New strategies of radiotherapy in breast cancer

Rodrigo Arriagada

Karolinska Institutet, Stockholm, Sweden
Institut Gustave-Roussy (IGR), Villejuif, University of Paris-South, France &

III Chilean Breast Cancer Consensus
Coquimbo, August 2009
Role of radiotherapy in breast cancer

I. Some reminders
   a) dose effect
   b) local control and survival
   c) late iatrogenic effects
   d) volumes to be treated

II. New treatment strategies
I a) Radiation dose effect and local control

a) Predicting dose effect
b) IGR-PMH (Princess Margaret Hospital) series on locally advanced disease (IJROBP, 1985). N: 463 pts.
c) Multivariate analysis modelisation
d) Linear dose effect over 35 Gy
e) Prediction of a boost effect
Predicting dose-effect in breast cancer
Arriagada R et al. IJROBP, 11, 1751-7, 1985

Absolute risk

Similar slopes for clinical and subclinical disease:

Boost effect: a 15 Gy dose increase decreases 2-fold the risk of LR
Prospective trials: corroboration

a) The Lyon study (N: 1,024 patients): + 10 Gy BCS for T ≤ 3 cm (RR: 0.66, multivariate analysis)

a) EORTC boost trial (N: 5,300 patients): + 16 Gy (RR: 0.51, multivariate analysis)

Boost vs no boost and age

≤ 40
HR: 0.51

41 - 50
HR: 0.65

51 - 60
HR: 0.64

> 60
HR: 0.51

Fig 3. Cumulative incidence of ipsilateral breast cancer recurrence according to age. Age (A) ≤ 40, (B) 41 to 50, (C) 51 to 60, and (D) > 60 years. HR, hazard ratio; O, occurrences; N, number of patients at risk.

Boost vs no boost and fibrosis

Fig 4. Cumulative incidence of moderate or severe fibrosis after 50 Gy irradiation or 50 Gy irradiation and a boost of 16 Gy.

Radiation dose effect in breast cancer

Arriagada R et al. Radiother Oncol 86, 285-6, 2008

Radiation dose effect:
After 35 Gy an additional dose of 15 Gy decreases relative risk two-fold
I b) Local control and survival effect

- Local control matters
- EBCTCG overview (2005)
Isolated loco-regional recurrences in the trials of any type of radiotherapy (RT) versus no RT

Absolute difference in risk of isolated local recurrence: 20%, mostly within the first 5 years.

EBCTCG, Lancet 366: 2087-2106, 2005
15-year breast cancer mortality in the trials of any type of radiotherapy (RT) versus no RT (Total: 24,000 women randomised in 46 trials)

Breast cancer mortality

Absolute difference in risk of death from breast cancer: 4%, mostly after the first 5 years.

Little difference in breast cancer mortality during the first 5 years.

EBCTCG, Lancet 366: 2087-2106, 2005
Breast cancer
More specific example: BCS ± radiotherapy

I. The EBCTCG 2000 overview showed a survival advantage for irradiated patients (n: > 7,000)

II. Local control matters

EBCTCG, Lancet 366: 2087-2106, 2005
BCS ± RT
6,097 node negative & 1,214 node positive

Isolated local recurrence

Breast cancer mortality

EBCTCG, Lancet 366: 2087-2106, 2005
Breast cancer
Mastectomy + axillary dissection ± radiotherapy

I. Overview 2006: 1 new trial, 11 updated
Total: 26 trials; 11,000 women, 7500 deaths
Median FU: 9 years

II. RT to chest wall and lymph node areas in most trials

III. Systemic therapy to both trial arms: 19 trials

EBCTCG, Overview 2006, PROVISIONAL RESULTS
### Effect of radiotherapy in the Mastectomy setting

Subgroup analyses: isolated local recurrence

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>RR</th>
<th>Abs 5-year gain</th>
<th>2 p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cNo</td>
<td></td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN-</td>
<td>1277</td>
<td>0.44</td>
<td>2.8 %</td>
<td>0.01</td>
</tr>
<tr>
<td>N+ 1-3</td>
<td>3316</td>
<td>0.25</td>
<td>15.7 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>N+ 4+</td>
<td>2813</td>
<td>0.30</td>
<td>22.3 %</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

cNo and pN-: smaller groups

EBCTCG, Overview 2006, PROVISIONAL RESULTS
### Effect of radiotherapy in the Mastectomy setting

