4th Symposium on Primary Breast Cancer in Older Women
Theme: Putting personalising care into practice

Friday 3 March 2017
East Midlands Conference Centre
University Park, Nottingham NG7 2RJ
www.nottingham.ac.uk/medicine/breastmeetings
Local and systemic therapies:

*Selecting for radiation therapy*

Philip Poortmans, MD, PhD
03 March 2017
Conflict of interest:

I am a radiation oncologist
Selecting for radiation therapy

1. Introduction

2. The role of radiation therapy

3. A particular case

4. Discussion

5. Conclusions
Selecting for RT: Introduction
Selecting for RT: Introduction

Cohort expectation of life at age 65 according to historic and projected mortality rates, persons who reached age 65 1850–2050, England and Wales
Selecting for RT: *Introduction*

Predicted relative survival up to 10 years after diagnosis for European women with breast cancer in 2000-2002
Evidence is what we need to fully inform the patient...
1. Introduction

2. The role of radiation therapy

3. A particular case

4. Discussion

5. Conclusions
Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials

Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)*

Lancet 2011; 378: 1707-16
Selecting for RT: *The role of RT*

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.

- **Any first recurrence**
  - 0 Gy BCS 31.0% ± 50 Gy 15.6%  BCS+RT
  - 10-y gain 15.4% (SE 1.1) Logrank 2p < 0.00001

- **Breast cancer mortality**
  - 0 Gy BCS 20.5% ± 50 Gy 17.2%  BCS+RT
  - 15-y gain 3.3% (SE 1.3) Logrank 2p = 0.005

EBCTCG Lancet 2011; 378: 1707–1716
Effect of RT after BCS on recurrence and breast cancer mortality in pN+ women.

- 1050 pN+ women

**Any first recurrence**

- BCS: 63.7%
- BCS + RT: 42.5%

- 0 Gy ± 50 Gy

**Breast cancer mortality**

- BCS: 51.3%
- BCS + RT: 42.8%

- 0 Gy ± 50 Gy

10-y gain 21.2% (SE 3.4)
Logrank 2p < 0.00001

15-y gain 8.5% (SE 3.4)
Logrank 2p = 0.01

2.5:1

-8.5%
Selecting for RT: The role of RT

RT after tumourectomy: not always required?

---

Overview of prospective clinical trials evaluating postoperative radiation therapy omission.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients</th>
<th>Study design</th>
<th>Local relapse</th>
<th>DFS</th>
<th>OS</th>
<th>Median FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al., 2002 [11]</td>
<td>1009</td>
<td>TAM vs. placebo + RT vs. TAM + RT</td>
<td>16.5% vs. 9.3% vs. 2.8% (p = 0.008; p &lt; 0.0001; p = 0.01)</td>
<td>–</td>
<td>93% vs. 94% vs. 93% (p = 0.93)</td>
<td>87.5 months</td>
</tr>
<tr>
<td>Fyles et al., 2004 [7]</td>
<td>769</td>
<td>TAM vs. TAM + RT</td>
<td>7.7% vs. 0.6% at 5 years (p &lt; 0.001)</td>
<td>84% vs. 91% at 5 years (p = 0.004)</td>
<td>92.8% vs. 93.2% (p = 0.83)</td>
<td>67.2 months</td>
</tr>
<tr>
<td>Pötter et al., 2007 [9]</td>
<td>869</td>
<td>TAM/Al vs. TAM/Al + RT</td>
<td>5.1% vs. 0.4% (p = 0.0001)</td>
<td>HR 3.48 (p = 0.0021)</td>
<td>94.5% vs. 97.9% (p = 0.18)</td>
<td>53.8 months</td>
</tr>
<tr>
<td>Hughes et al., 2013 [10]</td>
<td>636</td>
<td>TAM vs. TAM + RT</td>
<td>9% vs. 2% (p &lt; 0.001)</td>
<td>–</td>
<td>66% vs. 67% at 10 years (p = 0.64)</td>
<td>151.2 months</td>
</tr>
<tr>
<td>Blamey et al., 2013 [12]</td>
<td>1135</td>
<td>- without or with TAM - without or with RT 2 × 2 factorial design</td>
<td>- 13% vs. 4% - 11% vs. 3% Both treatments 0% (p &lt; 0.001)</td>
<td>–</td>
<td>96% at 10 years</td>
<td>167 months</td>
</tr>
<tr>
<td>Kunkler et al., 2013 [13]</td>
<td>1326</td>
<td>TAM/Al vs. TAM/Al + RT</td>
<td>4.1% vs. 1.3% (p = 0.0002)</td>
<td>–</td>
<td>93.9% vs. 93.9% (p = 0.34)</td>
<td>60 months</td>
</tr>
</tbody>
</table>

