Adjuvant Radiotherapy
Adjuvant Radiotherapy (RT)

- **Versions 2002 – 2018:**
  Blohmer / Budach / Friedrichs / Göhring / Huober / Janni / Kühn / Möbus / Scharl / Seegenschmiedt / Souchon / Thomssen / Untch / Wenz

- **Version 2019:**
  Budach / Rody / Wenz

**Search Strategy**

**Search Terms:** Radiotherapy Breast Cancer

**Source:** Pubmed 1/2010 – 1/2018

**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**


**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**

Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast

Preliminary Note

- The recommendations on adjuvant radiotherapy for breast cancer are based on a consensus discussion between experts of the AGO and DEGRO
- For technical details of radiotherapy we recommend to refer to the corresponding updated DEGRO practical guidelines 2014-2016


DEGRO practical guidelines: radiotherapy of breast cancer III--radiotherapy of the lymphatic pathways

DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer


Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): Whole Breast Irradiation

- Radiotherapy of the affected breast
- Hypofractionated radiotherapy (total dose approximately 40 Gy in 15-16 fractions within 3-5 weeks)
- Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in about 5-6 weeks)
- In case of life expectancy <10 years and pT1, pN0, R0, ER/PR positive, HER2 negative, endocrine therapy (all criteria) radiotherapy can be omitted after individual counseling accepting an increased risk of in breast recurrence

Oxford LoE | GR | AGO
---|---|---
1a | A | ++
1a | A | ++
1a | B | +
1a | B | +

7. Chan EK, Woods R2, McBride ML2, et al. Adjuvant hypofractionated versus conventional whole breast radiation therapy for early-
18. Haviland JS, Bentzen SM, Bliss JM et al On behalf of the START Trial Management Group. Prolongation of overall treatment time as a cause of treatment failure in early breast cancer: An analysis of the UK START (Standardisation of Breast Radiotherapy) trials of
radiotherapy fractionation. Radiotherapy and Oncology 121 (2016) 420–423

Additional Information with Regard to Effects of Breast Radiotherapy (BCT)

- **Hypofractionation:**
  - "Some normal tissue effects were less common after the 15 fraction regimen than the control schedule (breast shrinkage, telangiectasia, and breast oedema)."
  - In 1 of 5 trials: "There were significantly fewer distant relapses up to 10 years in the 40 Gy group (HR 0.74, 95% CI 0.59–0.94), which contributed to the significantly higher rates of disease-free survival and overall survival in the 40 Gy group compared with the 50 Gy group." (HR<sub>HR</sub>=0.8; p=0.042) (START B: Haviland JS et al. Lancet Oncol 2013; 14: 1086–94)

- **Elderly patients should be advised about the following:**
  - In older patients with PT1-2 (≤3 cm) pNO hormone receptor-positive breast cancer, breast irradiation for breast conserving therapy is able to reduce the risk of a local recurrence by about 8% over 10 years. A benefit with regard to metastasis-free survival and overall survival has not been found yet.


BSC > = 70y < 4cm cN0 : Tamoxifen vs. Tamoxifen + RT
Time: 1994-1999, since 8/1996 only pT1cN0 ER/PR+ or unknown allowed

<table>
<thead>
<tr>
<th></th>
<th>Tamoxifen</th>
<th>Tamoxifen plus Radiotherapy</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>@10 yrs (95% C.I.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local recurrence-free (Λ=8%)</td>
<td>90% (85%-93%)</td>
<td>98% (96%-99%)</td>
<td>HR=0.18 (95% CI, 0.07 to 0.42; P &lt; .001)</td>
</tr>
<tr>
<td>Mastectomy-free</td>
<td>96% (93% - 98%)</td>
<td>98% (96% - 99%)</td>
<td>HR=0.50 (95% CI, 0.17 to 1.48; n.s.)</td>
</tr>
<tr>
<td>Distant metastasis-free</td>
<td>95% (91% - 97%)</td>
<td>95% (92% - 97%)</td>
<td>HR=1.20 (95% CI, 0.63 to 2.32; n.s.)</td>
</tr>
<tr>
<td>Overall survival</td>
<td>66% (61% - 71%)</td>
<td>67% (62% - 72%)</td>
<td>HR=0.95 (95% CI, 0.77 to 1.18; n.s.)</td>
</tr>
</tbody>
</table>