**Subgroup analyses on breast cancer mortality**

<table>
<thead>
<tr>
<th>Factor</th>
<th>N</th>
<th>RR</th>
<th>Abs 20-year gain</th>
<th>2 p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cNo</td>
<td>1.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN-</td>
<td>1354</td>
<td>1.11</td>
<td>- 1.6 %</td>
<td>NS</td>
</tr>
<tr>
<td>N+ 1-3</td>
<td>3344</td>
<td>0.84</td>
<td>6.4 %</td>
<td>0.002</td>
</tr>
<tr>
<td>N+ 4+</td>
<td>2876</td>
<td>0.85</td>
<td>10.7 %</td>
<td>0.0008</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>0.89</td>
<td></td>
<td></td>
<td>0.00009</td>
</tr>
</tbody>
</table>

**cNo and pN- : smaller groups**

EBCTCG, Overview 2006, PROVISIONAL RESULTS
### Effect of radiotherapy in the Mastectomy setting

Subgroup analyses on OVERALL mortality

<table>
<thead>
<tr>
<th>Factor</th>
<th>Abs 20-year gain</th>
<th>2 p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pN-</td>
<td>-6.8 %</td>
<td>0.0005</td>
</tr>
<tr>
<td>N+ 1-3</td>
<td>2.7 %</td>
<td>0.05</td>
</tr>
<tr>
<td>N+ 4+</td>
<td>8.4 %</td>
<td>0.003</td>
</tr>
</tbody>
</table>

EBCTCG, Overview 2006, PROVISIONAL RESULTS
I c) Late iatrogenic effects

- Trials of ± RT were combined with those of less surgery + RT vs more surgery (38 trials: 29,587 women)
- Median follow-up: 10.3 years
- Excess incidence of contralateral breast cancer (rate ratio 1.22, SE 0.06, 2p = 0.0005).
- Excess of other second cancers (rate ratio 1.22, SE 0.06, 2p = 0.0002), heart disease (rate ratio 1.26, SE 0.06, 2p = 0.00001)
- Excesses were slight during the first 5 years, but continued after year 15.
Effect of RT on CBC incidence
(46 trials of adding radiotherapy, and 17 trials of radiotherapy vs more surgery)
(30,193 women)

EBCTCG, Overview 2006, PROVISIONAL RESULTS
Effect of RT on NON - BREAST CANCER MORTALITY

(33,738 women)

EBCTCG, Overview 2006, PROVISIONAL RESULTS
**Effect of radiotherapy on incidence of second cancers before recurrence of breast cancer**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Events</th>
<th>RR</th>
<th>2 p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1534</td>
<td>1.22 *</td>
<td>0.0002</td>
</tr>
<tr>
<td>Lung</td>
<td>255</td>
<td>1.60</td>
<td>0.0002</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>32</td>
<td>1.89</td>
<td>0.08</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>59</td>
<td>1.71</td>
<td>0.04</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>26</td>
<td>2.34</td>
<td>0.03</td>
</tr>
<tr>
<td>Other sites</td>
<td>1,020</td>
<td>1.07</td>
<td>NS</td>
</tr>
</tbody>
</table>

* 20-year loss: 1.8 % (9.9 % vs 11.7 %)

EBCTCG, Overview 2006, PROVISIONAL RESULTS
Effect of RT on
SECOND CANCERS
(29,094 women)

EBCTCG, Overview 2006, PROVISIONAL RESULTS
## Effect of radiotherapy on mortality from circulatory diseases

<table>
<thead>
<tr>
<th>Cause death</th>
<th>Events</th>
<th>RR</th>
<th>2 p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory disease</td>
<td>1598</td>
<td>1.26</td>
<td>0.00001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1185</td>
<td>1.28 *</td>
<td>0.00005</td>
</tr>
<tr>
<td>Stroke</td>
<td>352</td>
<td>1.12</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>61</td>
<td>1.69</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* 20-year loss: 1.5% (7.2 % vs 8.8 %)

EBCTCG, Overview 2006, PROVISIONAL RESULTS
Effect of RT on HEART DEATH

EBCTCG, Overview 2006, PROVISIONAL RESULTS
I d) Adjuvant RT: Volumes to be treated

Standard treatments

- **Whole breast** after breast-conserving surgery: all patients
- **Partial breast irradiation**: experimental
- **Tumour bed**: boost dose at least in younger patients, probably in all
- **Chest wall**: in high-risk patients (N+ and selected N-)
Adjuvant RT: Volumes to be treated

Confounded questions

• Most trials of post-mastectomy RT compared loco-regional recurrence rates with or without loco-regional RT

• Most trials of radiotherapy after breast-conserving surgery compared breast irradiation with no RT (without regional radiotherapy)

• Value of SC-IMC: only two relatively recent trials

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Adjuvant RT : Volumes to be treated
Axilla

• Useless if N- and in N+ with complete axillary dissection

• The risk of axillary recurrence is 1.2% *

• The risk of arm complications is increased *
  - Edema, impaired mobility, pectoral sclerosis
  - Brachial plexopathy
  - Sarcoma (Stewart & Treves lymphangiosarc.)