Abbreviations: DFS, disease-free survival; OS, overall survival; FU, follow up; TAM, tamoxifen; Al, aromatase inhibitors; RT, radiation therapy; HR, Hazard Ratio.
Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial

R.W. Blamey\textsuperscript{a,j}, T. Bates\textsuperscript{b,*j}, U. Chetty\textsuperscript{c,j}, S.W. Duffy\textsuperscript{d,j}, I.O. Ellis\textsuperscript{a,j}, D. George\textsuperscript{e,j}, E. Mallon\textsuperscript{f,j}, M.J. Mitchell\textsuperscript{a,j}, I. Monypenny\textsuperscript{g,j}, D.A.L. Morgan\textsuperscript{a,j}, R.D. Macmillan\textsuperscript{a,j}, J. Patnick\textsuperscript{h,j}, S.E. Pinder\textsuperscript{i,j}
Selecting for RT: *The role of RT*

![Graph showing survival to first local recurrence by treatment actually received.](image)

**Fig. 2.** Survival to first local recurrence by treatment actually received.
Selecting for RT: The role of RT

Even in these patients with tumours of excellent prognosis, LR after conservative surgery without adjuvant therapy was still very high. This was reduced to a similar extent by either radiotherapy or tamoxifen but to a greater extent by the receipt of both treatments.
..., LR after conservative surgery without adjuvant therapy was still very high...

Personal note:

Virtually none of those pts would get adjuvant systemic treatment according to the Dutch guidelines
Selecting for RT: *The role of RT*

RT after tumourectomy: not always required?

- 0.5% (1% still acceptable?) per year = limit for LRR

- Mind late relapses!

- Role of systemic treatment?
Selecting for radiation therapy

1. Introduction

2. The role of radiation therapy

3. A particular case

4. Discussion

5. Conclusions
Selecting for RT: A particular case

- Born in 1918 ...
- Menarche 15; G0P0A0; familiar –
- Fashion specialist – kept a shop, smoked till 4 years before diagnosis
- Clinical history: breast reduction; hormonal replacement therapy until diagnosis (Ovestin = estriol)

- July 1996 (78 years old): she felt a large tumour laterally located in the right breast
- Biopsy: invasive ductal carcinoma
Selecting for RT: A particular case

- Modified radical mastectomy:
  - 4.0 cm invasive ductal carcinoma; tumour free margins
  - Axilla: 6/12 with capsular invasion up to apex
  - ER +; PR -
- Large hematoma post-surgery ➔ lymphatic drainage
Selecting for RT: A particular case

- Surgeon: "Do we need to irradiate this nice old lady?"
- Rad.Onc: "Let me see and talk with her to evaluate the general condition."
  - Excellent health for the age; ......
  - Back pain +++: < osteoporosis; M0
  - Local-regional complaints: lymphatic drainage
- Radiation therapy: chest wall + axilla levels 3-4; 50 Gy / 25 fractions
- Tamoxifen
Selecting for RT: A particular case

Follow-up

- June 1999 (after <3 years): stopped tamoxifen because of side effects
- September 2001 (after 5 years): NED; stopped regular FU ➔ / 5 years
- September 2006 (after 10 years): !!!!

