Adjuvant Radiotherapy
Search Strategy
Search Terms: Radiotherapy Breast Cancer
Source: Pubmed 1/2010 – 1/2024

Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14,324 women in 16 trials.

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 8,135 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 practical guidelines.


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

- Radiotherapy of the affected breast
- Moderately hypofractionated radiotherapy (total dose approx. 40 Gy in 15-16 fractions within 3-5 weeks)
- Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day or 28.5 Gy in 5 fractions over 5 weeks = 1 fraction/week)
- Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions in 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, resulting in an increased risk for in-breast recurrence without impairing survival.

Oxford

<table>
<thead>
<tr>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>1b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>1a</td>
<td>B</td>
<td>+</td>
</tr>
</tbody>
</table>

Moderate Hypofractionation


**Ultra-Hypofractionation**


**Elderly patients with low-risk features**


6. 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
### Prospective observational studies of radiotherapy omission incorporating tumor biology and MRI

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Time-frame</th>
<th>Inclusion criteria</th>
<th>Follow up</th>
<th>Local recurrence (95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUMINA</td>
<td>500</td>
<td>2013-2017</td>
<td>≥55 years, pT1 pN0 R0 (≥1 mm) ER ≥1% PR ≥20% HER2 neg. Ki67 ≤ 13.25% (central lab)</td>
<td>5 y</td>
<td>2.3% (1.2-4.1%)</td>
</tr>
<tr>
<td>IDEA</td>
<td>200</td>
<td>2015-2018</td>
<td>50-69 years, pT1 pN0 R0 (≥2 mm) ER/PR pos. HER2 neg., Oncotype Dx RS ≤ 18</td>
<td>5 y</td>
<td>50-59 y. 3.3% 60-69 y. 3.6%</td>
</tr>
<tr>
<td>PROSPECT</td>
<td>201</td>
<td>2011-2019</td>
<td>≥50 years, unifocal cT1 cN0, no LVI, no EIC, R0 (≥2 mm), ER/PR pos. and/or HER2-pos., preoperative breast MRI</td>
<td>5 y</td>
<td>1.0% (-5.4%)</td>
</tr>
</tbody>
</table>

- **Discussion:**
  - Confidence intervals of local recurrence (LR) rates overlap with control arms of previous trials.
  - Uncontrolled trials with limited follow up.
  - CALGB 9343 and PRIME II showed a doubling LR rates after 10 years vs. 5 years in the control arms and an increasing benefit of radiotherapy with longer follow-up.
  - In PRIME II, low ER expression was associated with an increased LR rate in the control arm.
  - Compliance for endocrine therapy was higher than expected in clinical routine.

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


Clip placement


### EORTC 22881-10882: Boost vs. no Boost
(Endpoint: Any First Recurrence)

<table>
<thead>
<tr>
<th>@15 yrs/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>Overall Survival (Δ = -1.4%)</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>

<table>
<thead>
<tr>
<th>Cumulative Risk of Any First Recurrence</th>
<th>@15y</th>
<th>@20y</th>
<th>@15y</th>
<th>@20y</th>
<th>@15y</th>
<th>@20y</th>
<th>@15y</th>
<th>@20y</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (Δ ≥ 4%)</td>
<td>28.1%</td>
<td>32.1%</td>
<td>32.1%</td>
<td>32.1%</td>
<td>HR = 0.92 (0.81-1.04), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40 years (Δ &gt; 6%)</td>
<td>41.5%</td>
<td>48.1%</td>
<td>48.1%</td>
<td>56.8%</td>
<td>HR = 0.80 (0.56-1.15), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41–50 years</td>
<td>34.0%</td>
<td>35.6%</td>
<td>35.6%</td>
<td>44.2%</td>
<td>HR = 0.91 (0.71-1.16), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51–60 years</td>
<td>28.5%</td>
<td>28.6%</td>
<td>28.7%</td>
<td>34.7%</td>
<td>HR = 0.94 (0.76-1.21), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>27.4%</td>
<td>29.1%</td>
<td>29.1%</td>
<td>32.8%</td>
<td>HR = 0.94 (0.74-1.19), n.s.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Moderate hypofractionation with simultaneous-integrated boost

