De-mystifying partial breast radiotherapy

*Is less really less?*

Philip Poortmans, MD, PhD
I have no conflicts of interest
De-mystifying PBI: is less really less?

1. Introduction

2. Side-effects

3. Discussion

4. Conclusions
Demystifying Partial Breast Irradiation
Part 1: Why and how to do it?
De-mystifying partial breast radiotherapy: does it work and who should have it?

Charlotte Coles

UK Interdisciplinary Breast Cancer Symposium 2020
De-mystifying PBI: is less really less?

1. Introduction

2. Side-effects

3. Discussion

4. Conclusions
Is PBI really less: *Side-effects*

**Warning signals**

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**EDITORIAL**

REPORTS OF UNEXPECTED LATE SIDE EFFECTS OF ACCELERATED PARTIAL BREAST IRRADIATION—RADIOBIOLOGICAL CONSIDERATIONS

SØREN M. BENTZEN, PH.D., D.SC.,* AND JOHN R. YARNOLD, M.D., FRCR.†

Three reports: HypoF: 3.85 Gy in 10 F, twice daily (minimum 6h interval), 5 consecutive days

1) Chen et al.: „outcomes appear comparable“
2) Hepel et al.: „remarkably high moderate to severe late effects“
3) Jagsi et al.: „HypoF may be suboptimal...........“
Is PBI really less: *Side-effects*

**Warning signals**

**UNACCEPTABLE COSMESIS IN A PROTOCOL INVESTIGATING INTENSITY-MODULATED RADIOTHERAPY WITH ACTIVE BREATHING CONTROL FOR ACCELERATED PARTIAL-BREAST IRRADIATION**


*Hepel, *IJROBP* 2009;75:1290-96 (3D-CRT)*  
*Jagsi, *IJROBP* 2010;76:71-78 (IMRT)*
Is PBI really less: *Side-effects*

**Warning signals**

**Protocol NSABP B-39/ RTOG 0413**
- Phase III, conv. RT vs. APBI
- 2 x 3.85 Gy/d
- 38.5 Gy, 5 days
- ≥ 6hs interval

**Fibrosis:**
Grade 2-4: 25 % (1.5 years)
Grade 3-4: 8 %

*Hepel, IJROBP 2009;75:1290-96 (3D-CRT)  Jagsi, IJROBP 2010;76:71-78 (IMRT)*
Is PBI really less: Side-effects

Warning signals

WBI

<table>
<thead>
<tr>
<th>Quality</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>68 (42%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>74 (45%)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>16 (10%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>6 (4%)</td>
<td></td>
</tr>
<tr>
<td>Fair + poor</td>
<td>22 (13%)</td>
<td>13.4% (p&lt;.001)</td>
</tr>
</tbody>
</table>

5 Years

APBI

<table>
<thead>
<tr>
<th>Quality</th>
<th>No. of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>44 (26%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>71 (42%)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>49 (29%)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>7 (4%)</td>
<td></td>
</tr>
<tr>
<td>Fair + poor</td>
<td>56 (33%)</td>
<td>32.8%</td>
</tr>
</tbody>
</table>

5 Years

5 year cosmetic evaluation assessment on 335 / 2,135 patients

Twelve-year clinical outcomes and patterns of failure with APBI versus WBI: Results of a matched-pair analysis

Chirag Shah, John Vito Antonucci, John Ben Wilkinson, Michelle Wallace, Mihai Ghilezan, Peter Chen, Kenneth Lewis, Christina Mitchell, Frank Vicini*

Department of Radiation Oncology, William Beaumont Hospital, MI, USA

Is PBI really less: *Side-effects*

Real life data

**Results @ 5 years:**
- more subsequent mastectomy (4.0% vs. 2.2%)
- more acute complications:
  - hospitalization (9.6% vs. 5.7)
  - infection (8.1% vs. 4.5)
- more late complications:
  - rib fracture (4.2% vs. 3.6% in WBI)
  - fat necrosis (9.1% vs. 3.7%)
  - breast pain (14.9% vs. 11.7%)
- less pneumonitis (0.1% vs. 0.8%).