Adjuvant RT: Volumes to be treated
Supraclavicular nodes

- Useless if axilla N-
- Controversial in axilla N+
- The risk of complications is increased
  - Arm edema
  - Vascular complications
  - Pneumopathy
  - Brachial plexopathy

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Adjuvant RT : Volumes to be treated
Internal mammary chain (IMC)

• Controversial +++ (Lyon, EORTC trials)

• The risk of long-term complications is increased
  ➢ Heart irradiation
  ➢ Lung, oesophagus
  ➢ Vertebral bodies

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### IGR indication of adjuvant radiotherapy

**Summary (after complete surgical resection)**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>N</th>
<th>Breast/chest wall</th>
<th>SC - IMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast-conserving</td>
<td>N -</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>N +</td>
<td>Yes</td>
<td>Yes *</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>N -</td>
<td>No **</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>N +</td>
<td>Yes</td>
<td>Yes *</td>
</tr>
</tbody>
</table>

* Waiting for EORTC trial results
** Except if incomplete surgery, or grade III and IVE +++; if high risk: SUPREMO randomised trial
N+ and IMC irradiation
New chapter?

• Waiting for the EORTC long-term results
• Focus on high-risk population?

• N+ and central/internal quadrants: 50% N+? ¹
• Role of sentinel node (IMC biopsy)? ²
• Irradiation of IMC N+ patients? ³

¹ Arriagada R et al. Radiother Oncol 11: 213-22, 1988
II New radiotherapy strategies

→ Open questions

• Volumes:
  • Chest wall in N- at risk and some N+ (SUPREMO)
  • IMC + SC (EORTC closed, 4000 patients)
  • Accelerated partial breast irradiation (APBI)

• Doses
  • Boost: “super” boost in the younger (NKI)
  • DCIS: boost 16 Gy (BIG)
  • Hypofractionation
SUPREMO (BIG 2-04)
Selective Use of Postoperative Radiotherapy after Mastectomy

Phase III randomised trial of chest wall RT in intermediate-risk breast cancer

Accelerated partial breast irradiation (APBI)

Céline Bourgier, Hugo Marsiglia
Breast Unit - Radiation Oncology Department
Institut Gustave Roussy
Rationale of APBI and hypotheses

- Does the entire breast need to be treated?
- A more limited volume surrounding the tumor?
- A shorter treatment time?

- 80-90% of local relapses (LR) occur in the same site ("true recurrences")
- 10-20% of LR occur "elsewhere" in the breast
- Percentages are variable according to series and follow-up

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APBI concept

High dose / fraction and high total dose in a small breast volume

To spare normal tissues as lung and heart
To have a good aesthetic outcome

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APBI: definitions

- Small tumours

APBI allows:
- to reduce irradiated breast volume (target: lumpectomy cavity + 1-2 cm margin)
- A large radiation dose/fraction (brachytherapy or external RT)
- to complete treatment in ONE week after lumpectomy instead of 6-7 weeks

Courtesy A. Taghian
Different treatment modalities of APBI

- **Interstitial Brachytherapy:**
  - Low dose-rate
  - High dose-rate

- **Intracavitary therapy:**
  - Orthovoltage photons (Intrabeam, UK)
  - Intraoperative electrons (Milan)
  - Brachytherapy (Mammosite)
APBI 3D-conformal External Beam Radiation Therapy (3D-EBRT)

- 3 different techniques

  - Vicini (William Beaumont H, Royal Oak)
  
  - Formenti (MSKCC, New York)
  
  - Taghian (MGH, Boston) / IGR

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APBI 3D-conformal EBRT, Vicini

- Use of IMRT with Noncoplanar 3-, 4-, or 5- photon beams
- Patients are treated in supine position
APBI 3D-conformal EBRT, Formenti

- Opposed pair of mini-tangentials
- Patients treated on a dedicated table (prone position)
Lumpectomy cavity delineation

