Principles of breast radiation therapy

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Clinique des Grangettes
Genève
No Disclosures
Radiobiology - 101

![Graph showing surviving cells over time with RT fractions]

- Normal tissue cells
- Cancer cells
Local recurrence after BCS

**Table 5. Invasive (Nondiffuse) Cancers (N = 282): Distribution of Tumor Foci Versus Reference Tumor Size**

<table>
<thead>
<tr>
<th>Reference tumor size</th>
<th>No. of cases without tumor foci (%)</th>
<th>≤2 cm</th>
<th>Noninvasive tumor foci</th>
<th>Invasive tumor foci</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>*≤2 cm</td>
<td>53 (41)</td>
<td>22 (17)</td>
<td>37 (28)</td>
<td>18 (14)</td>
<td>130 (100)</td>
</tr>
<tr>
<td>*≤4 cm</td>
<td>101 (38)</td>
<td>54 (21)</td>
<td>71 (27)</td>
<td>38 (14)</td>
<td>264 (100)</td>
</tr>
<tr>
<td>*≤5 cm</td>
<td>105 (37)</td>
<td>56 (20)</td>
<td>75 (27)</td>
<td>46 (16)</td>
<td>282 (100)</td>
</tr>
</tbody>
</table>
Effect of radiotherapy

EBCTCG, Lancet, 2011
Whole breast irradiation
## Fractionation schedule

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>FU (years)</th>
<th>RT standard 25 x 2 Gy</th>
<th>RT hypofx</th>
<th>Reference</th>
</tr>
</thead>
</table>
| UK Start trial A | 1999 - 2002 | 2,236      | 7.4%                  | 8.8% (13 x 3 = 39 Gy)  
6.3% (13 x 3.2 = 41.6 Gy)  
5 weeks | Haviland, Lancet Oncol, 2013 |
| UK Start trial B | 1999 - 2002 | 2,215      | 5.5%                  | 4.3% (15 x 2.66 Gy = 40 Gy)  
3 weeks | Haviland, Lancet Oncol, 2013 |
| Canadian trial | 1993 - 1996 | 1,234      | 6.7%                  | 6.2% (16 x 2.66 Gy = 42.5 Gy)  
3 weeks | Whelan, NEJM, 2010 |
Whole breast irradiation +/- boost

EORTC 22881 - 10882

Bartelink, Lancet Oncol, 2015
A. No boost vs. Boost

- HR = 0.56 (99% CI: 0.34-0.92); p = 0.003

B. No boost vs. Boost

- HR = 0.66 (99% CI: 0.45-0.98); p = 0.007

C. No boost vs. Boost

- HR = 0.69 (99% CI: 0.46-1.04); p = 0.020

D. No boost vs. Boost

- HR = 0.66 (99% CI: 0.42-1.04); p = 0.019

Bartelink, Lancet Oncol, 2015
Local recurrence rate in 3 BCT trials with early breast cancer from 1980 - 2012

BCT arm of the BCT – Mastectomy trial

Boost arm of the Boost no Boost Trial

Young Boost Trial < 51 years

Bartelink, Radiother Oncol, 2012
<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>Patients</th>
<th>FU (years)</th>
<th>BCS + Tam</th>
<th>BCS + Tam + RT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB 9343</td>
<td>1994 - 1999</td>
<td>636</td>
<td>10</td>
<td>10%</td>
<td>2%</td>
<td>Hughes, JCO, 2013</td>
</tr>
<tr>
<td></td>
<td>&gt; 70 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian trial</td>
<td>1992 - 2000</td>
<td>769</td>
<td>5</td>
<td>7.7%</td>
<td>0.6%</td>
<td>Fyles, NEJM, 2004</td>
</tr>
<tr>
<td></td>
<td>&gt; 50 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRIME II</td>
<td>2003 - 2009</td>
<td>1,326</td>
<td>5</td>
<td>4.1%</td>
<td>1.3%</td>
<td>Kunkler, Lancet Oncol, 2015</td>
</tr>
<tr>
<td></td>
<td>&gt; 65 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis</td>
<td></td>
<td>3,190</td>
<td>5</td>
<td>6.5%</td>
<td>2.2%</td>
<td>Van de Water, Ann Surg Oncol, 2014</td>
</tr>
</tbody>
</table>
Trials ongoing

