Adjuvant Radiotherapy
**Adjuvant Radiotherapy (RT)**

- **Versions 2002 – 2020:**
  - Blohmér / Budach / Friedrichs / Göhring / Huober / Janni / Kühn / Möbus / Rody / Scharl / Seegenschmeldt / Souchon / Thomssen / Untch / Wenz

- **Version 2021:**
  - Budach / Friedrich / Krug

**Search Strategy**

Search Terms: Radiotherapy Breast Cancer
Source: Pubmed 1/2010 – 1/2021

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 AGO and DEGRO experts.
- For technical radiotherapy details, we refer to the corresponding updated DEGRO practice guidelines.


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

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<td>1a</td>
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</tbody>
</table>

**Hypofractionation**


Ultra-Hypofractionation


Elderly patients with low-risk features


Jan 18;127:12-20.

5. Kunkler et al. GS2-03. Prime 2 randomised trial (postoperative radiotherapy in minimum-risk elderly): Wide local excision and adjuvant hormonal therapy +/- whole breast irradiation in women =/> 65 years with early invasive breast cancer: 10 year results. SABCS 2020
Ultra-Hypofractionation


Ultra-Hypofractionation


Boost in general (EBRT/Brachytherapy, sequential)


Boost-RT in premenopausal p.
Boost-RT in postmenopausal p.


Simultaneous-integrated boost (conventionally fractionated RT)


Simultaneous-integrated boost (hypofractionated RT)

Intraoperative irradiation (IORT/IOERT)

As boost-irradiation followed by WBI


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


>70 yrs


Postoperative partial breast irradiation as sole radiotherapy modality (ABPI)

Interstitial brachytherapy


Intracavity balloon technique


IMRT (5x6 Gy)


3D-conformal RT (15x2.67 Gy over two weeks)


3D-conformal RT (10x3.85 Gy over two weeks)

3D-conformal RT (10x3.85 Gy over one week)
### Data on partial breast irradiation

**NSABP B-39/RT0G 0413 (Vicini FA et al. Lancet. 2019 Dec 14;394(10215):2155-2164.)**

- Randomised phase III equivalence trial, 4216 pat., 2005-2013, DCIS or invasive carcinoma ≤ 3 cm, 0-3 involved lymph nodes, age >18 y
- 50 Gy/25 fr. +/- boost vs. APBI with
  - 38.5 Gy/10 fr. in one week (external beam irradiation)
  - 34 Gy/10 fr. in one week (Multicatheter- or Single lumen-Brachytherapy)
- "We observed an HR of 1.22 with a 90% CI of 0.94–1.58, which did not meet the equivalence criteria and favoured whole-breast irradiation. The 10-year cumulative incidence of IBTR was 3.9% (95% CI 3.1–5.0) in the whole-breast irradiation group and 4.6% (3.7–5.7) in the APBI group for an absolute difference of 0.7%."*
- "Significantly more evaluable patients in the APBI group had recurrence-free interval events than patients in the whole-breast irradiation group" (figure 3). The 10-year point estimate of recurrence-free interval for the whole breast irradiation group was 93.4% (95% CI 92.1–94.6), and in the APBI group it was 91.8% (90.4–93.0; figure 3)."
- "Our findings support whole-breast irradiation but the absolute outcome difference compared with APBI is small, so partial breast irradiation might also be an acceptable treatment for some patients."*

Postmastectomy Radiotherapy (PMRT)* to the Chest Wall


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


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


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)

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) based on the initial stage prior to NACT (cN+, cT3/4a-d)


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: radiotherapy following mastectomy for invasive breast cancer.

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


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


Adjuvant Radiotherapy


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)


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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

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: radiotherapy following mastectomy.