PTV = CTV + 5mm
APBI 3D-conformal EBRT Boston - IGR

- A three-field technique
- Patients treated in supine position
Comparison of three APBI techniques

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Present series</th>
<th>Formenti et al. series*</th>
<th>Vicini et al. series†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>61</td>
<td>47</td>
<td>31</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Premenopausal and postmenopausal</td>
<td>Postmenopausal</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td>Maximum tumor size allowed</td>
<td>2 cm</td>
<td>2 cm</td>
<td>3 cm</td>
</tr>
<tr>
<td>Median tumor size (cm)</td>
<td>0.9 cm (0.1–2.0)</td>
<td>0.9 cm (0.13–1.9)</td>
<td>0.9 cm (0.1–2.7)</td>
</tr>
<tr>
<td>Negative margins</td>
<td>≥2 mm</td>
<td>≥5 mm</td>
<td>≥2 mm</td>
</tr>
<tr>
<td>Receptors</td>
<td>Negative or positive</td>
<td>Positive only</td>
<td>NA</td>
</tr>
</tbody>
</table>

Taghian, IJROBP 2006
## Comparison of three APBI techniques II

<table>
<thead>
<tr>
<th></th>
<th>Boston</th>
<th>Formenti</th>
<th>Vicini</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total dose</strong></td>
<td>32 / 36 / 40 Gy</td>
<td>30 Gy</td>
<td>38.5 Gy ICRU</td>
</tr>
<tr>
<td>to the 95% isodose</td>
<td>to the 95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>surface</td>
<td>isodose surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose / fraction</strong></td>
<td>4 Gy</td>
<td>6 Gy</td>
<td>3.85 Gy</td>
</tr>
<tr>
<td><strong>Radiation schedule</strong></td>
<td>Twice daily</td>
<td>in 2 weeks Days 1, 3, 5, 8, 10</td>
<td>Twice daily</td>
</tr>
<tr>
<td></td>
<td>1 week</td>
<td></td>
<td>1 week</td>
</tr>
</tbody>
</table>

Taghian, IJROBP 2006

- 2007 : > 200 pts
- 2007 : 78 pts
- 2007 : 91 pts
Ongoing randomised trials comparing WBRT vs. APBI

The largest is the NSABP-B39

In the APBI arm, most of patients are treated by the Vicini’s technique

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. expected to accrue</th>
<th>WBRT dose</th>
<th>APBI technique/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP B-39/ RTOG 0413</td>
<td>3000</td>
<td>45–50 Gy to whole breast + 10–16 Gy boost to tumour bed</td>
<td>Interstitial brachytherapy (34 Gy/10 F/5 D) MammoSite (34 Gy/10 F/5 D) 3D-Conformal EBRT (38.5 Gy/10 F/5 D)</td>
</tr>
</tbody>
</table>

> 3,000 patients already enrolled

R. Arriaga Data from NSABP B-39/RTOG 0413 Protocol
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Count</th>
<th>Treatment Details</th>
<th>Radiotherapy Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC-ESTRO Working Group</td>
<td>1170</td>
<td>50–50.4 Gy to whole breast + 10 Gy boost to tumour bed</td>
<td>Interstitial brachytherapy: 32 Gy/8 F (HDR), 31.3 Gy/7 F (HDR), 50 Gy (PDR)</td>
</tr>
<tr>
<td>University College of London</td>
<td>1600</td>
<td>WBRT (per centre protocol) + boost to tumour bed</td>
<td>Intra-operative, EBRT 20 Gy/1 F at the applicator surface (5 Gy/1 F at 1 cm)</td>
</tr>
<tr>
<td>European Institute of Oncology</td>
<td>824</td>
<td>50 Gy to whole breast + 10 Gy boost to tumour bed</td>
<td>Intra-operative, EBRT 21 Gy/1 F</td>
</tr>
</tbody>
</table>

Strnad & Polgar (GEC-ESTRO Working Group), Vaidya et al. (2004), and Veronesi et al. (2003)
## Ongoing randomised trials comparing WBRT vs. APBI

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPID, Ontario</td>
<td>2,128</td>
<td>42.5 Gy/16 f / 22 d</td>
<td>38.5 Gy/10 f / 5-8 d</td>
</tr>
<tr>
<td>IMPORT -LOW, UK</td>
<td>1,935</td>
<td>40 Gy/15 f / 21 d</td>
<td>40 Gy/15 f or 36 Gy low &amp; 40 Gy T</td>
</tr>
</tbody>
</table>

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Preliminary results

Median FU: 66 months (range, 18–101 months)

