Radiation therapy in breast cancer

Frank Zimmermann
Clinic of Radiotherapy and Radiation Oncology
Incidence (per 100,000/year)

Breast cancer  80
Endometrial carcinoma  14
Cervical cancer  11
Ovarial carcinoma  10
Vaginal-/Vulvacarcinoma  2
Risk factors for breast cancer

Gender
- Age

Life style
- Alcohol
- Xrays
- High BMI

Environ-mental
- Hormonal therapy

Hereditary
- Mutations BRCA1, BRCA2
- Former ovarian or endometrial cancer

Hormones
- Early menarche
- Late menopause

Age >35 at first nativity

Breast cancer in mother/sister
Treatment of breast cancer

- Diagnostic and pathology
- Psychooncology
  - Locoregional therapy (breast, lymph nodes)
    - Surgery and reconstruction
    - Radiotherapy
  - Systemic therapy
    - Chemotherapy
    - antihormonal therapy
    - Antibodies
Techniques and dose of radiation therapy
Positioning of the patient: Mammaboard
Technique of radiation therapy
Technique of radiation therapy
Technique of radiation therapy: IMRT vs. 3-D
## Dose of radiation therapy

<table>
<thead>
<tr>
<th><strong>Whole breast:</strong></th>
<th>45 – 50 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 x 1.8 – 2.0 Gy</td>
</tr>
<tr>
<td></td>
<td>39.9 – 42.5 Gy</td>
</tr>
<tr>
<td></td>
<td>5 x 2.66 Gy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Boost:</strong></th>
<th>10 – 16 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 x 2.0 or 2.66 Gy</td>
</tr>
</tbody>
</table>

NCCN, SIGN et al. guidelines in 2013
Sequence of adjuvant treatments
Sequencing chemo- and radiation therapy in early breast cancer: positive impact of irradiation

15-year gain 5.1% (SE 1.9)
Logrank 2p=0.006

N0: improvement by 5.1 %

Sequencing chemo- and radiation therapy in early breast cancer

Background:
- Chemotherapy improves 15-year survival
- Radiotherapy improves local control and cancer-specific survival

3 trials:
- Both, radio- and chemotherapy should start within 7 months after resection
- Toxicity with simultaneous RCT is slightly increased
- Sequence may depend on resection status

Hickey et al. Cochrane Collaboration 2013
Radiation therapy in breast conserving concepts
Relation of local recurrence rate and survival

Patients with local recurrences have decreased overall survival

Fisher, NEJM 2002
Comparison of lumpetomy + / - EBRT

Local Recurrence

- Postop RT
- No postop RT

Events:
- Postop RT: 41
- No postop RT: 78

P < 0.001

Local control improved by 55 %

Ford et al., Ann Oncol 2005
Influence of EBRT after lumpectomy on cancer-specific survival

N0: gain 5.1 %

N+: gain 7.1 %

Early Breast Cancer Trialists’ Collaborative Group, Lancet 2005
EBRT and local control: influence of age

<table>
<thead>
<tr>
<th>Age</th>
<th>5-y-rec. risk (%) + XRT</th>
<th>5-y-rec. risk (%) - XRT</th>
<th>Gain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>11</td>
<td>33</td>
<td>22</td>
</tr>
<tr>
<td>50 - 59</td>
<td>7</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>60 - 69</td>
<td>4</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>≥ 70</td>
<td>3</td>
<td>13</td>
<td>10</td>
</tr>
</tbody>
</table>

Metaanalysis of EBCTCG, nodal-negative tumors

Early Breast Cancer Trialists' Collaborative Group, Lancet 2005
Comparison of local resection with or without EBRT: local control

Recurrence rate: - 65%

Vinh-Hung et al. JNCI 2004
Comparison of local resection with or without EBRT: survival

Vinh-Hung et al., JNCI 2004
Mastectomy vs. local resection plus EBRT

Blichert-Toft et al. 2009
Dose and fraction in breast conserving therapy

- 50 Gy in 2.0 Gy vs. 42.5 Gy in 2.75 Gy
  - Local recurrence 6.7 vs. 6.2 %
  - Adverse cosmetic 28.7 vs. 30.2 %

- 50 Gy in 2.0 Gy vs. 41.6 Gy/39 Gy in 2.6 Gy
  - Local recurrence 3.6 vs. 3.5 vs. 5.2 %
  - No different side effects

- 50 Gy in 2.0 Gy vs. 40 Gy in 2.66 Gy
  - Local recurrence 3.3 vs. 2.2 %
  - Slightly less side effects with 40 Gy

Théberge et al. Sem Radiat Oncol 2011
Contraindication for breast conserving therapy

- Multicentric invasive carcinoma
- Extensive carcinoma in situ (diffuse micro-calcification)
- No compliance or acceptance of postoperative EBRT
- Pregnancy
- Technical limitations in postoperative EBRT
- Increased radiation sensitivity (i.e. collagenosis, AT, Nijmegen-Breakage-Syndrom, Xeroderma pigmentosum)
Local dose escalation (Boost)
Influence of local dose escalation on local recurrence rate