Thoracic wall boost irradiation

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

<table>
<thead>
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<th>Oxford</th>
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<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td>+*</td>
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</tbody>
</table>

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 chest wall is indicated, **axillary dissection or radiotherapy of the axilla**

1-2 pos SLN: Mastectomy: If RT of chest wall is indicated, **no axillary treatment** (criteria ACOSOG Z011)
EXPERT OPINION, extrapolated from:

1-2 pos SLN: Mastectomy: If RT of chest wall is not planned, **axillary dissection or radiotherapy of the axilla**
EXPERT OPINION, extrapolated from:

>=3 positive SLN: **Axillary LN dissection**
2. Donker M, Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC


>=3 positive SLN: Radiotherapy of the axilla


### Sentinel node negative


### Complete Axillary lymph node dissection after positive sentinel lymph node may be omitted in certain cases due to lack of benefit in prospectively randomized studies


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### Additional RT of the axilla after primary surgery

<table>
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<th>Oxford</th>
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</table>

| pN-status |        |    |    |
| pN0(sn)/pN1mic(sn) | 1b | B | -- |
| pN0/- after ALND | 1a | A | -- |
| pN+(sn) in analogy to ACOSOG Z0011 (no ALND) | 2b | B | + |
| pN+(sn) not fitting ACOSOG Z0011-criteria → RT in analogy to AMAROS | 1b | B | ++ |
| in( no ALND) | | | |

Incidental dose to parts of level III is inevitable. *The indication for supra/infracavicular and internal mammary node RT has to be assessed separately.* "Clinical border 5 mm below the axillary vein." *V*, 1%K, , no kidC, always in conjunction with supra/infracavicular RT.
Regional nodal irradiation without ALND in non-Z0011-eligible patients


Tumor residuals after axillary dissection

1. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Aktualisierung 2017 Version 4.2.
   Herausgeber: Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V.
Statement surgical intervention in the axilla before or after neoadjuvant chemotherapy


2. Galimberti V, Ribeiro Fontana SK, Maisonneuve P. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. Eur J Surg Oncol 2016;42(3) 361-8


Axillary intervention after PST


Tumor residuals after axillary dissection

1. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Aktualisierung 2017 Version 4.2. Herausgeber: Leitlinienprogramm Onkologie der AWMF, Deutschen Krebsgesellschaft e.V. und Deutschen Krebshilfe e.V.
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG)

<table>
<thead>
<tr>
<th>RT to supra-/infraclavicular lymphatic regions</th>
<th>Oxford</th>
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<tbody>
<tr>
<td>≥ 4 positive axillary lymph nodes (LN) or involved LN in level III or in supra-/infraclavicular LN</td>
<td>1b</td>
</tr>
<tr>
<td>1–3 positive axillary lymph nodes¹ in case of</td>
<td></td>
</tr>
<tr>
<td>- central or medial tumor and G2-3 or ER/PR-negative</td>
<td>2a</td>
</tr>
<tr>
<td>- premenopausal patient and G2-3 or ER/PR-negative</td>
<td></td>
</tr>
<tr>
<td>pN0 with central or medial tumors, if premenopausal and G2-3 and ER/PR-negative</td>
<td>2a</td>
</tr>
</tbody>
</table>

¹ not applicable for micrometastases

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

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


8. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

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


6. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

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


6. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

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


5. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

RT to Supra-/infraclavicular lymphatic regions if pN0 high risk, if radiotherapy of the internal mammarian inn. chain is indicated (see below)


6. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

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

1. Please check slide on radiotherapy after NACT
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)

Internal mammary lymph node region (IMN)

- pN0 high-risk with central or medial tumor and premenopausal and G2-3 and ER/PR-negative
- 1–3 positive axillary lymph nodes\(^1\) in case of - central or medial tumor and G2-3 or ER/PR-negative
- premenopausal patient and G2-3 or ER/PR-negative
- ≥ 4 positive axillary lymph nodes
- involved internal mammary lymph nodes
- In case of cardiac risk factors or if trastuzumab is given

<table>
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<tr>
<th>LoE</th>
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<tr>
<td>1b</td>
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<tr>
<td>2a</td>
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</tbody>
</table>