<table>
<thead>
<tr>
<th></th>
<th>RTOG 1005 (ASTRO 2022)</th>
<th>IMPORT-HIGH (Lancet 2023)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>2262</td>
<td>2617</td>
</tr>
<tr>
<td>Schedule Breast</td>
<td>40 Gy in 15 fx</td>
<td>36 Gy in 15 fx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 Gy in 15 fx</td>
</tr>
<tr>
<td>Schedule Boost</td>
<td>48 Gy in 15 fx</td>
<td>48 Gy in 15 fx vs. 53 Gy in 15 fx</td>
</tr>
<tr>
<td>Ipsilateral in-breast recurrence at 5 years</td>
<td>HR 1.32 (0.8-2.1)</td>
<td>HR 1.04 (0.56-1.92)</td>
</tr>
<tr>
<td></td>
<td>→ Non-inferiority for SIB</td>
<td>→ Non-inferiority for 48 Gy (absolute diff.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR 1.76 (1.01-3.04)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Toxicity grade ≥3 (ROTG)</td>
<td>Any moderate / marked breast AE</td>
</tr>
<tr>
<td></td>
<td>p = 0.79</td>
<td>p = 0.041 for SIB 48 Gy vs. sequential boost (less toxicity with SIB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p = 0.823 for SIB 53 Gy vs. sequential boost</td>
</tr>
</tbody>
</table>


Partial Breast Irradiation (PBI) after Breast Conserving Surgery (Invasive Cancer)

- Only for pT1 pN0 R0 G1-2, HR+, non-lobular, > 50 years, no extensive DCIS. For definition of target volume and practical conduct see DEGRO practical guidelines
- Postoperative partial breast irradiation
  - Interstitial Multicatheter-Brachytherapy
  - Intracavitary balloon-technique
  - Intensity-modulated radiotherapy (IMRT) (5 x 6 Gy in 1.5 weeks)
  - 3D-conformal radiotherapy (15 x 2.67 Gy in 3 weeks)
  - 3D-conformal radiotherapy (10 x 3.85 Gy in 1 week)
- Intraoperative Radiotherapy
  - As sole radiotherapy, during first breast surgery (IORT 50 kV, IOERT)
    - > 50 years
    - > 70 years
- Intraoperative clip placement at the tumor bed if partial breast irradiation is indicated

General guidelines
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 (10x3.85-4 Gy over two weeks)


3D-conformal RT (10x3.85 Gy over one week)


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+)

Recurrence and Survival: Long-term Results From the TARGIT-A Randomized Clinical Trial in Early Breast Cancer. JAMA Oncol. 2020 Jul 1;6(7):e200249.


>70 yrs


Clip placement


# Comparison of different techniques for partial breast irradiation

<table>
<thead>
<tr>
<th></th>
<th>Intraoperative radiotherapy</th>
<th>Multicatheter interstitial brachytherapy</th>
<th>External-beam radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>• Shortest possible treatment time</td>
<td>• High conformity</td>
<td>• Broad availability</td>
</tr>
<tr>
<td></td>
<td>• Direct visualization of the tumor bed</td>
<td>• Longest available follow-up</td>
<td>• Reproducibility</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>• Lack of complete knowledge of risk factors (e.g. margin status, lympho-vascular invasion)</td>
<td>• Availability limited to specialized centers with high expertise</td>
<td>• Risk of target miss due visualization of the tumor bed</td>
</tr>
<tr>
<td></td>
<td>• Potentially increased risk of fibrosis with additional whole-breast irradiation</td>
<td>• Additional invasive procedure</td>
<td>• Larger irradiated volume due to intra- and interfractional motion</td>
</tr>
<tr>
<td></td>
<td>• Availability limited to specialized centers</td>
<td>• Additional hospital stay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prolongation of anesthesia</td>
<td>• Risk of target miss due visualization of the tumor bed</td>
<td></td>
</tr>
</tbody>
</table>
Postmastectomy Radiotherapy (PMRT)* to the Chest Wall – Indication