- PBI is well-tolerated
- No differences on local relapses
- No differences on else-where local recurrences

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Polgar, 2007
<table>
<thead>
<tr>
<th>Consensus</th>
<th>Indication</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASTRO *</td>
<td>Clinical practice</td>
<td>“Suitable”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Cautionary”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Unsuitable”</td>
</tr>
<tr>
<td>Danish **</td>
<td>Inclusion criteria in APBI protocols</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparability among studies is low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More questions emerge than answers</td>
<td></td>
</tr>
<tr>
<td>St. Gallen ***</td>
<td>It should still be considered experimental</td>
<td></td>
</tr>
</tbody>
</table>

** Offersen BV et al. Radiother Oncol 90: 1-13, 2009
Proposal of the study
NKI – IGR - Karolinska

Markers placed in the tumor at the time of tumor biopsies

*Pre-operative RT*

Image guided RT (IGRT) with cone-beam accelerator

(daily CT scan on accelerator for set-up)

→ Optimal radiation dose delivery
Patient inclusion; n=120/3 yrs

- Women > 65 yrs
- Adenocarcinoma (no lobular ca)
- Unifocal lesion on mammography (no diffuse microcalcifications) and MRI
- Tumor 1,0 - 3,0 cm
- pN0 (sentinel node pre-RT)

10 x 4 Gy in 2 weeks
Preoperative partial breast irradiation

T: 1 - 3 cm, N(-) patients

**Diagnosis**
- Biopsy + FNA
- Tumor marking
- Blood samples
- US
- MRI
- PET*

**Radiotherapy**
- D - x
- 10-days RT
  - D1 - D12 40 Gy 10fx 2wks
- MRI PET*

**Sentinel node**
- FNA d2
- FNA d12

**Surgery at 6 weeks after RT**

**Biologic studies**
- Genomics
- Proteomics

* : optional
Radiation dose: ongoing boost trials

- **Younger patients** and BCS + RT: higher risk of local recurrence

- **DCIS**: local recurrence risk higher than 10% at five-years in BCS + RT (half of recurrences are invasive)
Local recurrence according to age
IGR database

IGR database: local recurrence according to age group

Trial Design: Bartelink et al.

T1-2, N0-1
Age < 50 yrs
Preoperative diagnosis
↓
Lumpectomy with free margins (Genomic study)
Sentinel node or axillary dissection
↓
Breast radiotherapy 50 Gy
↓
RANDOMISATION (n: 1,160 pts, 12 to 7% at 10 years)

Boost 16 Gy

Boost 26 Gy

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A randomised phase III study of radiation doses and fractionation schedules in non-low risk DCIS of the breast

Boon H Chua
Peter MacCallum Cancer Centre
Melbourne, Australia
STUDY DESIGN

Prospective multi-centre unblinded 2x2 factorial phase III randomised trial

Stratification

- Age (<50, 50+)
- Margin (<1mm, 1 mm+)
- Tamoxifen (yes, no)
- Centre

Treatment

- Whole breast RT
- Whole breast and boost RT
- Standard fractionation
- Shorter fractionation
**PROTOCOL THERAPY**

<table>
<thead>
<tr>
<th>Fractionation</th>
<th>Whole breast</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>50 Gy / 25 F</td>
<td>16 Gy / 8 F</td>
</tr>
<tr>
<td>Shorter</td>
<td>42.5 Gy / 16 F</td>
<td>15 Gy / 6 F</td>
</tr>
</tbody>
</table>

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ELIGIBILITY

Women with completely resected DCIS

• Age <50

• Age 50+ plus at least one of the following:
  – Symptomatic presentation
  – Palpable tumour
  – Multifocal disease
  – Tumour size 15+ mm
  – Intermediate/high nuclear grade
  – Central necrosis
  – Comedo histology
  – Radial resection margin <10 mm

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Switching to hypofractionation?

