Adjuvant Radiotherapy
Adjuvant Radiotherapy (RT)

 **Versions 2002–2015:**
  Blohmer / Budach / Friedrichs / Göhring / Janni / Kühn / Möbus / Scharl / Seegenschmiedt / Souchon / Thomssen / Untch / Wenz

 **Version 2016:**
  Thomssen / Budach / Wenz
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.

If agreement had not been reached in any statement, the corresponding DEGRO view is written in blue colour.
## Guidelines and Opinions

<table>
<thead>
<tr>
<th>Citation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Gallen 2015: Coates A, AnnOncol 2015;26:1533:</td>
<td>Two trials on hypofractionated radiotherapy to the conserved breast examined essentially similar regimens. <strong>Hypofractioned regimens involving 15 or 16 fractions are now widely accepted as standard of care.</strong></td>
</tr>
<tr>
<td>St. Gallen 2015: Gnant M, Breast Care 2015;10:124:</td>
<td>With respect to <strong>hypofractionated</strong> breast irradiation after breast conserving surgery, the panel felt that this is <strong>appropriate for patients aged 50+</strong> without chemotherapy or axillary involvement (89% Yes, 2% No, 9% Abstain), but also for patients <strong>younger than 50 years</strong> (71% Yes, 2% No, 27% Abstain), with uncertainty about patients with prior chemotherapy or axillary lymph node involvement (51% Yes, 18% No, 31% Abstain).</td>
</tr>
<tr>
<td>Statement J Harris, Dana Farber, Boston, SABCS 2015, PL1-01:</td>
<td>With regard to <strong>hypofractionated whole breast irradiation</strong>, cosmetic results are clearly better, patient satisfaction is improved, uncertainty about use in nodal RT. <strong>We are using it just in about all</strong> (266 cGy x 15 with boost in about ½).</td>
</tr>
</tbody>
</table>
Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer): Whole Breast Irradiation

LoE 1b B AGO ++

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Treatment Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 years</td>
<td>Hypofractionated RT with sequential boost or conventional RT with integrated or sequential boost</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>Low risk*: hypofractionated RT without boost (15-16 fractions)</td>
</tr>
<tr>
<td></td>
<td>High risk: RT as for &lt;50 years</td>
</tr>
<tr>
<td>Elderly</td>
<td>Individual counseling including omission of radiotherapy according to individual risk after geriatric assessment</td>
</tr>
<tr>
<td>Any age (lymph node areas)</td>
<td>If radiotherapy of the regional lymph nodes is included, conventionally fractionated RT (25-28 fractions)</td>
</tr>
</tbody>
</table>

*acc. definition for boost irradiation

Study participation recommended
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\textsubscript{OS}=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) pN0 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.
Radiotherapy for BCT in Elderly Patient with Life Expectancy less than 10 Years

- Omission of radiotherapy in low risk* elderly patients if adjuvant endocrine treatment (e.g. Tam 5-yrs) is consequently performed* AGO¹ 1b A +

DEGRO¹ 1b A +/-

Increase in local recurrence, no influence on OS, decrease in toxicity, salvage surgery and RT as an option in case of recurrence

*Age ≥ 70 year, pT1, pN0, HR positive, G1-2, HER2-negative, negative resection margin (width >1 mm)

¹different interpretation of published data by AGO and DEGRO
**BCS >=70y <4 cm cN0: Tamoxifen vs. Tamoxifen + RT**

Time: 1994-1999, since 8/1996 only pT1cN0 ER/PR+ or unknown allowed

<table>
<thead>
<tr>
<th>@10 yrs (95% C.I.)</th>
<th>Tamoxifen</th>
<th>Tamoxifen plus Radiotherapy</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence free (Δ=8%)</td>
<td>90% (85%-93%)</td>
<td>98% (96%-99%)</td>
<td>HR=0.18</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>(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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(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

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

- **Boost-RT** (improves local control, no survival benefit)
  - < 40 years
  - 40-60 years
  - > 60 years, if G3 or >pT1