• Prospective cohort studies evaluating risk of local recurrence following breast conserving surgery and endocrine therapy in low risk Luminal A breast cancer
  – LUMINA, Ontario Clinical Oncology Group
  – The IDEA Study (Individualized Decisions for Endocrine Therapy Alone), University of Michigan
  – The PRECISION Trial (Profiling Early Breast Cancer for Radiotherapy Omission), Dana-Farber Cancer Institute
Partial breast irradiation - principles

- Partial Breast Irradiation (PBI) is a radiotherapy approach that treats only the lumpectomy cavity plus a 1-2 cm margin.

- Recurrences far from the initial tumor location are rares (≤ 15-20%).

- 75% of the recurrences are at or near the lumpectomy site and recurrence rate elsewhere in the breast is similar to the rate of contra-lateral second primary breast cancer.

- Sometimes logistical problems with external radiotherapy.
# Selection criteria

<table>
<thead>
<tr>
<th>Selection criteria</th>
<th>ASTRO</th>
<th>GEC-ESTRO</th>
<th>ASTRO</th>
<th>GEC-ESTRO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Suitable</td>
<td>Suitable</td>
<td>Cautionary</td>
<td>Cautionary</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>Invasive ductal carcinoma</td>
<td>Invasive ductal carcinoma</td>
<td>ILC</td>
<td>ILC Pure DCIS ≤ 3 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EIC ≤ 3 cm</td>
<td>No EIC</td>
</tr>
<tr>
<td><strong>Tumor size</strong></td>
<td>≤ 2 cm</td>
<td>≤ 3 cm</td>
<td>2.1 – 3 cm</td>
<td>≤ 3 cm</td>
</tr>
<tr>
<td><strong>Multifocality</strong></td>
<td>Clinically unifocal with total size ≤ 2 cm</td>
<td>Unifocal</td>
<td>Clinically unifocal with total size 2.1 - 3 cm</td>
<td>Multifocal (limited within 2 cm of index lesion)</td>
</tr>
<tr>
<td><strong>Lymph-vascular invasion</strong></td>
<td>Not allowed</td>
<td>Not allowed</td>
<td>Limited/focal</td>
<td>Not allowed</td>
</tr>
<tr>
<td><strong>Estrogen receptor</strong></td>
<td>+</td>
<td>+ or -</td>
<td>-</td>
<td>+ or -</td>
</tr>
<tr>
<td><strong>Surgical margins</strong></td>
<td>Negative (≥ 2 mm)</td>
<td>Negative (≥ 2 mm)</td>
<td>Close (&lt; 2 mm)</td>
<td>Close (&lt; 2 mm)</td>
</tr>
<tr>
<td><strong>Lymph node status</strong></td>
<td>pN0 (i-, i+)</td>
<td>pN0 (i-, i+)</td>
<td>pN0 (i-, i+)</td>
<td>pN1mi, pN1a</td>
</tr>
</tbody>
</table>

Smith, IJROBP, 2009; Polgár, Radiother Oncol, 2010; Correa, Pract Rad Oncol, 2017
# APBI – intraoperative

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>FU (yr)</th>
<th>WBI</th>
<th>IORT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targit A 50 kV</td>
<td>2000 - 2012</td>
<td>3,451</td>
<td>2.5</td>
<td>1.3%</td>
<td>3.3% 20 Gy</td>
</tr>
<tr>
<td>Eliot Electrons</td>
<td>2000 - 2007</td>
<td>1,305</td>
<td>5</td>
<td>0.4%</td>
<td>4.4% 21 Gy</td>
</tr>
</tbody>
</table>
APBI - postoperative