- Whelan study (N = 1,234)
- UK randomised trials (N = 5,861)
- Recent published results:
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>hypo RT</th>
<th>FU (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whelan</td>
<td>1234, N-</td>
<td>42.5 Gy / 16 fx</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>/ 3 wks</td>
<td></td>
</tr>
<tr>
<td>Yarnold/</td>
<td>1410, all N</td>
<td>42.9 / 13 fx</td>
<td>10</td>
</tr>
<tr>
<td>Owen</td>
<td></td>
<td>39 Gy / 13 fx</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>/ 5 wks</td>
<td></td>
</tr>
<tr>
<td>START A</td>
<td>2236, all N</td>
<td>41.6 Gy / 13 fx</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39 Gy / 13 fx</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 wks</td>
<td></td>
</tr>
<tr>
<td>START B</td>
<td>2215, all N</td>
<td>40 Gy / 15 fx</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>/ 3 wks</td>
<td></td>
</tr>
</tbody>
</table>

Whelan TJ et al. Sem Radiat Oncol 18: 257-64, 2008
HERT
Cancer Care Ontario Regional Cancer Centres; Princess Margaret Hospital; Montreal General Hospital

Local recurrence free survival

N=1234

Short fractionated schedule
N=622
42.5Gy /16f

Long fractionated schedule
N=612
50Gy /25f

Median follow-up: 69 months

Whelan T et al. JNCI 94: 1143-50, 2002
Long-Term Results of a Randomized Trial of Accelerated Hypofractionated Whole Breast Irradiation (AHWBI) Following Breast Conserving Surgery

T Whelan, JP Pignol, J Julian, L Grimard, J Bowen, F Perera, K Schneider, A Fyles, S Gulavita, W Shelley, C Freeman, and M Levine
for the
Ontario Clinical Oncology Group
Effectiveness of radiation directly proportional to fraction size and total dose (TD)*

Regimens of equal effectiveness can be developed by increasing the fraction size with a modest reduction in TD

* Fowler JF. *Br J Radiol* 62:679-694; 1989
## Dose/Fraction and BED*

<table>
<thead>
<tr>
<th>Schedule BED</th>
<th>Fraction</th>
</tr>
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<tbody>
<tr>
<td>Gy / frac</td>
<td>Size (Gy)</td>
</tr>
<tr>
<td>$\alpha/\beta=3.5$</td>
<td></td>
</tr>
<tr>
<td>50 / 25</td>
<td>2.0</td>
</tr>
<tr>
<td>42.5 / 16</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* Biological Effective Dose; time factor not included
PATIENT POPULATION

**Inclusion Criteria**
- Invasive carcinoma of the breast
- Treated by BCS
- Axillary lymph nodes negative

**Exclusion Criteria**
- Disease involving margins of excision
- Breast width > 25 cm
Trial Design

Node-Negative Post BCS

Stratification
- Age: < 50y, ≥ 50y
- Size: < 2cm, > 2cm
- Systemic therapy: Tamoxifen, chemo, none
- Center

SWBI 50 Gy/25

AHWBI 42.5 Gy/16
1,234 Patients

Recruitment April ‘93 – September ‘96

Median follow-up is 12 years

SWBI 612 patients

AHWBI 622 patients
### BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>SWBI n=612</th>
<th>AHWBI n=622</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50 yrs</td>
<td>148 (24)</td>
<td>157 (25)</td>
</tr>
<tr>
<td>Tumor size $\geq$ 2 cm</td>
<td>203 (33)</td>
<td>190 (31)</td>
</tr>
<tr>
<td>ER negative</td>
<td>157 (26)</td>
<td>165 (26)</td>
</tr>
<tr>
<td>Tumor grade high</td>
<td>116 (21)</td>
<td>117 (20)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>266 (41)</td>
<td>265 (41)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>72 (11)</td>
<td>75 (11)</td>
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</table>
LOCAL RECURRENCE

Recurrence Probability

<table>
<thead>
<tr>
<th>Years Since Randomization</th>
<th>At Risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SWBI</td>
</tr>
<tr>
<td></td>
<td>612</td>
</tr>
<tr>
<td></td>
<td>597</td>
</tr>
<tr>
<td></td>
<td>578</td>
</tr>
<tr>
<td></td>
<td>562</td>
</tr>
<tr>
<td></td>
<td>550</td>
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<tr>
<td></td>
<td>533</td>
</tr>
<tr>
<td></td>
<td>499</td>
</tr>
<tr>
<td></td>
<td>485</td>
</tr>
<tr>
<td></td>
<td>470</td>
</tr>
<tr>
<td></td>
<td>449</td>
</tr>
<tr>
<td></td>
<td>410</td>
</tr>
<tr>
<td></td>
<td>317</td>
</tr>
<tr>
<td></td>
<td>218</td>
</tr>
<tr>
<td></td>
<td>AHWBI</td>
</tr>
<tr>
<td></td>
<td>622</td>
</tr>
<tr>
<td></td>
<td>609</td>
</tr>
<tr>
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<td>592</td>
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<tr>
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<td>569</td>
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<tr>
<td></td>
<td>548</td>
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<tr>
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<td>524</td>
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<td></td>
<td>500</td>
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<tr>
<td></td>
<td>472</td>
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<tr>
<td></td>
<td>447</td>
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<tr>
<td></td>
<td>406</td>
</tr>
<tr>
<td></td>
<td>330</td>
</tr>
<tr>
<td></td>
<td>214</td>
</tr>
</tbody>
</table>
OVERALL SURVIVAL