- **Intraoperative irradiation** (intraop APBI)
  - As boost-irradiation followed by WBI
  - As sole radiotherapy modality (IORT 50 kV, IOERT)**
    - >50 yrs**
    - >70 yrs**

- **Postoperative partial breast irradiation** as sole radiotherapy modality (APBI)
  - Interstitial brachytherapy
    - >70 yrs**
  - Intracavity balloon technique
  - IMRT***

* Study participation recommended; **only for pT1 pN0 R0 G1-2, HR+, non-lobular, no extensive DCIS, IORT during first surgery; ***no long term data
### 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>Overall Survival (\Delta = -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>

**Cumulative Risk of Ipsilateral Breast Tumor Recurrence**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>All patients (\Delta)</th>
<th>Boost (95% C.I.)</th>
<th>No boost (95% C.I.)</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40 years (\Delta = 11.6%)</td>
<td>24.4% (14.9–33.8)</td>
<td>36.0% (25.8–46.2)</td>
<td>HR = 0.56 (0.34–0.92) p = 0.003</td>
<td></td>
</tr>
<tr>
<td>41–50 years (\Delta = 5.9%)</td>
<td>13.5% (9.5–17.5)</td>
<td>19.4% (14.7–24.1%)</td>
<td>HR = 0.66 (0.45–0.98) p = 0.007</td>
<td></td>
</tr>
<tr>
<td>51–60 years (\Delta = 2.96%)</td>
<td>10.3% (6.3–14.3)</td>
<td>13.2% (9.8–16.7)</td>
<td>HR = 0.69 (0.46–1.04) p = 0.020</td>
<td></td>
</tr>
<tr>
<td>&gt;60 years (\Delta = 3.0%)</td>
<td>9.7% (5.0–14.4)</td>
<td>12.7% (7.4–18.0)</td>
<td>HR = 0.66 (0.42–1.04) p = 0.019</td>
<td></td>
</tr>
</tbody>
</table>

(Median F/U 17.2 y)

EORTC 22881-10882: Boost vs no Boost
(Endpoint: any first recurrence)

<table>
<thead>
<tr>
<th>Time</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>@15 yrs/20 yrs (95% C.I.)</td>
<td>Overall Survival (Δ= - 1.4%)</td>
<td>59.7% (56.3–63.0)</td>
<td>61.1% (57.6–64.3)</td>
</tr>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>@15 yrs @20 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (Δ≥4%)</td>
<td>@15y</td>
<td>28.1%</td>
<td>32.1%</td>
</tr>
<tr>
<td></td>
<td>@20y</td>
<td>32.8%</td>
<td>38.7%</td>
</tr>
<tr>
<td>≤40 years (Δ&gt;6%)</td>
<td>@15y</td>
<td>41.5%</td>
<td>48.1%</td>
</tr>
<tr>
<td></td>
<td>@20y</td>
<td>49.5%</td>
<td>56.8%</td>
</tr>
<tr>
<td>41–50 years</td>
<td>@15y</td>
<td>34.0%</td>
<td>35.6%</td>
</tr>
<tr>
<td></td>
<td>@20y</td>
<td>38.6%</td>
<td>44.2%</td>
</tr>
<tr>
<td>51–60 years</td>
<td>@15y</td>
<td>28.5%</td>
<td>28.7%</td>
</tr>
<tr>
<td></td>
<td>@20y</td>
<td>34.7%</td>
<td>36.2%</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>@15y</td>
<td>27.4%</td>
<td>29.1%</td>
</tr>
<tr>
<td></td>
<td>@20y</td>
<td>32.1%</td>
<td>32.8%</td>
</tr>
</tbody>
</table>