\(^1\) not applicable for micrometastases

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

Internal mammary lymph node region (IMN)

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


8. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018

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


8. Dodwell et al. Regional lymph node irradiation in early stage breast cancer: An EBCTCG meta-analysis of 13,000 women in 14 trials. Presented at SABCS 2018


6. Haviland JS, Mannino M, Griffin C et al. Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials. Radiother Oncol. 2018 Jan;126(1):155-162.
Radiotherapy following NACT

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Posttreatment</th>
<th>RT-BCS</th>
<th>PMRT</th>
<th>RT-RN</th>
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<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>ypT1+ o. ypN1+</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>cT1/2 cN1+</td>
<td>ypT0/o. ypN0</td>
<td>yes</td>
<td>Increased risk of relapse</td>
<td></td>
</tr>
<tr>
<td>cT1/2 cN0 (Soncr. bilateral)</td>
<td>ypT0/o. ypN0</td>
<td>Ja</td>
<td>nein</td>
<td>nein</td>
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Locally advanced: T3-4 or cN2-N3,


Molecular predictors and use of radiotherapy

- Results of gene expression profiling should not be used for indication of radiotherapy

Use of concomitant systemic therapy with adjuvant locoregional radiotherapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>LoE</th>
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<tbody>
<tr>
<td>Trastuzumab/Pertuzumab*</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>T-DM1</td>
<td>1b</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>2b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Checkpoint inhibitors</td>
<td>2b</td>
<td>C</td>
<td>+</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>2b</td>
<td>B</td>
<td>+**</td>
</tr>
<tr>
<td>CDK4/6-inhibitors</td>
<td>4</td>
<td>C</td>
<td>+/+-***</td>
</tr>
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* concurrent Trastuzumab/Pertuzumab and parasternal radiotherapy should be avoided
** with hypofractionated RT approx. 40 Gy, consider dose reduction of Capecitabine. Pat. at high-risk for locoregional recurrence
*** In currently available phase III-trials (monarchE, PALLAS, Penelope-B) RT was given before initiation of CDK4/6-inhibitors. No definitive signs of significantly increased toxicity with concomitant RT in the palliative setting.

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**

**Checkpoint inhibitors concurrent with radiotherapy**
Extrapolated from trial results in other tumor entities and from current clinical trial in breast cancer

**Capecitabine and radiotherapy**
CDK4/6-Inhibitors


Adjuvant Radiotherapy
Simultaneous Capecitabine with locoregional radiotherapy

- Prospective phase trial, 32 pat. with LABC, sim. def./neoad. chemoradiotherapy, median total dose 66 Gy
- "The first 9 patients analyzed [...] received CAP 825 mg/m² twice daily continuously beginning on the first day of RT. Because of observed excess grade 3 toxicity the protocol was amended, and subsequent patients received CAP only on RT days (5 days per week)."
- "Noncontinuous CAP dosing was much better tolerated than continuous dosing. Thirteen of 26 patients (50%) had grade ≥3 and higher treatment-related dermatologic toxicity."

Alhanafy et al. Menoufia Medical Journal 2015, 28:325-332
- Randomized phase II-trial, 100 pat., adj. Radiotherapy 40 Gy/15 fr. +/- CAP 825 mg/m² Mo-Fr, LABC
- " [...] concurrent capecitabine was feasible with a high percent of patients (96%), [...] only two out of 50 (4%) patients had capecitabine dose modification ...".
- "All early toxicities were GI/GII. Radiation dermatitis had a peak incidence in the last few fractions of the radiation therapy and the week after radiotherapy; no treatment interruption was needed and the incidence was close in both groups".
- Radiation dermatitis grade I 14% vs. 18%; grade ≥2 4% vs. 4%
**Smoking and Risk of secondary lung cancer**

- **Increased risk of lung cancer secondary to breast cancer radiotherapy in smokers**
- Inform patients about risk
- Recommend to stop smoking

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