Survival Probability

At Risk:
- SWBI: 612 606 594 583 573 559 535 519 505 487 453 355 242
- AHWBI: 622 617 605 592 576 562 539 517 495 482 455 369 241

Years Since Randomization
## LOCAL RECURRENCE RATES AT 10 YEARS

<table>
<thead>
<tr>
<th>Stratum</th>
<th>SWBI</th>
<th>AHWBI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>10.7</td>
<td>7.5</td>
</tr>
<tr>
<td>≥ 50</td>
<td>5.4</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Tumor Size (cm)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>6.1</td>
<td>5.4</td>
</tr>
<tr>
<td>≥ 2</td>
<td>7.8</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>Systemic Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.9</td>
<td>6.5</td>
</tr>
<tr>
<td>No</td>
<td>7.4</td>
<td>5.8</td>
</tr>
</tbody>
</table>
## COSMETIC OUTCOME
### BY TIME AND TREATMENT*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Year</th>
<th>5 Year</th>
<th>10 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SWBI</strong></td>
<td>83% (604)</td>
<td>77% (498)</td>
<td>79% (423)</td>
<td>71% (216)</td>
</tr>
<tr>
<td><strong>AHWBI</strong></td>
<td>84% (616)</td>
<td>77% (518)</td>
<td>78% (448)</td>
<td>70% (235)</td>
</tr>
</tbody>
</table>

* % excellent or good (# evaluable)
CONCLUSIONS

AHWBI

- Demonstrated excellent local control
- Was not associated with long-term morbidity
  - Skin and soft tissue toxicity
  - Breast cosmesis
  - Non-cancer deaths
CONCLUSIONS

AHWBI

- More convenient
- Less costly*
- May be considered an important option for women with $T_{1-2} N_0$ breast cancer treated with BCS

Hypofractionation in breast-conserving surgery

START trials: inclusion criteria

- Operable invasive breast cancer
- pT1-3a, pN0-1
- Requiring RT after BCS or mastectomy
  - In fact: > 80 - 90% BCS
  - T 3 cm or + : 10%
- Mean age: 57 yrs
- 75% N(-)
Hypofractionation in breast-conserving surgery

| Total dose (Gy) | Dose/fraction | Number of fractions | Weeks | 5-year LRR (%) | 10-year BRR (%) | p | 5-year DM (%) | 5-year OM (%) | p (DM/OM) (DM/OM) | Breast changes* | 95% CI |
|-----------------|----------------|---------------------|-------|----------------|----------------|---|---------------|---------------|----------------|----------------|----------------|---------|
| RMH/GOC (N=1410) |
| 50              | 2              | 25                  | 5     | 7.9            | 12.1           |   | NR            | NR            |                | 6.4%†           | 3.6-9.2%       |
| 39              | 3              | 13                  | 5     | 9.1            | 14.8           |   |                |                |                | 3.9%           | 1.8-6.1%       |
| 42.9            | 3              | 25                  | 5     | 7.1            | **9.6**        | 0.027‡ |                |                |                | **11.2%**       | 7.8-14.7%     |
| STARTA (N=2236) |
| 50              | 2              | 25                  | 5     | 3.6            |                |   | 9.8           | 11.1          |                | 1§             |                |
| 41.6            | 3              | 13                  | 5     | 3.5            |                |   | 9.5           | 11.3          |                | 1.09           | 0.85-1.40     |
| 39              | 3              | 13                  | 5     | 5.2            |                |   | NS            | 11.9          | 10.7           | 0.69           | 0.52-0.91     |
| STARTB (N=2215) |
| 50              | 2              | 25                  | 5     | 3.3            |                |   | 10.2          | 11            |                | 1§             |                |
| 40              | 2.67           | 15                  | 3     | 2.2            |                | 0.35| 7.6           | 8             | 0.01/0.03      | 0.83           | 0.66-1.04     |

RMH= Royal Marsden Hospital. GOC=Gloucestershire Oncology Centre. LRR=locoregional recurrence rate. BRR=breast recurrence rate. DM=distant metastasis. OM=overall mortality. N=study size. NR=not reported. NS=not statistically significant. *Breast appearance assessed by photographs. Marked changes for RMH/GOC trial and mild plus marked changes for START trials. †5-year rates. ‡Difference between 39 Gy and 42.9 Gy groups. §Hazard ratio.