Postmastectomy Radiotherapy (PMRT)** to the Chest Wall

<table>
<thead>
<tr>
<th>Indication</th>
<th>Oxford / AGO</th>
<th>LoE / GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 3 tumor infiltrated lymph nodes (Lnn.)</td>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. high risk</td>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. low risk*</td>
<td>5 D +/-</td>
<td></td>
</tr>
<tr>
<td>1–3 tumor infiltrated Lnn. (every risk)</td>
<td>1a A +</td>
<td></td>
</tr>
<tr>
<td>T3 / T4</td>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>pT3 pN0 R0 (and no additional risk factors)</td>
<td>2b B +/-</td>
<td></td>
</tr>
<tr>
<td>If R0 is impossible to reach (for invasive tumor)</td>
<td>1a A ++</td>
<td></td>
</tr>
<tr>
<td>In young pts with high risk features</td>
<td>2b B ++</td>
<td></td>
</tr>
<tr>
<td>After neoadjuvant chemotherapy (NACT) based on the initial stage prior to NACT (cN+, cT3/4a-d)</td>
<td>2a B +</td>
<td></td>
</tr>
<tr>
<td>Omission of RT if ypT0 ypN0 after NACT**</td>
<td>2b B +/-</td>
<td></td>
</tr>
</tbody>
</table>

The indications for PMRT and regional RT are independent of adjuvant systemic treatment 1a A

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1 different interpretation of published data by AGO and DEGRO

*For definition of risk, go to Further information; **Study participation recommended
Radiotherapy of the Axilla

- Tumor residuals after axillary dissection
  - Oxford / AGO LoE / GR: 5 D ++

- Sentinel node negative
  - Oxford / AGO LoE / GR: 1b B - -

- Axillary dissection not indicated e.g. cN0, SLN pos. (see chapter surgery)
  - Oxford / AGO LoE / GR: 2a B -

- Extracapsular tumor spread (ECS)
  - Oxford / AGO LoE / GR: 2b B - -

- Axillary micrometastases or isolated cells found in regional lymph nodes
  - Oxford / AGO LoE / GR: 1b B - -
Axillary Interventions in Patients with Positive Sentinel Lymph Nodes

1-2 pos. SLN: Axillary dissection or RT of the axilla

- if BCT and ACOSOG Z011-criteria fulfilled
  - No axillary treatment
- if mastectomy, PMRT indicated and ACOSOG Z011-criteria fulfilled
  - No further axillary treatment

1b B +/-

- if BCT and ACOSOG Z011-criteria not met
- if mastectomy: PMRT and ACOSOG Z0011-criteria not met, or PMRT not planned

1b B ++

>=3 pos. SLN:

- Axillary dissection
- Radiotherapy of the axilla

1b B ++

*Study participation recommended
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG)

**RT to supra-/infraclavicular lymphatic regions**

- ≥pN2a or Level III involved
  
  > pN1a high risk*
  
  *tumor central or medial and
  (G2-3 or ER/PgR-negative)
  *tumor lateral and premenopausal and
  (G2-3 or ER/PgR-negative)

- pN0 high risk** with central or medial tumors
  
  ** premenopausal and G2-3 and ER/PgR-negative

- After NACT/NAT (indications as for PMRT)
  
  AGO¹ 2b B +/-

- After NACT/NAT if cN+ (indications acc. PMRT)
  
  DEGRO¹ 2b A +

¹ different interpretation of published data by AGO and DEGRO
Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN)

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

- **pN0** high risk*** with central or medial tumor
  ***premenopausal and G2-3 and ER/PgR-negative

- **pN1a** high risk*
  *tumor central or medial, and
  (G2-3 or ER/PgR-negative)
  *tumor lateral and premenopausal and
  (G2-3 or ER/PgR-negative)

- **pN2a** high risk**
  **G2-3 or ER/PgR-negative

- **pN1b-c, pN2c, pN3b**

- **IMC-RT**, if cardiac risk factors are present
  or if trastuzumab is given

- **After NACT/NAT** (indications as for PMRT) AGO¹

- **After NACT/NAT if cN+** (ind. acc. PMRT) DEGRO¹

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¹ different interpretation of published data by AGO and DEGRO