- Interstitial brachytherapy
  - 34 Gy/ 10 fractions, 2 fractions/day, 5 days

- Brachytherapy with MammoSite
  - 34 Gy/ 10 fractions, 2 fractions/day, 5 days

- External radiotherapy (IMRT)
  - 38.5 Gy/ 10 fractions, 2 fractions/day, 5 days
## Randomized phase III trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients</th>
<th>Control arm</th>
<th>Experimental arm</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-39/RTOG 0413</td>
<td>2005 - 2013</td>
<td>4,214</td>
<td>WBI 50 Gy +/- boost</td>
<td>34 Gy brachytherapy 34 Gy MammoSite or 38.5 Gy External RT</td>
<td></td>
</tr>
<tr>
<td>Canada RAPID</td>
<td>2006 - 2011</td>
<td>2,135</td>
<td>WBI 42.5 - 50 Gy +/- boost</td>
<td>38.5 Gy External RT</td>
<td></td>
</tr>
<tr>
<td>Italy IRMA</td>
<td>2007 -</td>
<td>3,302</td>
<td>WBI 45 - 50 Gy +/- boost</td>
<td>38.5 Gy External RT</td>
<td></td>
</tr>
<tr>
<td>UK Import Low</td>
<td>2006 - 2010</td>
<td>2,018</td>
<td>WBI 40 Gy (15 Fx)</td>
<td>40 Gy in 15 fx External RT</td>
<td>Coles, Lancet, 2017</td>
</tr>
</tbody>
</table>
UK Import Low Trial

Whole Breast

Reduced Dose

Partial

Coles, Lancet, 2017
• Local relapse rates very low for all groups
• Partial and Reduced dose radiotherapy are NOT inferior to Whole Breast Irradiation
• Photographic, patient, and clinical assessments recorded significantly lower adverse effects after reduced-dose or partial-breast radiotherapy compared with whole-breast radiotherapy

### UK Import Low Trial - results

<table>
<thead>
<tr>
<th>Local Relapse</th>
<th>WBI N = 674</th>
<th>Reduced dose N = 673</th>
<th>Partial N = 669</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-years cumulative incidence estimate (95% CI)</td>
<td>1.1% (0.5 – 2.3)</td>
<td>0.2% (0.02 – 1.2)</td>
<td>0.5% (0.2 – 1.4)</td>
</tr>
</tbody>
</table>

Coles, Lancet, 2017
Toxicity

“THE DOSE MAKES THE POISON”

APPLE SEEDS
CONTAIN AMYGDALIN ~0.6g/kg of seeds

PEARS
CONTAIN FORMALDEHYDE ~0.06g/kg

POTATOES
CONTAIN SOLANIN ~0.2g/kg (higher in green potatoes)

COURGETTES
CONTAIN CUCURBITACIN E Variable (higher in bitter courgettes)
Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D.,

RESULTS
The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72). Rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per gray (95% confidence interval, 2.9 to 14.5; P<0.001), with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. The proportional increase in the rate of major coronary events per gray was similar in women with and women without cardiac risk factors at the time of radiotherapy.
Cardiac toxicity

- Perfusion defects after irradiation of the left-sided breast have been revealed in up to 40% of patients within 2 years after treatment.

- Defects occurred in approximately 10% to 20% of patients with less than 5% of their left ventricle included within the RT field and in 50% to 60% of patients with more than 5% included.

- These perfusion defects are associated with corresponding wall-motion abnormalities.

Marks, IJROBP, 2005
Breath hold
Cosmesis

Fig. 2. Global score in each treatment arm after surgery. 0 = excellent; 1 = good; 2 = fair; 3 = poor.

Fig. 3. Global score in each treatment arm at 3-year follow-up. 0 = excellent; 1 = good; 2 = fair; 3 = poor.
Conclusions

• Local control matters

• Radiotherapy halves the local recurrence rate after BCS

• Local control has improved significantly over time

• Less is more:
  – Hypofractionation: shorter overall treatment time
  – Patient population without need for postoperative radiotherapy is under evaluation
  – Partial breast irradiation: reduction of treatment volume and treatment time

• Aim to reduce toxicity and improve quality of life
Loco-regional radiotherapy
Volume of radiotherapy

- Most common site of recurrence following mastectomy is the chest wall
  - 15 - 20%

- Periclavicular recurrences are more common in patients with 4 or more positive axillary nodes
  - 10%