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 tumor infiltrated lymph nodes (LN)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>1–3 tumor infiltrated LN (high-risk)</td>
<td>1a</td>
<td>A</td>
<td>+</td>
</tr>
<tr>
<td>1–3 tumor infiltrated LN (low-risk*)</td>
<td>5</td>
<td>D</td>
<td>+/-</td>
</tr>
<tr>
<td>T3 / T4</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>pT3 pN0 R0 (and no additional risk factors)</td>
<td>2b</td>
<td>B</td>
<td>+/-</td>
</tr>
<tr>
<td>If R0 is impossible to reach (for invasive tumor)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>In young pts with high-risk features</td>
<td>2b</td>
<td>B</td>
<td>++</td>
</tr>
<tr>
<td>The indications for PMRT and regional RT are independent of adjuvant systemic treatment</td>
<td>1a</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Inflammatory breast cancer: PMRT and regional nodal irradiation</td>
<td>2c</td>
<td>B</td>
<td>++</td>
</tr>
</tbody>
</table>

* For definition of low-risk, see next slide Radiotherapy of the Chest Wall After Mastectomy (PMRT)


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

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

Post-mastectomy radiotherapy (PMRT) and regional nodal irradiation for patients with inflammatory breast cancer


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


Moderate Hypofractionation


Moderate hypofractionation and breast reconstruction

Ultra-Hypofractionation


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


**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


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


**Boost in PMRT**

- An additional boost irradiation to a part of the chest wall has not been shown to improve DSS and overall survival
- An additional boost irradiation to a part of the chest wall should be given in case of R1 / R2-resection, if secondary resection is not feasible
- In case of tumor extension 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

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

© AGO e. V. in der DGGG e.V. sowie in der DKG e.V.
Guidelines Breast
Version 2024.1E
www.ago-online.de

LoE: Level of Evidence  
GR: Grade of Recommendation  
AGO: Association of German Radiation Oncologists
Radiotherapy of Axillary Lymph Nodes in Patients with Positive Sentinel-Lymph Nodes**, Who Did not Undergo Axillary Dissection

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2b</td>
<td>B</td>
<td>+*</td>
</tr>
<tr>
<td>BCS and ACOSOG Z0011-criteria met</td>
<td>Radiotherapy of the breast including LN level 1 + 2 to 5 mm below the axillary vein (PTV)</td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

BCS and ACOSOG Z0011-criteria met
- Radiotherapy of the axillary lymph nodes (analog AMAROS)

ME and chest wall RT indicated and ACOSOG Z0011-criteria not met or ME and chest wall RT not planned
- Radiotherapy of the axillary lymph nodes (analog AMAROS)

≥ 3 pos. SLN
- Radiotherapy of the axillary lymph nodes (analog AMAROS)

* Study participation recommended
** Macrometastases
§ < T3, no palpable LN, R0, 1-2 positive SN, 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

EXPERT OPINION, extrapolated from:

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


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
Regional nodal irradiation without ALND in non-Z0011-eligible patients


Axillary soft tissue involvement


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.
### Additional RT of the Axilla after Neoadjuvant Therapy

(in case of an indication for RT of the breast/chest wall\(^1\)+/- supra- / infraclavicular and internal mammary node RT\(^2\))

Expansion of the PTV (planning target volume) to level I-II\(^3\)

