Gy/F)

*P*(1-sided) = 0.02

*Coles L et al SABCS 2018*
CONCLUSIONS

• Largest & most mature reported adverse effects data of breast simultaneous boost within a clinical trial

• At 3 years, there is evidence of a dose response for adverse effects within the boost volume

• A SIB dose schedule of 48 Gy/15F is comparable to the control sequential boost schedule in terms of adverse effects

• Longer term follow-up & local relapse data needed before firm conclusions can be drawn regarding benefit or otherwise of dose-escalated IMRT SIB

Coles L et al SABCS 2018
Partial Breast Irradiation (PBI)

“radiation of the site of excision and adjacent tissue only”
Different PBI techniques

• No dedicated/Dedicated IOERT suite
• Mobile IOERT accelerator (ELIOT)
• Low-energy-x-ray system (TARGIT)

• HDR/LDR-BRT interstitial
• HDR-BRT balloon catheter (Mammosite)

• External Beam RT/3D-CRT/IMRT
Why accelerated partial breast (APBI) irradiation?

• APBI is based on rationale that most local recurrences occur at primary site
• Delivered to the surgical cavity with a margin of normal tissue and is given in one week or less
• Several techniques exist, many are resource intensive
• 3D-CRT or IMRT are non-invasive and use modern technology
RAPID trial

PRIMARY ENDPOINT: To determine if APBI using 3D-CRT was non-inferior to WBI following BCS in terms of Ipsilateral Breast Tumor Recurrence (IBTR)

SECONDARY ENDPOINTS: RFS, EFS, OS, toxicity, cosmetics outcome
Trial Design

2135 Patients

APBI: 1070 Patients

WBI: 1065 Patients

Inclusion Criteria:

- Invasive breast cancer or DCIS
- ≤ 3 cm in size
- Microscopically clear margins post-BCS
- Node negative

Exclusion Criteria:

- < 40 years of age
- Lobular histology only
- Multi-centric disease

Sample Size based on risk of IBTR=1.5% at 5 years, non-inferiority margin=1.5% (HR<2.02): 64 events in 2128 patients

APBI: accelerated partial breast irradiation
WBI: whole breast irradiation
Accelerated partial breast irradiation

- 3-5 non-coplanar fields using 3D-CRT or IMRT
- Treat surgical cavity + 1cm margin of surrounding breast tissue
- **Dose:** 38.5 Gy/10 fractions given BID (>6h between fractions)
- Dosimetric restrictions
- RTQA program

Whole breast irradiation

- Standard tangential fields
- **Dose:** 50 Gy/25 fractions or 42.5 Gy/16 fractions
- **Boost:** 10 Gy/4-5 fractions for moderate-to-high risk cases
Ipsilateral breast cancer recurrence

Years Since Randomization

<table>
<thead>
<tr>
<th></th>
<th>APBI –</th>
<th>WBI –</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>37</td>
<td>28</td>
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</table>

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Ipsilateral breast cancer recurrence

<table>
<thead>
<tr>
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<th>WBI –</th>
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</thead>
<tbody>
<tr>
<td>37 events</td>
<td>28 events</td>
<td></td>
</tr>
<tr>
<td>HR=1.27 (90%CI, 0.84-1.91)</td>
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Years Since Randomization

Whelan T, SABCS 2018
DFS

<table>
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<tr>
<th>APBI –</th>
<th>WBI –</th>
</tr>
</thead>
<tbody>
<tr>
<td>61 events</td>
<td>49 events</td>
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</table>

HR = 1.20 (95% CI, 0.83-1.76)

Whelan T, SABCS 2018
Mortality

Years since Randomization

<table>
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<tr>
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<th>APBI</th>
<th>WBI</th>
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</thead>
<tbody>
<tr>
<td>Events</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td>HR</td>
<td>1.18, (95%CI, 0.84-1.64)</td>
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</tbody>
</table>

Whelan T, SABCS 2018
Radiation Toxicity (Grade ≥ 2)

Acute

Grade 2: 26%
Grade 3: 44%

Late

Grade 2: 28%
Grade 3: 12%

Grade 2: 4%
Grade 3: 1%

p<0.001

APBI
WBI

Whelan T, SABCS 2018
Conclusions

- APBI non-inferior to WBI in preventing local recurrence
- IBTR rate very low; Absolute differences very small
- APBI associated with less acute toxicity but increased late toxicity and adverse cosmesis
- Unable to recommend the twice-a-day regimen
- Once-a-day treatment may not adversely affect cosmesis, and is being investigated
RT after primary mastectomy ± reconstruction

- T3 or T4 disease or axillary node positivity
- deep positive margin
- dosing schedule: 40.05Gy/15x
- alternatively 50Gy/25x may be indicated in some cases following immediate reconstruction although evidence for superior cosmesis is not available

RT after neoadjuvant therapy then mastectomy

- Pathologically positive axillary nodes after neoadjuvant treatment (ypN+)
- Large primary tumour or triple-negative disease plus cytologically positive axillary nodes and/or clinically suspicious enlargement at presentation, even when axillary nodes are pathologically negative after neoadjuvant treatment (i.e. status ypN-)
- Treat according to initial clinical stage of the disease

RT or surgery of the axilla after a positive sentinel node in breast cancer patients?

