ESMO Preceptorship Programme

Breast Cancer

Multidisciplinary management, standards of care, therapeutic targets and future perspectives

Lisbon, Portugal

16-17 September 2016

Principles of breast radiation therapy

Philip Poortmans, MD, PhD

16 September 2016

Past-President

Department of Radiation Oncology

Radboudumc
Principles of breast radiation therapy

• Introduction

• Tasks of the radiation oncologist

• Indications

• Side-effects

• New developments

• The future
Erfahrungen über die Verträglichkeitsgrenze für Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden*).

Von

H. Holthusen, Hamburg.

*) Vortrag vor der Deutschen Röntgengesellschaft am 24. April 1936
Introduction

- Delivery of the total dose in several small fractions
Introduction

A graph showing the number of cells over time. The graph compares normal cells and malignant cells. Normal cells remain at 100% throughout the time period, while malignant cells decrease over time.
Groei van een tumor die in drie maanden in volume verdubbelt. Vanaf het moment waarop de tumor wordt ontdekt, kan een periode van 10 jaar liggen.

tumoren te klein om te kunnen worden waargenomen

tumoren waarneembaar met speciale techniek

tumoren klinisch waarneembaar

256 cm³
16 cm³
1 cm³

tijd (jaar) 0 1 2 3 4 5 6 7 8 9 10 11 12 13
Principles of breast radiation therapy

- Introduction
- Tasks of the radiation oncologist
- Indications
- Side-effects
- New developments
- The future
Tasks of the radiation oncologist

The patient is the centre of the medical universe around which all our work revolves and towards which all our efforts tend.

J.B. Murphy
1857 - 1916
The CT scan enables the making of an individualised treatment plan.
Tasks of the radiation oncologist

CT scan: positioning

LASER limes for positioning of the patient.
Tasks of the radiation oncologist

CT scan: positioning
Medio-lateral field

Latero-medial field

IM-MS field
Tasks of the radiation oncologist

- Chest wall
- Supraclavicular
- IMC
- ± axilla
Principles of breast radiation therapy

- Introduction
- Tasks of the radiation oncologist
- Indications
- Side-effects
- New developments
- The future
Indications: breast conserving therapy

<table>
<thead>
<tr>
<th>5-year local recurrence risk (%) in trials of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) RT after BCS (node-negative)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RT versus control</th>
<th>Absolute reduction (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>11 vs 33</td>
</tr>
<tr>
<td>50–59</td>
<td>7 vs 23</td>
</tr>
<tr>
<td>60–69</td>
<td>4 vs 16</td>
</tr>
<tr>
<td>≥70</td>
<td>3 vs 13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour grade</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>4 vs 14</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>9 vs 26</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>12 vs 34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumour size (T category)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–20 mm (T1)</td>
</tr>
<tr>
<td>21–50 mm (T2)</td>
</tr>
<tr>
<td>&gt;50 mm (T3 or T4*)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ER status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-poor</td>
</tr>
<tr>
<td>ER-positive</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of involved nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3</td>
</tr>
<tr>
<td>≥4</td>
</tr>
<tr>
<td>All women</td>
</tr>
</tbody>
</table>

LR - 70%

EBCTCG Lancet 2005; 366: 2087–2106
Indications: breast conserving therapy

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
Indications: breast conserving therapy

Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10,801 women (67% with pathologically node-negative disease) in 17 trials. Further details are in webappendix p 5. RR = rate ratio. Rate ratios in this figure include all available years of follow-up.
Indications: breast conserving therapy

Any event - 54%

Figure 3: Event rates for any (locoregional or distant) first recurrence (% per year) and recurrence rate ratios for various factors, considered separately, during years 0–9 in women with pathologically node-negative disease (n=7287)
Any event – 24,6

Any event – 8,9

Table 2: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence in women with pathologically node-negative disease (n=7287), subdivided by patient and trial characteristics
We did improve BCT rates!

Indications: breast conserving therapy

Update 2016: 1.8% LRR at 9 years !!!