<table>
<thead>
<tr>
<th>N-status pre/post NACT</th>
<th>pN-status</th>
</tr>
</thead>
<tbody>
<tr>
<td>cN0 / ycN0</td>
<td>ypN0(sn)</td>
</tr>
<tr>
<td>cN0 / ycN0</td>
<td>ypN1mic(sn) / ypN+(sn) (no ALND)</td>
</tr>
<tr>
<td>cN+ / ycN0</td>
<td>ypN0 / ypN0(i+)(sn/TAD)</td>
</tr>
<tr>
<td>cN+/cN+ / ycN0</td>
<td>ypN1mic(sn/TAD) / ypN+(sn/TAD) (no ALND)</td>
</tr>
<tr>
<td>cN0/cN+</td>
<td>ypN0/+ after ALND</td>
</tr>
<tr>
<td>cN0/cN+</td>
<td>Extensive perinodal soft tissue involvement in the axilla</td>
</tr>
<tr>
<td>cN0/cN+</td>
<td>Residual tumor in the axilla after ALND</td>
</tr>
</tbody>
</table>

\(^1\)Incidental dose to parts of level I/II is inevitable. \(^2\)The indication for supra-/infraclavicular and internal mammary node RT has to be assessed separately. \(^3\)Cranial border 5 mm below the axillary vein. \(^4\)Study participation recommended.

---

**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**


Axillary soft tissue involvement

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.
Impact of axillary soft tissue involvement on regional recurrence

- Analysis according to extracapsular extension (ECE) and axillary soft tissue involvement (AXT).
  - No ECE or AXT in 57.7%
  - ECE only in 24.9%
  - AXT only in 2.6%
  - ECE and AXT in 13.9%
- On multivariate analysis, AXT was significantly associated with distant failure (HR 1.61, p < 0.001), locoregional failure (HR 2.31, p < 0.001) and axillary failure (HR 3.33, p = 0.003).
- Regional nodal irradiation improved locoregional control in patients with ECT and/or AXT (HR 0.5, p = 0.03). Delivering a dose of < 50 Gy with conventional fractionation was associated with a higher risk of axillary failure.
- AXT was also associated with distant failure, locoregional failure and axillary failure in patients that underwent neoadjuvant chemotherapy.

Regional nodal irradiation

<table>
<thead>
<tr>
<th>RT to the supra-/infraclavicular and internal mammary region</th>
</tr>
</thead>
<tbody>
<tr>
<td>- ≥ 4 involved axillary lymph nodes¹</td>
</tr>
<tr>
<td>- 1–3 involved axillary lymph nodes¹</td>
</tr>
<tr>
<td>- Central or medial tumor</td>
</tr>
<tr>
<td>- HR-negative</td>
</tr>
<tr>
<td>- pN0 and premenopausal with central or medial tumor and G3 and HR-negative</td>
</tr>
<tr>
<td>- Clinical involvement of the above mentioned regions</td>
</tr>
<tr>
<td>- In case of left-sided breast cancer with elevated cardiac risk or if simultaneous HER2-targeted therapy is given</td>
</tr>
</tbody>
</table>

¹ not applicable for micrometastases


RT plus concurrent Trastuzumab +/- Pertuzumab

RT to Supra-/infraclavicular lymphatic regions after NACT/NAT (indications as for PMRT)
1. Please check slide on radiotherapy after NACT
Regional nodal irradiation: EBCTCG-metaanalysis 2023

<table>
<thead>
<tr>
<th>Patient number</th>
<th>EBCTCG-metaanalysis („newer trials“, recruitment 1989 onwards)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median FU</td>
<td>13.7 years</td>
</tr>
<tr>
<td>Design</td>
<td>7 randomized controlled trials and 1 national prospective cohort study</td>
</tr>
<tr>
<td>Target volume</td>
<td>92% in the experimental arm had internal mammary irradiation</td>
</tr>
<tr>
<td>Results</td>
<td>Absolute reduction at 15 years</td>
</tr>
<tr>
<td>Any recurrence</td>
<td>RR 0.88 (95%-CI 0.81-0.95)</td>
</tr>
<tr>
<td>Breast-cancer mortality</td>
<td>RR 0.87 (95%-CI 0.80-0.94)</td>
</tr>
<tr>
<td>Mortality w/o recurrence</td>
<td>RR 0.90 (95%-CI 0.84-0.96)</td>
</tr>
<tr>
<td>Any death</td>
<td>RR 0.90 (95%-CI 0.84-0.96)</td>
</tr>
</tbody>
</table>