All $p<0.001$

Is PBI really less: *Side-effects*

More recent prospective clinical trials
Intensity modulated partial breast radiotherapy (IMPORT) for women with early breast cancer: First analysis of local relapse (CRUK/06/003)

Dr Charlotte Coles

### Results: Effect on healthy tissues – clinician-reported

<table>
<thead>
<tr>
<th></th>
<th>Whole N=674</th>
<th>Reduced N=674</th>
<th>Partial N=670</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with moderate/marked side effects (%)</td>
<td>134 (20)</td>
<td>108 (16)</td>
<td>92 (14)</td>
</tr>
<tr>
<td>5 year event-free for mod/marked side effects (95% CI)</td>
<td>72.1% (66.0 - 77.3)</td>
<td>78.9% (74.2 - 82.8)</td>
<td>80.9% (75.8 - 85.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.77 (0.60, 0.99)</td>
<td>0.68 (0.52, 0.89)</td>
<td></td>
</tr>
<tr>
<td>Log rank p-value</td>
<td>p=0.042</td>
<td>p=0.004</td>
<td></td>
</tr>
</tbody>
</table>

- Reduced long term side effects for Partial & Reduced RT
- Greatest improvement with Partial RT

*Courtesy Coles C et al.*
First results from the clinically controlled randomized DBCG PBI trial

BV Offersen¹, MS Thomsen¹, HM Nielsen¹, EH Jacobsen², M Berg², MH Nielsen³, E Lorenzen³, L Stenbygaard⁴, I Jensen⁴, AN Petersen⁵, M Josipovic⁵, M-B Jensen⁶, J Overgaard⁷, on behalf of the DBCG RT Committee

¹Dept Oncology Aarhus, ²Dept Oncology Vejle, ³Dept Oncology Odense, ⁴Dept Oncology Aalborg, ⁵Dept Oncology, Rigshospitalet, ⁶DBCG, ⁷Dept Expt Clin Oncology Aarhus, Denmark
## Patient satisfaction with treated breast

<table>
<thead>
<tr>
<th></th>
<th>Whole breast</th>
<th>%</th>
<th>Partial breast</th>
<th>%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 (poor)</td>
<td>4</td>
<td>1.1</td>
<td>1</td>
<td>0.3</td>
<td>0.72</td>
</tr>
<tr>
<td>Grade 1 (fair)</td>
<td>18</td>
<td>5.1</td>
<td>20</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Grade 2 (good)</td>
<td>178</td>
<td>82.9</td>
<td>179</td>
<td>82.0</td>
<td></td>
</tr>
<tr>
<td>Grade 3 (excellent)</td>
<td>113</td>
<td></td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 (unanswered)</td>
<td>38</td>
<td>10.8</td>
<td>43</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>708</td>
<td>351</td>
<td>357</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Year 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0 (poor)</td>
<td>1</td>
<td>0.6</td>
<td>4</td>
<td>2.3</td>
<td>0.12</td>
</tr>
<tr>
<td>Grade 1 (fair)</td>
<td>10</td>
<td>5.5</td>
<td>7</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Excellent/good</td>
<td>78</td>
<td>91.2</td>
<td>88</td>
<td>92.5</td>
<td></td>
</tr>
<tr>
<td>Grade 4 (unanswered)</td>
<td>5</td>
<td>2.8</td>
<td>2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>181</td>
<td></td>
<td>172</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Purpose and background

To report interim **cosmetic** and **toxicity** results in a subgroup of patients enrolled in IRMA trial

**IRMA trial (NCT 01803958)**

Multicentric randomized trial (Italy, Netherlands, Spain, Switzerland, Israel)

Non inferiority study (APBI vs WBI)

**Primary Objective**

Local control (incidence of ipsilateral recurrences)

**Secondary Objectives**

OS, Cosmesis, Toxicity

https://clinicaltrials.gov/ct2/show/NCT01803958  www.irmatrial.it
Conclusion

APBI with 3D-CRT resulted in *better acute toxicity*, *similar late toxicity* and *good/excellent cosmetic results* compared with standard WBI.

Additional follow-up is needed to confirm these results.

SUBMITTED FOR LBA ESTRO 2020!!!!
Is PBI really less: *Side-effects*

More recent prospective clinical trials

**Florence trial:**

- EORTC QLQ-C30 scale & QLQ-BR23 module
- APBI $\rightarrow$ improved short-term and 2-year HRQoL
  - Body image perception and future perspective: $p = 0.0001$
  - Breast and arm symptoms: $p < 0.01$

Is PBI really less: *Side-effects*

More recent prospective clinical trials

Late toxicity and cosmesis after APBI with brachytherapy vs WBI – 5-year results of the GEC-ESTRO phase III trial

*Study chairmen: Vratislav Strnad & Csaba Polgár*

Conclusions

• 5-year toxicity profiles and cosmetic results were similar in patients treated with BCS followed by either APBI with interstitial brachytherapy or conventional WBI

• Significantly fewer grade 2-3 late skin side-effects after APBI with interstitial brachytherapy

De-mystifying PBI: is less really less?

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Is PBI really less: Discussion

Radiobiology
Is PBI really less: Discussion

Radiobiology

„The challenge is to quantify the effect of reduced volume when applying WBI dose response date to APBI“

➢ Volume effect?

➢ Dose-volume-parameters?
Is PBI really less: Discussion

Radiobiology

Overdose?