Hughes KE et al J Clin Oncol 2013; 31:2382-2387


Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation

Boost-RT (improves local control, no survival benefit)

- Premenopausal
  - Postmenopausal, if >T1 G3, HER2-positive, triple negative, EIC (at least 1 factor)
- Intraoperative irradiation (intraop. APBI)
  - As boost-irradiation followed by WBI
  - As sole radiotherapy modality (IORT 50 kV, IOERT)**
    - >50 years**
    - >70 years**
- Postoperative partial breast irradiation as sole radiotherapy modality (APBI)
  - Intersitial brachytherapy
    - >70 years**
  - Intracavity balloon technique
  - IMRT***
    - only for pT1 pN0 R0 G1-2, HR+, non-lobular, no extensive DCIS, IORT during first surgery; continuous parameter with regard to risk of relapse

* Study participation recommended; ** no long term data

Oxford LoE GR AGO

- Boost-RT (improves local control, no survival benefit)
  - Premenopausal
  - Postmenopausal, if >T1 G3, HER2-positive, triple negative, EIC (at least 1 factor)
  - Intraoperative irradiation (intraop. APBI)
  - As boost-irradiation followed by WBI
  - As sole radiotherapy modality (IORT 50 kV, IOERT)**
    - >50 years**
    - >70 years**
  - Postoperative partial breast irradiation as sole radiotherapy modality (APBI)
    - Intersitial brachytherapy
      - >70 years**
    - Intracavity balloon technique
    - IMRT***
      - only for pT1 pN0 R0 G1-2, HR+, non-lobular, no extensive DCIS, IORT during first surgery; continuous parameter with regard to risk of relapse
**Boost-RT in postmenopausal p.**


**Intraoperative irradiation (IORT/IOERT)**

**As boost-irradiation followed by WBI**


**As sole radiotherapy modality**

IORT using 50 kV (pT1 pN0 R0 G1-2, non-lobular, age >50 y, no extensive DCIS, IORT during first surgery, HR+)


>70 yrs


5. Vaidya JS, Wenz F, Bulsara M et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy
(TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). Health Technol Assess 2016;20(73).


Postoperative partial breast irradiation as sole radiotherapy modality (ABPI)

Interstitial brachytherapy


Interstitial brachytherapy >70 yrs


Intracavity balloon technique

IMRT


### EORTC 22881-10882: Boost vs no Boost (Endpoint: Ipsilateral Breast Recurrence)

<table>
<thead>
<tr>
<th>@20 yrs (95% C.I.)</th>
<th>Boost (n=2.661)</th>
<th>No boost (n=2.657)</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival (Δ= 1.4%)</strong></td>
<td>59.7% (56.3–63.0)</td>
<td>61.1% (57.6–64.3)</td>
<td>HR 1.05 (0.92–1.19) n.s.</td>
</tr>
</tbody>
</table>

**Cumulative Risk of Ipsilateral Breast Tumour Recurrence**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Boost (95% C.I.)</th>
<th>HR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>12.0% (9.8–14.4)</td>
<td>HR=0.65 (0.52–0.81); p=0.0001</td>
</tr>
<tr>
<td>&lt;40 years (Δ=11.6%)</td>
<td>24.4% (14.9–33.8)</td>
<td>HR=0.56 (0.34–0.92); p=0.003</td>
</tr>
<tr>
<td>41–50 years (Δ=5.9%)</td>
<td>13.5% (9.5–17.5)</td>
<td>HR=0.66 (0.45–0.98); p=0.007</td>
</tr>
<tr>
<td>51–60 years (Δ=2.9%)</td>
<td>10.3% (6.3–14.3)</td>
<td>HR=0.69 (0.46–1.04); p=0.020</td>
</tr>
<tr>
<td>&gt;60 years (Δ=3.0%)</td>
<td>9.7% (5.0–14.4)</td>
<td>HR=0.66 (0.42–1.04); p=0.019</td>
</tr>
</tbody>
</table>


7. NCCN Guidelines for Treatment of Cancer by Site  


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with > 3 tumor infiltrated lymph nodes (Lnn.)