### Fractionation of Radiotherapy in Case of Regional Nodal Irradiation

<table>
<thead>
<tr>
<th>Oxford</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventionally fractionated radiotherapy (total dose about 50 Gy in approx. 25-28 fractions within 5–6 weeks)</td>
<td>1a</td>
<td>A</td>
<td>++</td>
</tr>
<tr>
<td>Moderately hypofractionated radiotherapy (total dose approx. 40–43.5 Gy in 15-16 fractions within 3–5 weeks)</td>
<td>1b</td>
<td>B</td>
<td>+</td>
</tr>
<tr>
<td>Ultra-hypofractionated RT (total dose 26 Gy in 5 fractions over one week = 1 fraction/day)</td>
<td>2b</td>
<td>B</td>
<td>-</td>
</tr>
</tbody>
</table>

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.
7. Meattini I, Becherini C, Boersma L et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast


1. 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.


Role of locoregional radiotherapy after neoadjuvant chemotherapy

Mamounas et al. SABCS 2023 – GS02-07 (NSABP B-51/RTOG 1304)
- Prospective randomized controlled trial, 1641 pts., 2013-2020, median follow-up 59.5 months
- cT1-3 cN1 (FNA/CNB) → ypN0 (SLNB/ALND) after standard neoadjuvant chemotherapy
- Randomization:
  - BCS: RT breast vs. RT breast + regional nodal irradiation
  - Mastectomy: No RT vs. Post-mastectomy RT + regional nodal irradiation
- Primary endpoint: Invasive breast cancer recurrence-free interval
  - 80% power to detect 4.6% absolute reduction (HR 0.65) – superiority trial, 172 events
- Patient characteristics: 80% cT1-2, 58% BCS, 55% SLNB, 78% pCR in breast, 20% TNBC, 20% Lum
- Results:
  - No improvement in BCRFI (HR 0.88), isolated locoregional recurrence-free interval (HR 0.37), distant recurrence-free interval (HR 1.00), DFS (1.06) and OS (HR 1.12)
- Discussion:
  - Short follow-up (benefit of RNI appeared in EBCTCG-metaanalysis after 10-15 years)
  - Underpowered for primary analysis (109/172 planned events)
  - Trial should have been designed as a non-inferiority trial
  - Underrepresented subgroups: cT3, ypT+
  - Not applicable to: cT4 cN2-3

## Use of Concomitant Systemic Therapy with Adjuvant Locoregional Radiotherapy

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<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>
<tr>
<td>Olaparib****</td>
<td>2b</td>
<td>C</td>
<td>+/-</td>
</tr>
</tbody>
</table>

* Simultaneous parasternal RT should be avoided in patients with HER2-positive tumors and tumor-localisation on the left side
** With hypofractionated RT approx. 40 Gy, consider dose reduction of Capecitabine, Pat. with 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.
**** In currently available phase III-trials, RT was given before initiation of Olaparib.

Trastuzumab +/- Pertuzumab concurrent with radiotherapy

8. Von Minckwitz G, Procter M, de Azambuja E et al., Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer, N


**Tamoxifen concurrent with radiotherapy**


**AI (letrozole, anastrozole) concurrent with radiotherapy**


5. Azria D, Belkacemi Y, Romieu G, et al. Concurrent or sequential adjuvant letrozole and radiotherapy after conservative surgery for

T-DM1 concurrent with radiotherapy

Checkpoint-inhibitors concurrent with radiotherapy

Capecitabine and radiotherapy


CDK4/6-Inhibitors


Olaparib


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### Smoking and Risk of Secondary Lung Cancer

<table>
<thead>
<tr>
<th>Oxford LoE</th>
<th>GR</th>
<th>AGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

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

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Guidelines Breast Version 2024.1E
www.ago-online.de

Increased risk of lung cancer secondary to breast cancer radiotherapy in smokers

Inform patients about risk

Recommend smoking cessation

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