- Acceleration 2 F/d, fraction size, interval of 6h to short?
- Dependent on $\alpha/\beta$ and recuperation “half times”: 65-68 Gy!!!!!
- Resulting late effects (note: no increase in acute toxicity was noted!)

Hepel, IJROBP 2009;75:1290-96 (3D-CRT)  Jagsi, IJROBP 2010;76:71-78 (IMRT)
Retrospective study of LDR brachytherapy volumes as boost: 4-fold increase in risk of fibrosis for each 100 cm³ increment in boost volume → very steep volume response.

Is PBI really less: Discussion

Radiobiology

The importance of incomplete repair is underestimated with this type of APBI, expressing a strong dose-volume effect.

The toxic events correlated clearly with several dose–volume parameters.
Is PBI really less: *Discussion*

*Target volumes*
Is PBI really less: Discussion

Target volumes

- Tumour
- Microscopic extension
- Region with microscopic extension, within 2 cm of primary tumour

✓ Radio-opaque wire (scar & palpable area) to guide.
✓ Pre-operative localisation of tumour (phys ex, imaging).
✓ Features visible on the planning CT: clips, surgical effects, ...

Is PBI really less: *Discussion*

**Target volumes**

Is PBI really less: *Discussion*

*Target volumes*

**Primary tumour bed:**

Representing original tumour site

\~ GTV

\neq surgical bed

\= virtual point

\neq CTV boost/APBI.

A lot of uncertainties!!!
Is PBI really less: Discussion

Target volumes

Target volume delineation of primary tumour bed:

- by dedicated RO’s
- no clips
- no seroma

Is PBI really less: Discussion

Target volumes - oncoplastic surgery
Is PBI really less: *Discussion*

*Target volumes - oncoplastic surgery*
Is PBI really less: *Discussion*

**Target volumes - oncoplastic surgery**

WS: Whole surgical Scar  
ImTV: Imaging related Target Volume  
ETB: Estimated Tumour Bed  
CTV: Clinical Target Volume

Is PBI really less: Discussion

The missing link: preoperative RT?

Current Perspective

Preoperative breast radiation therapy: Indications and perspectives

S.V. Lightowlers a,*, L.J. Boersma b, A. Fourquet c, Y.M. Kirova c, B.V. Offersen d, P. Poortmans c, A.N. Scholten e, N. Somaiah f, C.E. Coles g

Is PBI really less: *Discussion*

**The missing link: preoperative RT?**

<table>
<thead>
<tr>
<th>Title</th>
<th>Type of study</th>
<th>Patient recruitment target</th>
<th>Study design</th>
<th>Primary endpoint</th>
<th>RT technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAPBI-2</td>
<td>Phase III randomised trial</td>
<td>500 patients</td>
<td>Preoperative vs. postoperative accelerated partial breast irradiation</td>
<td>Cosmetic outcome, assessed by digital photographs, patient's questionnaires and specialist's questionnaires</td>
<td>Partial breast IMRT 28.5Gy in 5 fractions over 1 week</td>
</tr>
</tbody>
</table>

Table 2: Novel trials involving preoperative radiation therapy currently in the set up phase, or recruiting patients (footnote 1). *APBI, accelerated partial breast irradiation; **IMRT, intensity modulated radiation therapy; †DIEP, deep inferior epigastric perforator; ***SIB, simultaneous integrated boost.

Is PBI really less: *Discussion*

**Preoperative APBI – PAPBI-1**

- Multi-centric international phase II trial
- N=139/140 patients
- Feasibility of preoperative APBI done by external beam radiotherapy

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Is PBI really less: *Discussion*

*Preoperative APBI – PAPBI-1*

**Pre- vs. post:**
Increased homogeneity in contouring

*Van Der Leij F, Radiother Oncol 2014*
Is PBI really less: Discussion

Preoperative APBI – PAPBI-1

RAPID trial

PAPBI trial

Role of removal of high dose irradiated volume?

De-mystifying PBI: is less really less?

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Is PBI really less: **Conclusions**