Table: Summary of results of UK randomised trials of hypofractionated radiotherapy in breast cancer
Hypofractionation in breast-conserving surgery

START trials: comments

• These randomised trials now suggest that different fractionation radiation schemes will lead to minimum outcome differences for patients with early BC

• H&N cancers: hyperfractionation better results

• Different biological features in breast cancer

Hypofractionation in breast-conserving surgery

RMH / START trials: comments

• The 3.3 Gy schedule (total dose of 42.9 Gy) gave the best local control at 5 years but the worst cosmetic results
• However, with a dose per fraction 3.2 Gy or lower, results were similar to conventional fractionation
• START B: hypofractionation related with better survival outcome, without effect on local control: false negative result?

Hypofractionation in breast-conserving surgery

START trials: comments

• The heterogeneity on surgical extent and systemic treatments should have been corrected through the randomisation

• However, the most important limitations are the rather short follow-up (5-6 years)

• Convenient schedule: reduces patient visits and waiting lists in several cancer centres

Hypofractionation in breast-conserving surgery

Caution: late effects

• Cosmesis is worse after 5-year follow-up (1)
• Radiation late side-effects increase with time (2)
• Toxicity increased if chemotherapy is added, significant rise in congestive heart failure after 10-years follow-up (3)

Modified dose treatment schedules

a) Large randomised trials (Whelan, Yarnold et al, UK START trials)

b) Importance of long-term follow-up (> 15 yrs)

→ Late iatrogenic effects, including cosmesis

New radiation approaches in breast cancer

CONCLUSIONS I

• Areas of true controversy are decreasing regarding adjuvant radiotherapy
• Local control and radiation technique matter
• Lymph node irradiation? Waiting for results of randomised trials: High-risk patients
• Main challenge: to decrease hazards
  ⇒ Good indications (consistent high-risk)
  ⇒ Excellent radiation techniques
• N-: to define consistent risk factors

R. Arriagada
CONCLUSIONS II

• Exploring:
  • Super-boost in younger patients
  • Boost in DCIS
  • Partial breast irradiation
  • Hypofractionated radiotherapy

Need for a long-term follow-up
New radiation approaches in breast cancer

CONCLUSIONS III

• Long-term follow-up of good quality is extremely important

• It should also be applied to all new radiation approaches and others adjuvant treatments

• If not, long-term complications will remain unknown

R. Arriagada
## Practical attitudes local treatments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IGR</th>
<th>Karolinska</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin involved</td>
<td>&lt; 2 mm</td>
<td>&lt; 1mm</td>
</tr>
<tr>
<td>Optimal BCS – RT</td>
<td>&lt; 6 wks</td>
<td>&lt; 8 wks</td>
</tr>
<tr>
<td>If adjuvant CT</td>
<td>After CT</td>
<td>After CT</td>
</tr>
<tr>
<td>BRCA testing (high risk)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prophylactic bilateral mastectomy if BC</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Practical attitudes local treatments II

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Karolinska</th>
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<tbody>
<tr>
<td>Post-mastectomy RT</td>
<td>N+</td>
<td>&gt; 3 N+</td>
</tr>
<tr>
<td>T3</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>T4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>N (-)</td>
<td>g3, LVI+++</td>
<td>No</td>
</tr>
<tr>
<td>RT after neo-adjuvant</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>BCS: breast</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>DCIS breast</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Boost for IC</td>
<td>All</td>
<td>&lt; 40 yrs</td>
</tr>
<tr>
<td>DCIS boost</td>
<td>Trial</td>
<td>No</td>
</tr>
<tr>
<td>Partial Bl</td>
<td>Trial</td>
<td>No</td>
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<td>IGR</td>
<td>Karolinska</td>
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<tr>
<td>---------------------------------</td>
<td>----------</td>
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</tr>
<tr>
<td>Lymph node RT</td>
<td>N+</td>
<td>&gt; 3 N+</td>
</tr>
<tr>
<td>Hypofractionated RT 42.56 Gy / 16 f</td>
<td>Poor PS</td>
<td>R breast</td>
</tr>
<tr>
<td>Neo-adjuvant therapy</td>
<td>&gt; 3 cm</td>
<td>&gt; 4 – 5 cm</td>
</tr>
</tbody>
</table>

R. Arriagada