EORTC 22881: improvement of 3.0 %

Bartelink et al., NEJM 2001
Influence of local dose escalation on local recurrence rate

**Fig 2.** Cumulative incidence of recurrence of tumor as first event in the ipsilateral breast after 50 Gy whole-breast irradiation or 50 Gy whole-breast irradiation and a boost of 16 Gy. HR, hazard ratio; O, occurrences; N, number of patients at risk.
Influence of local dose escalation on local recurrence (according to age)

Fig. 1. Cumulative incidence of recurrence of tumor in the ipsilateral breast after 50 Gy irradiation or 60 Gy irradiation and a boost by age. O, occurrences; N, number of patients at risk.

Fig. 3. Cumulative incidence of ipsilateral breast cancer recurrence according to age. Age (A) is 40, (B) 41 to 50, (C) 51 to 60, and (D) > 60 years. O, occurrences; N, number of patients at risk.
Dose escalation – Comparison of techniques

EORTC 22881, n = 2661, local recurrence rate

Electrons 4,8 %  
Photons 4,0 %  
Brachytherapy 2,5 %  
(Intrabeam 1.8 %)

Poortmans et al., RTO 2004; Vaidya et al. IJROB 2011
Indications for local dose escalation

- Tumorsize > 2 cm
- Close resection margin ≤ 2 mm
- Extensive intraductale component
- Lymphangiosis
- G 3
- Neg. receptorstatus
- Patient premenopausal / < 60 years
- Multifocal tumor

Aebi et al., Ann Oncol 2011
Side effects of local dose escalation

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

nodal-positive patients, n = 318, 20 y. follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>- XRT (%)</th>
<th>+ XRT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rec.-free survival</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>Cancer-spec. surv.</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>Overall survival</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td>Cardial toxicity</td>
<td>0,6</td>
<td>1,8</td>
</tr>
</tbody>
</table>

Ragaz et al., JNCI 2005
Indications for radiation therapy after mastectomy

- pT3
- pT4
- ≥ 1 involved LNs / > 4 involved LNs
- R1-Resection
- R2-Resection

Aebi et al., Ann Oncol 2011
Relative indications for radiation therapy after mastectomy

- Age < 40 y.
- Lymph- or blood-vessel invasion
- Tumorsize > 3 cm
- G 3
- Multicentricical or multifocal
Radiation therapy of lymphatic nodes
Toxicity of axillary irradiation

<table>
<thead>
<tr>
<th></th>
<th>Arm problems (n=467)</th>
<th>- ax. XRT (%)</th>
<th>+ ax. XRT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no AD</td>
<td>26/95 (27)</td>
<td>1/3 (33)</td>
<td></td>
</tr>
<tr>
<td>AD, N+</td>
<td>52/108 (48)</td>
<td>90/127 (71)</td>
<td></td>
</tr>
<tr>
<td>AD, N-</td>
<td>63/132 (48)</td>
<td>1/2 (50)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Lymphedema (n = 112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no AD</td>
<td>2/28 (7)</td>
</tr>
<tr>
<td>AD, N+</td>
<td>1/27 (4)</td>
</tr>
<tr>
<td>AD, N-</td>
<td>1/25 (4)</td>
</tr>
</tbody>
</table>

Kwan et al, JCO 2002
Radiation therapy of lymphatic nodes

- > 3 involved axillary lymph nodes
- infiltration of level III
- (extracapsular spread)
- (incomplete axillary dissection (< 10 LN))
- no axillary dissection
- paraclavicular lymph node metastases
Benefit of radiation therapy of lymphatic nodes in 2648 patients

Smith et al, JCO 2005
Radiation therapy of locoregional tumor recurrence
## Recurrence rates after secondary treatment

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastectomy</td>
<td>10 %</td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>25 %</td>
</tr>
<tr>
<td>Lumpectomy + radiation therapy</td>
<td>10 %</td>
</tr>
</tbody>
</table>

5-y overall survival rate: ~ 75 %

Distant progression relevant for prognosis, but local control relevant for quality of life, too

*Hannoun-Levi et al. Cancer Treat Rev 2013*
Radiation therapy of locoregional tumor recurrence

In principle feasible

Techniques depend on availability and previous treatments
- EBRT (can be hyperfractionated)
- Brachytherapy (can be pulsed dose rate)

Cumulative doses of up to 120 Gy

2-y local control rate: > 50 %
Worse prognosis: with lymph node recurrences

Hannoun-Levi, IJROBP 2005; Deutsch, IJROBP 2002; Resch, Radiology 2002
Radiation therapy of locoregional tumor recurrence

Resch, Radiology 2002
Radiation therapy of locoregional tumor recurrence
Accelerated partial breast irradiation (APBI)
Rationale for partial breast irradiation

Majority of recurrences in former tumor bed
[Faverly et al., Cancer 2001]