- Axillary recurrences are less frequent after adequate axillary dissection (10 nodes or more removed)
  - 5%

- Tumor relapse at the internal mammary region is rarely reported

Locoregional radiotherapy
Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial

Mila Donker, MD, Geertjan van Tienhoven, MD, Marieke E Straver, MD, Philip Meijnen, MD, Prof Cornelis J H van de Velde, MD, Prof Robert E Mansel, MD, Prof Luigi Cataliotti, MD, A Helen Westenberg, MD, Prof Jean H G Klinkenbijl, MD, Lorenzo Orzalesi, MD, Willem H Bouma, MD, Huub C J van der Mijle, MD, Grard A P Nieuwenhuijzen, MD, Sanne C Veltkamp, MD, Leen Slaets, PhD, Nicole J Duez, MSc, Peter W de Graaf, MD, Thijs van Dalen, MD, Andreas Marinelli, MD, Herman Rijna, MD, Prof Marko Snoj, MD, Prof Nigel J Bundred, MD, Jos W S Merkus, MD, Prof Yazid Belkacemi, MD, Prof Patrick Petignat, MD, Dominic A X Schinagl, MD, Corneel Coens, MSc, Carlo G M Messina, MD, Jan Bogaerts, PhD, Prof Emiel J T Rutgers, MD

Published Online: 15 October 2014
AMAROS

After Mapping of the Axilla: Radiotherapy Or Surgery

- cT1-2, cN0, a positive sentinel node
- Treatment:
  Axillary node dissection versus radiotherapy of the axilla
- 4823 patients were randomized between 2001 and 2010
- 1425 patients had a positive sentinel node
- Median FU was 6.1 years
- Outcome:
  - Axillary recurrence at 5 years: Surgery vs Radiotherapy
    - 0.43% vs 1.19%
  - DFS at 5 years: 86.9% vs 82.7% (HR=1.18, p=0.18)
  - OS at 5 years: 93.3% vs 92.5% (HR=1.17, p=0.34)

Donker, Lancet Oncol, 2014
AMAROS

After Mapping of the Axilla: Radiotherapy Or Surgery

<table>
<thead>
<tr>
<th>Clinical sign of lymphoedema in the ipsilateral arm</th>
<th>Axillary lymph node dissection</th>
<th>Axillary radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3/655 (&lt;1%)</td>
<td>0/586 (0%)</td>
<td>0.25</td>
</tr>
<tr>
<td>1 year</td>
<td>114/410 (28%)</td>
<td>62/410 (15%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 years</td>
<td>84/373 (23%)</td>
<td>47/341 (14%)</td>
<td>0.003</td>
</tr>
<tr>
<td>5 years</td>
<td>76/328 (23%)</td>
<td>31/286 (11%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm circumference increase ≥10% of the ipsilateral upper or lower arm, or both</th>
<th>Axillary lymph node dissection</th>
<th>Axillary radiotherapy</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>33/655 (5%)</td>
<td>24/586 (4%)</td>
<td>0.497</td>
</tr>
<tr>
<td>1 year</td>
<td>32/410 (8%)</td>
<td>24/410 (6%)</td>
<td>0.332</td>
</tr>
<tr>
<td>3 years</td>
<td>38/373 (10%)</td>
<td>22/341 (6%)</td>
<td>0.080</td>
</tr>
<tr>
<td>5 years</td>
<td>43/328 (13%)</td>
<td>16/286 (6%)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Data are n/N (%), unless otherwise specified.

Table 2: Lymphoedema

Donker, Lancet Oncol, 2014
Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

EORTC IM-MS trial

• Role of internal mammary and medial supraclavicular lymph-node irradiation

• Centrally or medially located primary tumor OR

• Externally located tumor with axillary involvement

• Treatment:
  – breast-conserving surgery and WBI
  – mastectomy with or without PMRT
  – randomization between RT of IM-MS or not

Poortmans, NEJM, 2015
**EORTC IM-MS trial**

- 4004 patients were randomized between 1996 and 2004
- Median follow-up: 10.9 years