**Much variation between techniques**

<table>
<thead>
<tr>
<th>Comparison of PBI techniques</th>
<th>3D CRT</th>
<th>Interstitial brachytherapy HDR, LDR, PDR</th>
<th>MammoSite</th>
<th>Target, 50 kV X-rays</th>
<th>IORT, electrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage of target</td>
<td>Best</td>
<td>Variable</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Thickness of cavity wall irradiated</td>
<td>1–2 cm</td>
<td>Dose prescribed to 1 cm from surface of applicator</td>
<td>Dose prescribed to 1 mm from surface of applicator, 5–7 Gy 10 mm from applicator</td>
<td>Dose prescribed to 90% isodose line, 80% isodose at 13 mm (3 MeV)–24 mm (9 MeV)</td>
<td></td>
</tr>
<tr>
<td>Dose homogeneity</td>
<td>Best</td>
<td>Fair</td>
<td>Fair</td>
<td>Fair</td>
<td>Fair</td>
</tr>
<tr>
<td>Sparing of normal breast / other organs</td>
<td>Least</td>
<td>Good</td>
<td>Best</td>
<td>Varies with location</td>
<td></td>
</tr>
<tr>
<td>Skin dose</td>
<td>Least</td>
<td>Least</td>
<td>Variable</td>
<td>Least (can shield)</td>
<td>Least</td>
</tr>
<tr>
<td>Technical feasibility for various size, shape or location of cavity</td>
<td>Suitable for virtually all cases</td>
<td>Not suitable if inadequate tissue or near axilla</td>
<td>Not suitable for large/irregular cavities, or at the periphery of the breast</td>
<td>Not suitable for tumors near brachial plexus/axilla or skin</td>
<td></td>
</tr>
<tr>
<td>Expertise required</td>
<td>Average</td>
<td>High</td>
<td>Average</td>
<td>High</td>
<td>Very high</td>
</tr>
<tr>
<td>Potential for wide spread use</td>
<td>Very good</td>
<td>Fair</td>
<td>Very good</td>
<td>Fair</td>
<td>Limited</td>
</tr>
<tr>
<td>Main drawback</td>
<td>Relatively higher dose to normal tissue and breathing motion</td>
<td>Adequacy of target coverage in some cases and wider applicability</td>
<td>Cavity shape and size. Although easy to use, stringent QA is required. Skin dose may be high</td>
<td>Very limited depth irradiated; cavity shape and size. Histology not available</td>
<td>Wider applicability. Histology not available. Based on quadrantectomy</td>
</tr>
</tbody>
</table>

**TV def**

+++  ++  --/-  ---  +/-

Is PBI really less: *Conclusions*

*Much variation between techniques*

<table>
<thead>
<tr>
<th>Intraoperative RT</th>
<th>Brachytherapy</th>
<th>External Beam Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TARGET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 Gy/1 fr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(low energy X-rays 50 kV)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ELIOT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 Gy/1 fr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(3-12 MeV)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LINAC – based IORT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(4–20 MeV)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GEC-ESTRO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MIB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32 Gy/8fr HDR,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30.3 Gy/7fr HDR,</td>
<td></td>
<td></td>
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<tr>
<td>50 Gy PDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NSABP/RTOG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MIB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 Gy/10fr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(5-10 days)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Twice daily</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NSABP/RTOG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.5 Gy/10fr (5-10 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RAPID</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.5 Gy/10fr (5-8 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IRMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.5 Gy/10fr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Once daily</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMPORT-LOW</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Gy/15fr</td>
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<td></td>
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<tr>
<td><strong>DBCG</strong></td>
<td></td>
<td></td>
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<tr>
<td>40 Gy/15fr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FLORENCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 Gy/5fr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MDA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34 Gy/10fr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MIB – multicatheter brachy; B- balloon e.g., mammoSite

*Slide courtesy O. Kaidar-Person*
Technique not the other way around!
Is PBI really less: Conclusions

• TV delineation = challenge +++

• TV delineation + oncoplastic surgery = (challenge)²

• Close collaboration surgeons and RO = essential before, during and after surgery

• Discuss use of oncoplastic surgery: tool but not goal!
Is PBI really less: *Conclusions*

*Finding the equilibrium between dose & volume*

<table>
<thead>
<tr>
<th>Dose</th>
<th>Local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractionation</td>
<td>Cosmetic</td>
</tr>
<tr>
<td>Volume</td>
<td>Convenience</td>
</tr>
</tbody>
</table>
Is PBI really less: Conclusions

The next challenge?

ExclUsive endocrine Therapy Or PBI (EUROPA)

ClinicalTrials.gov Identifier: NCT04134598

Phase 2-3 trial will open soon

Icro Meattini, Etienne Brain, Isacco Desideri, Marije Hamaker,

Orit Kaidar-Person, Matteo Lambertini, Guido Miccinesi, Nicola Russell,

Calogero Saieva, Luca Visani, Philip Poortmans, Lorenzo Livi
Eligible patients group
Women ≥70 years of age
cT1-2 cN0 breast cancer

BCS with or without SNB

pT1 pN0 invasive BC
Luminal A-like: ER+ (≥50%) and PgR+ (>20%), HER2-, Ki67 ≤20%

Signed informed consent

Randomization 1:1 stratified by age, G8 tool score, and Institution

Exclusive PBI
Exclusive ET (control)

Follow-up according to protocol

Is PBI really less: Conclusions
Is PBI really less: *Acknowledgements*

- Birgitte Offersen
- Icro Meattini
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- Etienne Brain
- Giovanni Frezza
- Bruno Meduri
- Charlotte Coles
- Sara Lightowlers
- Vratislav Strnad
- Csaba Polgár
- And many others!