- Identification obligation introduced in NL
- Age was not 88 but 98 !!!!
- NED; very active; travelling much.
- Drove car about 5 x / week: driving licence prolonged for 5 years.
- Some local & regional complaints ➔ continuation of lymphatic drainage
Selecting for RT: A particular case

Follow-up:

- 2008 (after 12 years): pleural effusion → Arimidex; stopped because it was cardiac & M0
- 2008: very ill due to abdominal problem → complete recovery
- 2010: fall in shower → osteoporotic vertebral fractures
- 2011: died at the age of 103,5
1. Introduction

2. The role of radiation therapy

3. A particular case

4. Discussion

5. Conclusions
This well-received book, now in its fifth edition, is unique in providing a detailed description of the technological basis of radiation therapy. Another novel feature is the collaborative writing of the chapters by North American and European authors. This considerably broadens the book's perspective and increases its applicability in daily practice throughout the world. The book is divided into two sections. The first covers basic concepts in treatment planning, including essential physics and biological principles related to time-dose fractionation, and explains the various technological approaches to radiation therapy, such as intensity-modulated radiation therapy, tomotherapy, stereotactic radiotherapy, and high and low dose rate brachytherapy. Issues relating to quality assurance, technology assessment, and cost-benefit analysis are also reviewed. The second part of the book discusses in depth the practical clinical applications of the different radiation therapy techniques in a wide range of cancer sites. All of the chapters have been written by leaders in the field. This book will serve to instruct and acquaint teachers, students, and practitioners in the various fields of oncology with the basic technological factors and approaches in radiation therapy.
Selecting for RT: Discussion

- Breast
- Boost
- PBI
- Thoracic wall
- LN supraclavicular
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary
- Heart
Selecting for RT: *Discussion*

Free respiration

Breath hold

*Courtesy of Marianne Aznar, Rigshospitalet, Copenhagen*
Selecting for RT: *Discussion*

*We did improve BCT rates!*

Update 2016: 1.8% LRR at 9 years !!!
Selecting for RT: *The role of RT*

Dutch population based cancer registry

2000-2004 cohort: 37,207 patients

- 58.4% BCT
- 41.6% MRM
Selecting for RT: *The role of RT*

Dutch population based cancer registry

2000-2004 cohort: 37,207 patients
- 58.4% BCT
- 41.6% MRM

![Graph showing cumulative overall survival for T1-2N0-1 with BCT and MRM compared to Breast conserving therapy and Mastectomy.](image)
GEC-ESTRO Recommendations


Csaba Polgár, Erik Van Limbergen, Richard Pötter, György Kovács, Alfredo Polo, Jaroslaw Lyczek, Guido Hildebrandt, Peter Niehoff, Jose Luis Guinot, Ferran Guedea, Bengt Johansson, Oliver J. Ott, Tibor Major, Vratislav Strnad, On behalf of the GEC-ESTRO breast cancer working group

doi:10.1016/j.ijrobp.2009.02.031

CONSENSUS STATEMENT

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

Benjamin D. Smith, M.D., Douglas W. Arthur, M.D., Thomas A. Buchholz, M.D., Bruce G. Haffty, M.D., Carol A. Hahn, M.D., Patricia H. Hardenbergh, M.D., Thomas B. Julian, M.D., Lawrence B. Marks, M.D., Dorin A. Todor, Ph.D., Frank A. Vicini, M.D., Timothy J. Whelan, M.D., Julia White, M.D., Jennifer Y. Wu, M.D., and Jay R. Harris, M.D.
Selecting for RT: Discussion