Patients > 70 J., stage I, rec. pos. and breast conserving resection with low benefit by adjuvant radiation therapy
[Hughes et al., NEJM 2004]

Shortend overall treatment time

Potential for improving cosmetic results (by skin sparing)
Techniques of partial breast irradiation

- Interstitial brachytherapy
- 3-D-conformal EBRT
- MammoSite ®
- Intraoperative electron-beam irradiation (IOERT)
- IntraBeam ®
Interstitial brachytherapy (implantation during resection)

Catheter placement during resection
Interstitial brachytherapy (implantation after resection)

Catheters in position
CT-scan
Dose distribution
Partial breast irradiation with electrons
3-D-conformal EBRT

Arrangement of beams and Dose distribution
Intraoperative irradiation with balloon brachytherapy (MammoSite®, Axxent X-ray)
Intraoperative electron irradiation (IOERT)

Positioning of PB-protection

Positioning of the e⁻-beam
Intraoperative irradiation with IntraBeam®

Device and tubes

Intraoperative positioning after resection
Recommendations for accelerated partial breast irradiation (APBI)

Interst. Brachy.: local control 95-97 % (5 y.)(retrospective)
3-D-conformal: local control 94 % (phase-II)
MammoSite®: local control 96-99 % (retrospective)(4-5 y.)
IOERT: local control 99 % (4 y.)(phase-II)
IntraBeam®: local control 95-99 % (4 y.)(phase-III) (14 % add. postop. EBRT)

Recommendations for accelerated partial breast irradiation (APBI)

- No apparent difference in techniques
  (maybe dependent on personal experience)

- Indication: age > 50/60 y, tumor size < 3 cm/pT1, neg. margins, L0, V0, N0, no DCIS, unicentric, BCR1/2 neg., ER pos., inv. Ductal

- Dosimetric guidelines should be respected

Dose of accelerated partial breast irradiation

Brachytherapy: 2 x / day
10 x 3.4 Gy

External beam: 2 x / day
10 x 3.85 Gy

Intraoperative: 20 – 25 Gy

NCCN, SIGN et al. guidelines in 2013
Ductal carcinoma in situ (DCIS)
Adjuvant radiation therapy in DCIS

Figure 3

Less invasive breast cancer after radiation therapy

Has to outweighed against cosmetic consequences

Viani et al., Radiation Oncology 2007
Adjuvant radiation therapy in DCIS

**Figure 2**

No influence of DCIS-recurrence rate
Side effects of radiation therapy
Side effects of radiation therapy

- Dermatitis and alteration of skin colour (often)
- Local edema (often)
- Cosmetic alterations (sometimes)
- Lymphedema (depends on LN-treatment; rare)
- Pneumonitis (< 3 %)
- Rib fracture (~ 1 %)
- Intramammary pain (25 %)

Andersen et al., Breast 2012
Side effects of EBRT

At the end of EBRT

3 months after EBRT

4 days after EBRT
Side effects of EBRT: old and new therapies

After mastectomy and cobalt

After lumpectomy and linac
Cardial toxicity of radiation therapy

Retrospective analysis in 7303 patients

<table>
<thead>
<tr>
<th></th>
<th>right (%)</th>
<th>left (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>all cardial events</td>
<td>9,8</td>
<td>9,5</td>
</tr>
<tr>
<td>coronaropathy</td>
<td>3,7</td>
<td>3,9</td>
</tr>
<tr>
<td>- Increase of ~ 4 % / Gy, recommendation: mean &lt; 3 Gy!</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular problems</td>
<td>1,4</td>
<td>1,2</td>
</tr>
<tr>
<td>Cardial insufficiency</td>
<td>4,4</td>
<td>4,1</td>
</tr>
</tbody>
</table>

Mège et al., Cancer/Radiother 2011
Treatment of side effects

- No prophylactic measures (besides technique)
- Dermatitis: creme and clean
- Pneumonitis: prednisolon 60 mg / macrolid-antib.
- Fibrosis: Vit. E / tocopherol and pentoxifylline
- Lymph drainage
- Analgetics
Conclusion: radiation therapy

- After breast conserving surgery: about 65 %-reduction of local recurrence rate
- Technique: 3-D-conformal EBRT (low risk cancer APBI; no superior technique)
- Dose prescription: 1.8-2.66 Gy SD in EBRT, 39.9-50.4 Gy TD in EBRT; with risk factors local dose escalation
- Side effects: dermatitis, fibrosis, lymphedema, pneumonitis, rib fracture, late myocarditis
## Follow-up

<table>
<thead>
<tr>
<th>Postop year</th>
<th>1-3</th>
<th>4-5</th>
<th>&gt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>3 - 4x / year</td>
<td>2x / year</td>
<td>1x / year</td>
</tr>
<tr>
<td>Mammography +/- Ultrasound (MRI)</td>
<td></td>
<td></td>
<td>1x / year</td>
</tr>
<tr>
<td>Further examinations</td>
<td></td>
<td></td>
<td>According to symptoms</td>
</tr>
</tbody>
</table>