Indications: mastectomy

Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists’ Collaborative Group)*
Indications: mastectomy
Indications: mastectomy

Indications: general

- “Always” as part of breast conserving therapy
- After mastectomy based on risk factors: tumour size; grade; lymph node involvement; resection margins; tumour type; vasculair invasion
- Local control en survival last decennia even better after BCT!
- Dose and target volumes depending on tumour-, patient- and other treatment-characteristics
- On-going research in de-escalation in patients with a favourable prognosis!
Principles of breast radiation therapy

• Introduction

• Tasks of the radiation oncologist

• Indications

• Side-effects

• New developments

• The future
Side-effects

- Arm edema
- Impairment of shoulder movement
- Brachial plexus damage
- Telangiectasia
- Change in breast appearance
- Subcutaneous fibrosis
- Pneumonitis and lung fibrosis
- Ischemic heart disease
- Secondary malignancy
Side-effects: grading: fibrosis

• Grade 0 = none

• Grade 1 = barely palpable

• Grade 2 = definite increased density & firmness

• Grade 3 = marked density, retraction & fixation

Side-effects: grading: skin colour

0  No difference in colour between the breasts, neither on skin nor areola/nipple

1  Nipple/areola or skin darker/lighter on treated side compared to untreated side

2  Both nipple/areola and skin darker/lighter on treated side compared to untreated side

3  Marked difference in colour between treated and untreated breast, either in skin or nipple/areola or both

Side-effects: grading: telangiectasia

Small dilated vessels

0 = none
1 = <1/cm²
2 = 1-4/cm²
3 = >4/cm²

Grade 1

Grade 2 = 1-4/cm²

Grade 3 = >4/cm²

Side-effects: influencing factors

- Radiation therapy
- Surgery
- Systemic therapy
- Comorbidity
- Individual radiosensitivity: genetics
- Unknown
Side-effects: factors: *radiation therapy*

**EORTC Boost trial**

"dose-response" for fibrosis

![Graph showing cumulative incidence of moderate or severe fibrosis after 50 Gy irradiation or 50 Gy irradiation and a boost of 16 Gy.](image)

**Fig 4.** Cumulative incidence of moderate or severe fibrosis after 50 Gy irradiation or 50 Gy irradiation and a boost of 16 Gy.
Side-effects: factors: radiation therapy

Standard

“IMRT”

cosmetic change:
- 14% “a lot”
- 43% “some”

Donovan, Yarnold et al. Radiother Oncol 2007
Side-effects: factors: surgery

Past

Present

Menke et al, NTVG 2007
Non-anthracycline (CMF) ChT

Congestive heart failure risk
Side-effects: factors: systemic therapy

Radiation myelitis after 28 Gy concurrent with trastuzumab

New treatments ➔ new risks!
Side-effects: factors: *comorbidity*

Age 60; BC → TE + SNB + RT

G2 breast toxicity; pictures after 4.5 years

“smoking & DM”
Side-effects: factors: *comorbidity*

Age 64; BC pT1cmG2N0M0 ➔ TE + SNB + RT (SIB)

G3 breast toxicity; pictures after 1.5 years

“*muscular reuma*”
Side-effects: factors: *comorbidity*

*“Radiation-induced morphea of the breast”*
Variations in risk of normal tissue toxicity after RT (within normal range)

Use clinical data and molecular pathology to identify genetic risk factors and targets for intervention

More sensitive

More resistant

Andreassen et al, CIRRO project
Overview

Radiation Fibrosis — Current Clinical and Therapeutic Perspectives

C.B. Westbury *, J.R. Yarnold †

*Department of Oncology, UCL Cancer Institute, London, UK
†Division of Radiotherapy and Imaging, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK

Received 14 July 2011; received in revised form 7 February 2012; accepted 12 April 2012
Principles of breast radiation therapy

- Introduction
- Tasks of the radiation oncologist
- Indications
- Side-effects
- New developments
- The future
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.
**Primary Tumour Bed (PTB):**