Prospective clinical trials evaluating (accelerated) partial breast irradiation.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Local relapse</th>
<th>DFS</th>
<th>OS</th>
<th>Median FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dodwell et al., 2005 [27]</td>
<td>Phase II WBI vs. APBI</td>
<td>174</td>
<td>4% vs. 12% (p = 0.05)</td>
<td>—</td>
<td>27% vs. 30% (p = 0.75)</td>
<td>96 months</td>
</tr>
<tr>
<td>Chen et al., 2010 [28]</td>
<td>Phase II 3D CRT APBI</td>
<td>94</td>
<td>1.1% at 4 years</td>
<td>95% at 4 years</td>
<td>97% at 4 years</td>
<td>50.4 months</td>
</tr>
<tr>
<td>Vicini et al., 2010 [29]</td>
<td>Phase II 3D CRT APBI</td>
<td>52</td>
<td>6% at 4 years</td>
<td>84% at 4 years</td>
<td>96% at 4 years</td>
<td>54 months</td>
</tr>
<tr>
<td>Lei et al., 2013 [30]</td>
<td>Phase II IMRT APBI</td>
<td>136</td>
<td>0.7% at 4 years</td>
<td>—</td>
<td>96.8% at 4 years</td>
<td>53.1 months</td>
</tr>
<tr>
<td>Veronesi et al., 2013 [32]</td>
<td>Phase III WBI vs. IORT</td>
<td>1305 (654 IORT vs. 651 EBRT)</td>
<td>0.4% vs. 4.4% at 5 years (p &lt; 0.0001)</td>
<td>—</td>
<td>96.8% vs. 96.9% at 5 years (p = 0.59)</td>
<td>69.6 months</td>
</tr>
<tr>
<td>Vaidya et al., 2014 [31]</td>
<td>Phase III WBI vs. IORT</td>
<td>3451 (1730 EBRT vs. 1721 IORT)</td>
<td>1.3% vs. 3.3% at 5 years p = 0.042</td>
<td>—</td>
<td>96.1% vs. 94.7% at 5 years (p = 0.099)</td>
<td>29 months</td>
</tr>
<tr>
<td>Livi et al., 2015 [33]</td>
<td>Phase III WBI vs. IMRT APBI</td>
<td>520 (260 WBI vs. 260 APBI)</td>
<td>1.4% vs. 1.5% (p = 0.86)</td>
<td>—</td>
<td>96.6% vs. 99.4% at 5 years (p = 0.057)</td>
<td>60 months</td>
</tr>
<tr>
<td>Strnad et al., 2016 [34]</td>
<td>Phase III WBI vs. IBT</td>
<td>1184 (551 WBI vs. 633 APBI)</td>
<td>0.92% vs. 1.44% (p = 0.42)</td>
<td>94.45% vs. 95.03% at 5 years (p = 0.79)</td>
<td>95.55% vs. 97.27% at 5 years (p = 0.11)</td>
<td>79.2 months</td>
</tr>
</tbody>
</table>
Selecting for RT: Discussion

Treatment times are shortening!

**FAST-Forward**

Randomise to one of three treatments:

- **Control Group**
  - 40.05 Gy / 15 Fr
  - 3 weeks
  - 2.67 Gy/F

- **Test Group 1**
  - 27.0 Gy / 5 Fr
  - 1 week
  - 5.4 Gy/F

- **Test Group 2**
  - 26.0 Gy / 5 Fr
  - 1 week
  - 5.2 Gy/F

*16 Gy or 10 Gy in 2 Gy fractions sequential electron or photon boost to the tumour bed is allowed in all 3 treatment arms (boost decision to be declared before randomisation for each individual patient)*
Selecting for RT: *Discussion*

**Wound Response Signature**

In vitro Wound Model – 516 genes

Prognostic Significance in

- Breast
- Lung
- Gastric cancer
Selecting for RT: *Discussion*

*Predict of Local Recurrence in Early Breast Cancer*

![Graphs showing the prediction of local recurrence in early breast cancer](image)