**Outcome:**

<table>
<thead>
<tr>
<th></th>
<th>Local</th>
<th>vs</th>
<th>Local + IM-MS</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS at 10 years:</td>
<td>69.1%</td>
<td>vs</td>
<td>72.1%</td>
<td>0.89</td>
<td>0.04</td>
</tr>
<tr>
<td>OS at 10 years:</td>
<td>80.7%</td>
<td>vs</td>
<td>82.3%</td>
<td>0.87</td>
<td>0.06</td>
</tr>
<tr>
<td>Breast cancer mortality:</td>
<td>14.4%</td>
<td>vs</td>
<td>12.5%</td>
<td>0.82</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Toxicity:**

- Pulmonary fibrosis: 1.7% vs 4.4% (p<0.0001)
- Cardiac fibrosis: 0.6% vs 1.2% (p=0.006)
- Cardiac disease: 5.6% vs 6.5% (p=0.25)
- Lymphedema: 10.5% vs 12%

Poortmans, NEJM, 2015
Regional Nodal Irradiation in Early-Stage Breast Cancer

NCIC-CTG MA.20 intergroup trial

• Role of regional nodal irradiation in early breast cancer

• High-risk node-negative or node-positive breast cancer

• Treatment:
  – Breast-conserving surgery and adjuvant treatment
  – WBI (50 Gy) or
  – WBI + RNI (50 Gy to IMC, supraclavicular area and axilla level III or (if < 10 nodes removed or > 3 nodes positive) level I to III

Whelan, NEJM, 2015
NCIC-CTG MA.20 intergroup trial

- 1832 patients were randomized between 2000 and 2007
- Median follow-up: 9.5 years

**Outcome:**

<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>vs</th>
<th>WBI + RNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRR FS at 10 years</td>
<td>92.2%</td>
<td>vs</td>
<td>95.2%</td>
</tr>
<tr>
<td>(HR=0.59, p=0.009)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFS at 10 years</td>
<td>77.0%</td>
<td>vs</td>
<td>82.0%</td>
</tr>
<tr>
<td>(HR=0.76, p=0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS at 10 years</td>
<td>81.8%</td>
<td>vs</td>
<td>82.8%</td>
</tr>
<tr>
<td>(HR=0.91, p=0.38)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer mortality</td>
<td>12.3%</td>
<td>vs</td>
<td>10.3%</td>
</tr>
<tr>
<td>(HR=0.80, p=0.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Toxicity:**

<table>
<thead>
<tr>
<th></th>
<th>WBI</th>
<th>vs</th>
<th>WBI + RNI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 or more pneumonitis</td>
<td>0.2%</td>
<td>vs</td>
<td>1.2%</td>
</tr>
<tr>
<td>(p=0.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphedema</td>
<td>4.5%</td>
<td>vs</td>
<td>8.4%</td>
</tr>
<tr>
<td>(p=0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Whelan, NEJM, 2015
N1-3 patients

1133 pN1–3 women with Mast+AD and systemic therapy

A  Locoregional recurrence first

- Log-rank 2p<0.00001

- 17.4% with RT, 21% No RT

B  Any first recurrence

- 10-year gain 11.7% (SE 3.2)
- RR 0.67 (95% CI 0.55–0.82)
- Log-rank 2p=0.00009

- 35.6% with RT, 45.5% No RT

C  Breast cancer mortality

- 20-year gain 7.9% (SE 3.3)
- RR 0.78 (95% CI 0.64–0.94)
- Log-rank 2p=0.01

- 46.8% with RT, 49.4% No RT

EBCTCG, Lancet, 2014
SIDE EFFECTS

ONE PILL CAN CHANGE YOUR LIFE

IN THEATERS FEBRUARY 8
Morbidity

- Lymphedema
- Mobility of the shoulder and arm
- Brachial plexopathy
Conclusion: patient selection is key

• pN0
  – no nodal irradiation
• More than 3 axillary nodes positive
  – nodal irradiation

• Dilemma
  – patients with 1 – 3 positive axillary nodes
  – consider regional node irradiation of the following factors:
    • Age under 50 years, extensive lymph-vascular invasion,
      G III, unfavorable molecular profile and large size