Represents the original tumour

\sim \text{GTV}

\neq \text{surgical bed}

\equiv \text{virtual point}

A lot of uncertainties!!!
New developments: to start with

Target volume delineation of primary tumour bed:

- by dedicated RTO’s
- no clips
- no seroma
New developments: to start with

- Breast
- Thoracic wall
- LN axilla level IV
- LN axilla level III
- LN axilla level II
- LN axilla Rotter
- LN axilla level I
- LN internal mammary

1) Brachiocephalic vein
2+7) Subclavian vessels
3+8) Axillary vessels
4) Internal jugular vein
5) External jugular vein
6) Brachiocephalic trunk
9) Common carotid artery
10) Vertebral artery
New developments: *to start with*

**Level 1** - **level 2** - **Rotter** - **level 3** - **level 4**

*Offersen BV, et al. Radiother Oncol 2015;114:3-10.*
New developments: to start with

Aims:

- Prepare guidelines for volume delineation for all structures relevant in radiation therapy for breast cancer.
- Work towards an agreement and endorsement by all relevant parties in Europe.
- Publish & make available in the form of an atlas by electronic means.
- Support translation into a number of major European languages.
New developments: dose homogeneity

Standard vs. “IMRT”

Cosmetic change:
- 14% “a lot”
- 43% “some”

Cosmetic change:
- 7% “a lot”
- 31% “some”

Donovan, Yarnold et al. Radiother Oncol 2007
New developments: *dose homogeneity*

<table>
<thead>
<tr>
<th>Volumetric IMRT:</th>
<th>3D-CRT:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better TV coverage</td>
<td>More experience</td>
</tr>
<tr>
<td>Improved dose homogeneity</td>
<td>No “low dose bath”</td>
</tr>
</tbody>
</table>

---

Massabeau C. Med Dosim. 2012
New developments: *lowering the cardiac dose*

Free respiration

Breath hold

*Courtesy of Marianne Aznar, Rigshospitalet, Copenhagen*
New developments: *combining it all*

*RT of the thoracic wall - with IM-MS: the next steps.*
BVI photon technique including the IMC
5-field electron technique including the IMC
RT techniques: $vmDIBH + IMRT$
New developments: *combining it all*

**RT techniques: vmDIBH + IMRT**

<table>
<thead>
<tr>
<th></th>
<th>Free breathing</th>
<th></th>
<th>Breath hold</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D-CRT</td>
<td>vIMRT</td>
<td>3D-CRT</td>
<td>vIMRT</td>
</tr>
<tr>
<td>Heart $V_{30\text{Gy}}$ (%)</td>
<td>2.7</td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Heart $V_{20\text{Gy}}$ (%)</td>
<td>7.7</td>
<td></td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>IL Lung $V_{20\text{Gy}}$ (%)</td>
<td>16.4</td>
<td></td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>IL Lung $V_{10\text{Gy}}$ (%)</td>
<td>26.5</td>
<td></td>
<td>23.25</td>
<td></td>
</tr>
<tr>
<td>CL breast $D_{\text{mean}}$(Gy)</td>
<td>0.29</td>
<td></td>
<td>0.62</td>
<td></td>
</tr>
</tbody>
</table>

New developments: *combining it all*

RT techniques: *vmDIBH + IMRT*

<table>
<thead>
<tr>
<th></th>
<th>Free breathing</th>
<th>Breath hold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D-CRT</td>
<td>vIMRT</td>
</tr>
<tr>
<td>Heart $V_{30\text{Gy}}$ (%)</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>Heart $V_{20\text{Gy}}$ (%)</td>
<td>7.7</td>
<td>0.6</td>
</tr>
<tr>
<td>IL Lung $V_{20\text{Gy}}$ (%)</td>
<td>16.4</td>
<td>5.8</td>
</tr>
<tr>
<td>IL Lung $V_{10\text{Gy}}$ (%)</td>
<td>26.5</td>
<td>16.4</td>
</tr>
<tr>
<td>CL breast $D_{\text{mean}}\text{(Gy)}$</td>
<td>0.29</td>
<td>3.7</td>
</tr>
</tbody>
</table>