- **Training**
  - High Risk
  - Low Risk
  - P = 0.00014

- **Validation**
  - High Risk
  - Low Risk
  - P = 0.0005
Selecting for RT: *Discussion*

**Side effects**

<table>
<thead>
<tr>
<th>Radiation therapy:</th>
<th>21\textsuperscript{st} C, only local RT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Inconvenience</td>
<td>- 7→5→3→1 weeks</td>
</tr>
<tr>
<td>- Skin</td>
<td>- Lowered</td>
</tr>
<tr>
<td>- Breast tissue</td>
<td>- No boost (\rightarrow) low</td>
</tr>
<tr>
<td>- Pulmonary</td>
<td>- Unlikely</td>
</tr>
<tr>
<td>- Heart</td>
<td>- Unlikely</td>
</tr>
<tr>
<td>- Secondary tumours</td>
<td>- Seldom</td>
</tr>
<tr>
<td>- CL breast: more</td>
<td>- Less for older pts/proper techniques</td>
</tr>
</tbody>
</table>
Selecting for RT: Discussion

Endocrine therapy:

- Early side effects.
- Late side effects.
- Compliance.
## Selecting for RT: Discussion

<table>
<thead>
<tr>
<th>Stage</th>
<th>Benefit HT DFS (%)</th>
<th>Benefit HT OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(all 65y;N0;ER+;Her-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a-bG1 3</td>
<td>4.9-9.5</td>
<td>0.3-1.4</td>
</tr>
<tr>
<td>T1cG1</td>
<td>5.7-8.2</td>
<td>0.9</td>
</tr>
<tr>
<td>T1cG2</td>
<td>7.8-11.1</td>
<td>2.0</td>
</tr>
<tr>
<td>T1cG3</td>
<td>9.6-13.9</td>
<td>3.3</td>
</tr>
<tr>
<td>T2&lt;3cm G1</td>
<td>8.1-11.6</td>
<td>2.4</td>
</tr>
<tr>
<td>T2&lt;3cm G2</td>
<td>10.8-15.7</td>
<td>4.3</td>
</tr>
<tr>
<td>T2&lt;3cm G3</td>
<td>12.7-18.7</td>
<td>5.9</td>
</tr>
</tbody>
</table>
## Selecting for RT: Discussion

<table>
<thead>
<tr>
<th>Stage</th>
<th>Benefit HT DFS (%)</th>
<th>Benefit HT OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(all 65y; N0; ER+ ; Her-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a-b G1 3</td>
<td>4.9-9.5</td>
<td>0.3-1.4</td>
</tr>
<tr>
<td>T1c G1</td>
<td>5.7-8.2</td>
<td>0.9</td>
</tr>
<tr>
<td>T1c G2</td>
<td>7.8-11.1</td>
<td>2.0</td>
</tr>
<tr>
<td>T1c G3</td>
<td>9.6-13.9</td>
<td>3.3</td>
</tr>
<tr>
<td>T2&lt;3cm G1</td>
<td>8.1-11.6</td>
<td>2.4</td>
</tr>
<tr>
<td>T2&lt;3cm G2</td>
<td>10.8-15.7</td>
<td>4.3</td>
</tr>
<tr>
<td>T2&lt;3cm G3</td>
<td>12.7-18.7</td>
<td>5.9</td>
</tr>
</tbody>
</table>
Selecting for RT: Discussion

Effect of RT after BCS on recurrence and breast cancer mortality in pN0 women.
Selecting for RT: Discussion

Figure 4: Absolute 10-year risks (%) of any (locoregional or distant) first recurrence with and without radiotherapy (RT) following breast-conserving surgery (BCS) in pathologically node-negative women by patient and trial characteristics, as estimated by regression modelling of data for 7287 women.
Figure 4: Absolute 10-year risks (%) of any (locoregional or distant) first recurrence with and without radiotherapy (RT) following breast-conserving surgery (BCS) in pathologically node-negative women by patient and trial characteristics, as estimated by regression modelling of data for 7287 women.
Selecting for RT: *Discussion*