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) high risk

8. NCCN Guidelines for Treatment of Cancer by Site


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) low risk


6. NCCN Guidelines for Treatment of Cancer by Site

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with T3 / T4 breast cancer


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with pT3 pN0 R0 breast cancer (and no additional risk factors)


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with if R0 is impossible to reach (for invasive tumor)


6. Rowell NP. Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother
Postmastectomy Radiotherapy (PMRT) to the Chest Wall in young pts with high risk features


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. after neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d)


4. Rusthoven CG, Rabinovitch RA, Jones BL et al. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant

Omission of Postmastectomy Radiotherapy (PMRT) to the Chest Wall after NACT in case of ypT0 ypN0 after NACT


Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment


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.

DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer.


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**Omission of Postmastectomy Radiotherapy (PMRT) to the Chest Wall after NACT in case of ypT0 ypN0 after NACT**


**Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment**

DEGRO practical guidelines for radiotherapy of breast cancer IV: radiotherapy following mastectomy for invasive breast cancer.

**Boost in PMRT**

- An additional boost irradiation to a part of the chest wall has not been shown to improve DFS and overall survival\(^1\).
- An additional boost irradiation to a part of the chest wall should be given in case of R1/R2-resection, if a secondary resection is not feasible\(^2\).
- In case of extension of the tumor to the pectoral resection margin, but no clinical signs of extension beyond the fascia, the resection margin should be regarded as R0 (provided, that the pectoral fascia was resected). A boost radiotherapy is not required in this situation\(^3\).

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>D</td>
<td>++</td>
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</tr>
</tbody>
</table>

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**Boost Thoraxwand und Gesamtüberleben**

Radiotherapy of axillary lymph node dissection or negative sentinel node biopsy

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>D</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>B</td>
<td>--</td>
</tr>
</tbody>
</table>


Tumor residuals after axillary dissection

1. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms Langversion 3.0, Aktualisierung 2012 AWMF-Register-Nummer: 032 – 045OL Leitlinie. Herausgeber: Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V.

Sentinel node negative


Axillary dissection not indicated e.g. cN0, SLN positive (see surgical chapter)


Extracapsular tumor spread (ECS)


Axillary micrometastases or isolated cells found in regional lymph nodes

Radiotherapy of axillary lymph nodes in patients with positive sentinel-lymph nodes**, who did not undergo axillary dissection

<table>
<thead>
<tr>
<th>BCS and ACOSOG Z0011-criteria* met</th>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy of the breast including LN level 1 + 2 to 5 mm below the axillary vein (PTV)</td>
<td>2b</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>BCS and ACOSOG Z0011-criteria* not met</td>
<td>1b</td>
<td>B</td>
<td>++*</td>
</tr>
<tr>
<td>Radiotherapy of the axillary Lymph nodes (analog AMAROS)</td>
<td>1b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>ME and chest wall RT indicated and ACOSOG Z011-criteria* not met or ME and chest wall RT not planned</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Radiotherapy of the axillary Lymph nodes (analog AMAROS)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

* = Study participation recommended
** = Macrometastases
* = <T3, no palpable LN, R0, 1-2 positive SN, no extracapsular extension, no NACT

1-2 pos SLN: BCT: No further treatment to the axilla neither axillary dissection nor RT of the axilla (criteria according ACOSOG Z011)


1-2 pos SLN: BCT: Axillary dissection


1-2 pos SLN: BCT: radiotherapy of the axilla


1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, axillary dissection or radiotherapy of the axilla


1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, no axillary treatment (criteria ACOSOG Z011)

EXPERT OPINION, extrapolated from:


1-2 pos SLN: Mastectomy: If RT of chestwall is not planned, axillary dissection or radiotherapy of the axilla

EXPERT OPINION, extrapolated from:


>=3 positive SLN: Axillary LN dissection

1. Giuliano AE, Hunt KK, Ballmann KV, et al. Axillary dissection vs no axillary dissection in women with breast invasive cancer and


>=3 positive SLN: Radiotherapy of the axilla


Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG) (15/20)


### Supra-/infraclavicular lymphatic regions

**RT to Supra-/infraclavicular lymphatic regions if ≥ pN2a**

- ≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in the supra/infraclavicular LN (1b A ++)
- 1-3 positive axillary lymph nodes\(^1\) in case of
  - central or medial tumor and G2-3 or ER/PgR-negative
  - premenopausal patient and G2-3 or ER/PgR-negative (2a B +)
- pN0 with central or medial tumors, if premenopausal and G2-3 and ER/PgR-negative (2a B +/-)