AMAROS trial
Inclusion
Invasive breast cancer 0.5-5 cm
Clinically N0
BCT or mastectomy
Any age

The primary endpoint was non-inferiority of 5-year axillary recurrence, considered to be not more than 4% for the axillary radiotherapy group compared with an expected 2% in the axillary lymph node dissection group.
Axillary recurrence rate - Primary analysis

Primary analysis - median follow-up: 6.1 years (on 31 Oct 2012)
AxSN+ ITT population

5-year cumulative incidence rate of axillary recurrence:
ALND 0.43% (95%CI: 0.00; 0.92)  (4 / 744 patients)
AxRT 1.19% (95%CI: 0.31; 1.19)  (7 / 681 patients)
<< hypothesis (2%)
Consequence: planned comparison is underpowered

Cumulative incidence analysis considers death as a competing risk
10 year: Axillary recurrence rate

AxSN+ ITT population

10-year cumulative incidence rate of axillary recurrence:
ALND 0.93% (95%CI: 0.18; 1.68) (7 / 744 patients)
AxRT 1.82% (95%CI: 0.74; 2.94) (11 / 681 patients)

Cumulative incidence analysis considers death as a competing risks. HR and Wald p-value based on Fine & Gray model

HR: 1.71; 95%CI: 0.67-4.39
P = 0.365
Disease-free survival

AxSN+ ITT population

Events: local recurrence (incl. ipsilateral DCIS), axillary recurrence, distant metastasis, second primary (including contralateral DCIS), death. If multiple events occurred within a 1-month time window, the following prioritization was applied: distant progression, axillary recurrence, local recurrence, second primary, death. HR and Wald p-value based on Cox proportional hazard model.

HR: 1.19; 95% CI: 0.97 - 1.46
P = 0.105

<table>
<thead>
<tr>
<th>Type of first DFS event</th>
<th>ALND</th>
<th>ART</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant progression</td>
<td>86</td>
<td>88</td>
<td>174</td>
</tr>
<tr>
<td>Axillary recurrence</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Second primary</td>
<td>55</td>
<td>71</td>
<td>126</td>
</tr>
<tr>
<td>Death as first event</td>
<td>18</td>
<td>14</td>
<td>32</td>
</tr>
</tbody>
</table>
**Overall survival**

AxSN+ ITT population

- **HR:** 1.17; 95% CI: 0.89-1.52
- **P:** 0.258

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>ALND (N=744)</th>
<th>ART (N=681)</th>
<th>Total (N=1425)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>67 (9.0)</td>
<td>70 (10.3)</td>
<td>137 (9.6)</td>
</tr>
<tr>
<td>Other malignancy</td>
<td>14 (1.9)</td>
<td>22 (3.2)</td>
<td>36 (2.5)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (2.3)</td>
<td>9 (1.3)</td>
<td>26 (1.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (0.8)</td>
<td>11 (1.6)</td>
<td>17 (1.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>744</td>
<td>717  685  617  520  299  8  0</td>
</tr>
<tr>
<td>112</td>
<td>681</td>
<td>669  633  571  479  280  9  1</td>
</tr>
</tbody>
</table>

HR and Wald p-value based on Cox proportional hazard model.
Lymphedema: clinical observation and/or treatment

Years after sentinel node biopsy

P-value from exact Fisher’s test
Conclusion

• Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients after 10 years, and no differences in DFS and OS

• Diagnosis of axillary lymph node recurrence after 5 yrs is a very rare event

• Significantly less lymphedema after AxRT after 5 years
Palliative RT in breast cancer

- Bone metastasis
- Brain metastasis
- Sy VCS
- Locally advanced disease including ulceration, bleeding, arm edema, or brachial plexopathy.
- Patients with isolated locoregional recurrence of breast cancer following local therapy

Quality of life could be greatly improved by timely applied RT
Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer


Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.
Survival was calculated from the time of enrollment to the time of death, if it occurred during the study period, or to the time of censoring of data on December 1, 2009. Median estimates of survival were as follows: 9.8 months (95% confidence interval [CI], 7.9 to 11.7) in the entire sample (151 patients), 11.6 months (95% CI, 6.4 to 16.9) in the group assigned to early palliative care (77 patients), and 8.9 months (95% CI, 6.3 to 11.4) in the standard care group (74 patients) (P=0.02 with the use of the log-rank test). After adjustment for age, sex, and baseline Eastern Cooperative Oncology Group performance status, the group assignment remained a significant predictor of survival (hazard ratio for death in the standard care group, 1.70; 95% CI, 1.14 to 2.54; P=0.01). Tick marks indicate censoring of data.
Potential of radiation therapy to convert the tumor into an in situ vaccine

Lauber K et al. Front. Oncol., 2012
Abscopal effect of radiotherapy

Refractory metastatic NSCLC patient
Progression after 3 lines of chemotherapy and chest RT: multiple lung, bone and liver metastases
RT to one liver metastase + 6 GY x 5 (TD 30 Gy) + Ipilimumab 3 mg/kg after first RT x 4, 3 w cycles + 2 consolidation cycles of IPI

NED after 62 months of follow up

Golden EB, Formenti SC, Oncoimmunology 2014
Conclusion

- After BCS, breast RT halves the rate at which the disease recurs and reduces the breast cancer death rate about a sixth
- Metaanalysis of the lymph node RT - newer trials shown significant risk of breast cancer and overall mortality reduction
- Newer RT techniques provide much better dose distribution and homogeneity and organs at risk protection with acceptable cosmetic effect
- RT has impact on disease control improvement comparable or even better than many systemic treatment options