Interaction systemic and locoregional treatments

Figure: Combined hypothetical benefit of local tumour control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumour.
Selecting for RT: Discussion

Cohort expectation of life at age 65 according to historic and projected mortality rates, persons who reached age 65 1850–2050, England and Wales

![Graph showing the cohort expectation of life at age 65 for males and females from 1850 to 2050. The graph indicates a rise in life expectancy over time, with females generally having a higher expectation than males.](image)
Selecting for radiation therapy

1. Introduction

2. The role of radiation therapy

3. A particular case

4. Discussion

5. Conclusions
1

Estimate life expectancy
Define tumour risk
Selecting for RT: Conclusions

3

Shared decision making
Selecting for RT: Conclusions

**Early stage, low risk**

Short life expectancy:  - Surgery alone
- Endocrine alone
- Nothing?

Long life expectancy:  - Surgery + RT
Selecting for RT: *Conclusions*

**Early stage, low risk**

---

**Study information**

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Partial Breast Irradiation versus Endocrine Therapy for women age ≥70 years with Luminal-A early stage breast cancer: a randomized phase III trial comparing Quality of Life by Patient Reported Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short title (max 50 characters)</strong></td>
<td>APBI or ET for elderly with early breast cancer</td>
</tr>
<tr>
<td><strong>Study Number</strong></td>
<td>EORTC-1625 QoL-ROG-ETF-BCG</td>
</tr>
</tbody>
</table>

**Outline form**

| **Leading Group** | EORTC ROG |
Eligible patients group
Females ≥ 70 years of age
cT1-2, N0 breast cancer

BCS with or without SNB

pT1 (<2cm) invasive BC
cN0 or pN0(i+)
- Luminal-A on basis of IHC: ER+ and/or PgR+ (PgR at least >20%), HER2-, Ki67<20%

Signed informed consent

Randomization

Exclusive APBI

Exclusive ET

Follow-up according to protocol
Selecting for RT: Conclusions

Early stage, low risk

Tailored treatment in Older Patients

TOP-1: Omission of radiotherapy in elderly patients with low risk breast cancer
INCLUSION CRITERIA:
- ≥70 years
- after breast conserving surgery
- tumor Ø <1 cm grade 1-2, tumor Ø 1-2 cm grade 1
- tumor ER>50% positive, HER2 negative
- sNO or sND(itc)
- surgical resection margins free of tumor

TOP-1 STUDY

Directly
At 1 year
At 2 years
At 3 years
At 4 years
At 5 years

Questionnaire

GUIDELINES CWO 2010:
ADJUVANT RT AFTER BSC

NO INFORMED CONSENT TOP-1

LOCAL RECURRENT RATE AT 5 YEARS
Selecting for RT: Conclusions

Early stage, with risk factors

Short life expectancy:  - Surgery with
                       - Systemic T?
                       - RT?

Long life expectancy:  - Surgery with
                       - Systemic T
                       - RT
Selecting for RT: Conclusions

Advanced stage, with risk factors

Short life expectancy: - Surgery with
- Systemic T
- RT

Long life expectancy: - Surgery with
- Systemic T
- RT
Selecting for RT: Conclusions

Source: Globocan, 2008. Rates shown are age-standardised rate per 100,000 using the standard world population.
We should mind not to kill our patients by kindness.

Birgitte Vrou Offersen, Aarhus, DK, 2013
Selecting for RT: Conclusions

Trust comes on foot and leaves on horseback!
Selecting for RT: Acknowledgements

- Harry Bartelink
- Laurence Collette
- Sarah Darby
- Birgitte Offersen
- Roberto Orecchia
- Oliver Ott
- John Yarnold
- Icro Meattini
- Meritxell Arenas
- Lorenzo Livi
- And many others!