\(^{1}\) not applicable for micrometastases

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Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG) (15/20)


**RT to Supra-/infraclavicular lymphatic regions if Level III involved**


**RT to Supra-/infraclavicular lymphatic regions if pN1a high risk**


RT to Supra-/infraclavicular lymphatic regions if pN1a low risk

RT to Supra-/infraclavicular lymphatic regions after NACT/NAT (indications as for PMRT)

4. Rusthoven CG, Rabinovitch RA, Jones BL, et al. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN) - Slide 16/20

**Internal mammary lymph node region (IMN)**

- **pN0 high risk with central or medial tumor and premenopausal and G2-3 and ER/PgR-negative**
  - LoE: 1b
  - GR: B
  - AGO: +/-

- **1–3 positive axillary lymph nodes\(^1\) in case of**
  - Central or medial tumor and G2-3 or ER/PgR-negative
  - Premenopausal patient and G2-3 or ER/PgR-negative
  - LoE: 2a
  - GR: B
  - AGO: +

- **≥ 4 positive axillary lymph nodes**
  - LoE: 2a
  - GR: B
  - AGO: +

- **Involved internal mammary lymph nodes**
  - LoE: 2a
  - GR: B
  - AGO: +

- **In case of cardiac risk factors or trastuzumab is given**
  - LoE: 2b
  - GR: A
  - AGO: --

\(^1\) Not applicable for micrometastases

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**Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)**

**RT to Internal mammary lymph node region (IMC) if pN0 high risk with central/medial tumors**


RT to Internal mammaria lymph node region (IMN) if pN1-pN2 and HR positive in patients who had systemic chemotherapy

# Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

<table>
<thead>
<tr>
<th>Adjuvant treatment</th>
<th>n*</th>
<th>Hazard ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adjuvant reported</td>
<td>625</td>
<td>0.91 (0.59 - 1.39)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>954</td>
<td>1.05 (0.84 - 1.32)</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td>1185</td>
<td>0.82 (0.63 - 1.06)</td>
</tr>
<tr>
<td>Both (endocrine th. and chemotherapy)</td>
<td>1200</td>
<td>0.72 (0.55 – 0.94)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4004</strong></td>
<td><strong>0.88 (0.76 – 1.01)</strong></td>
</tr>
</tbody>
</table>

* missing data on 40 patients

Poortmans et al. ECCO Amsterdam 2013
Radiotherapy following NACT

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>RT-BCS</th>
<th>PMRT</th>
<th>RT-RN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced</td>
<td>pCR / no PCR</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>cT1/2 cN1+</td>
<td>ypT0 / ypN0 + (no pCR)</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>cT1/2 cN1+</td>
<td>ypT0/1 ypN0</td>
<td>yes</td>
<td>Increased risk of relapse 1</td>
<td></td>
</tr>
<tr>
<td>cT1/2 cN0 [Ki67+ PgR+]</td>
<td>ypT0/1 ypN0 Ja</td>
<td>nein</td>
<td>nein</td>
<td></td>
</tr>
</tbody>
</table>

Locally advanced: T3-4 or cN2-N3,

BCS: Breast conserving surgery, PMRT: Post mastectomy radiotherapy, RN: Regional nodes

1 Criteria for increased risk of relapse:
- pN0 premenopausal high risk: central or medium tumor localization, and (G2-3 and ER/PgR-negative)
- pretreatment pN1a / cN+ high risk: central or medium tumor localization and (G2-3 or ER/PgR-negative) or premenopausal, lateral tumor localization and (G2-3 or ER/PgR-negative) * = confirmed by core biopsy


Trastuzumab* concurrent with radiotherapy (*in HER2 pos tumors parasternal RT should generally be avoided; no concurrent trastuzumab in parasternal RT)


Tamoxifen concurrent with radiotherapy


AI (letrozole, anastrozole) concurrent with radiotherapy


**Pertuzumab concurrent with radiotherapy**


**T-DM1 concurrent with radiotherapy**


**Checkpointinhibitors concurrent with radiotherapy**

Extrapolated from trial results in other tumor entities and from current clinical trial in breast cancer

**Capecitabine and radiotherapy**


Other compounds (bevacizumab)