New developments: *combining it all*

RT techniques: *vmDIBH + IMRT*

<table>
<thead>
<tr>
<th></th>
<th>Free breathing</th>
<th>Breath hold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D-CRT</td>
<td>vIMRT</td>
</tr>
<tr>
<td>Heart $V_{30\text{Gy}}$ (%)</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>Heart $V_{20\text{Gy}}$ (%)</td>
<td>7.7</td>
<td>0.6</td>
</tr>
<tr>
<td>IL Lung $V_{20\text{Gy}}$ (%)</td>
<td>16.4</td>
<td>5.8</td>
</tr>
<tr>
<td>IL Lung $V_{10\text{Gy}}$ (%)</td>
<td>26.5</td>
<td>16.4</td>
</tr>
<tr>
<td>CL breast $D_{\text{mean}}$(Gy)</td>
<td>0.29</td>
<td>3.7</td>
</tr>
</tbody>
</table>

The future, according to some scientists, will be exactly like the past, only far more expensive.

*John Sladek, American Science Fiction author, 1937-2000.*
Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial

By the EORTC Breast Cancer Group and Radiation Oncology Group
In collaboration with the Dutch BOOG Group and ALMANAC Trialists’ Group

Emiel J.T. Rutgers
The Netherlands Cancer Institute, Amsterdam

Clinical trial information: NCT00014612
Trial design

Stratification: institution
Adjuvant systemic therapy by choice

Lymphedema: clinical observation and/or treatment

Years after randomization

- ALND
- AxRT

Years after randomization:
- 1 year: 40.0% with ALND, 21.7% with AxRT
- 3 years: 29.8% with ALND, 16.7% with AxRT
- 5 years: 28.0% with ALND, 13.6% with AxRT

P < 0.0001 for all time points compared to AxRT.
Conclusion

Both ALND and AxRT provide excellent and comparable locoregional control in AxSN+ patients

Significantly less lymphedema after AxRT

AxRT can be considered standard
Principles of breast radiation therapy

- Introduction
- Tasks of the radiation oncologist
- Indications
- Side-effects
- New developments
- The future
The future: *target volumes*

Future work

• **Involvement of surgeons:**
  – Optimal positioning of clips
  – Information on the position of tumor ↔ scar

• **Involvement of pathologist:**
  – 3D information on resection margins

• **Involvement of radiologists:**
  – Use of MRI (usually not available in RT position)

• **Involvement of radiation oncologist:**
  – Pre-operative localization of tumour:
    • physical examination
    • pre-operative planning-CT scan

*Boersma L, Poortmans P et al. R&O 2012*
The «omics" are here?

The future: preventing radioresistance & complications

Combining radiation therapy with:

• Chemotherapy
• Hyperbaric oxygen
• Hyperthermia
• Targeted therapy
• Immunotherapy
The future: particle therapy
The future: particle therapy

Proportional Depth Dose (PDD)

Relative Dose (%) vs. Depth (cm)

- 10 Megavoltage photons
- 16 GigaVolt protons
- Proton mix
• Effective in curative setting
• Effective in palliative setting
• The cheapest oncological treatment
• Favourable cost-benefit ratio
• Local treatment – interaction with systemic treatments
• Increasing demand
Side-effects

- Arm edema ➔ no surgery + RT
- Impairment of shoulder movement ➔ no surgery + RT
- Brachial plexus damage ➔ limit dose (RBE)
- Telangiectasia ➔ avoid skin folds
- Change in breast appearance ➔ homogenisation
- Subcutaneous fibrosis ➔ homogenisation
- Pneumonitis and lung fibrosis ➔ limit lung dose
- Ischemic heart disease ➔ limit heart dose
- Secondary malignancy ➔ avoid other RF
Acknowledgements:

The organising team of this great course

My colleagues:

⇒ RO’s & all others!!!!!!

Colleagues and staff of EORTC and ESTRO

Colleagues and staff of BOOG, IKNL, EBCTCG, ....

Numerous patients

And so many others!