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**Oxford /AGO LoE / GR**

<p>| | | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1b</td>
<td>B</td>
<td>+/-</td>
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<td>2a</td>
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<td>2b</td>
<td>B</td>
<td>+/-</td>
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<tr>
<td>2b</td>
<td>A</td>
<td>+</td>
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</tbody>
</table>
Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes

(median follow-up 10.9 yrs)

<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>Total</td>
<td>4004</td>
<td>0.88 (0.76 – 1.01)</td>
</tr>
</tbody>
</table>

* missing data on 40 patients
Concomitant Use of Systemic Therapy with Radiotherapy

- **Trastuzumab** concurrent with radiotherapy
  - Oxford / AGO LoE / GR
  - 2b B +

- Tamoxifen concurrent with radiotherapy
  - Oxford / AGO LoE / GR
  - 2b B +

- AI (letrozole, anastrozole) concurrent with radiotherapy
  - Oxford / AGO LoE / GR
  - 2b B +

*in HER2 pos. tumors parasternal RT should generally be avoided; no concurrent trastuzumab in parasternal RT*
Interaction between smoking and risk of irradiation-induced side effects

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

Oxford / AGO
LoE / GR

1a A
++
++
**Adjuvant Radiotherapy – (2/19)**

*Further information:*

**Search Strategy**

Search Terms: Radiotherapy Breast Cancer


**References (Overviews):**

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.


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

Further information:

AGO – Arbeitsgemeinschaft für Gynäkologische Onkologie e.V.
DEGRO - Deutsche Gesellschaft für Radioonkologie e.V.

References:

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


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


No further information

References:

Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) - Whole Breast Irradiation (5/19)
(Hypofractionation)

Further information:

Basically, data on hypofractionation in PMRT and BCT are valid for all subgroups and age groups. However, for concerns with long term toxicity (data are not yet sufficient), hypofractionation is opened for specific patient groups as recommended in this slide. Although some data showed that also integration of boost irradiation into hypofractionation protocol is feasible, it is not accepted as a standard. Treatment of these patients in ongoing clinical trials is recommended.

Update 2016:
According the St. Gallen-Consensus, hypofractioned breast irradiation after breast conserving surgery involving 15 or 16 fractions are now widely accepted as standard of care (Coates A, AnnOncol 2015;26:1533:). The panel felt that this is appropriate for patients aged 50+ without chemotherapy or axillary involvement, but also for patients younger than 50 years, with uncertainty about patients with prior chemotherapy or axillary lymph node involvement. At the San Antonio Breast Cancer Symposium 2015, JR Harris, Harvard Medical School, Boston, stated with regard to hypofractionated whole breast irradiation, that cosmetic results are clearly better, and patient satisfaction is improved; he added that some uncertainty exists about use in nodal RT. However in conclusion he reported that in his department they are using it just in about all (266 cGy x 15 with boost in about ½). (Harris JR SABCS 2015)

References:


Additional Information with Regard to Effects of Breast Radiotherapy (BCT) (6/19)

Further information:

Additional information with regard to effects of radiotherapy in breast conservation (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 trails: “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>OS</sub>=0.8; p=0.042)


Elderly patients should be counseled about:

Absolute benefit of WBRT in older women with pT1-2 (up to 3 cm) pN0, HR-positive breast cancer after BCS and endocrine therapy is small (2-8 % after ten yrs) and decreases with increasing age. No advantage with regard to secondary mastectomy, metastasis-free survival and overall survival has been observed.

References:


Radiotherapy in Elderly Patient Life Expectancy less than 10 Years (7/19)

Further information:

Hughes KS et al. 2013: N=636 eligible: WE+Tam RT vs WE + Tam med F/U 12.6 yrs.;
We would suggest that in this older population, comorbid conditions, not specific breast cancer treatments, dictate survival, and the biology of the tumor dictates the rate of IBTR, not the length of life.

References:

2. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM; on behalf of the PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol. 2015 Jan 27.
BCS $\geq 70\text{y} < 4\text{ cm cN0}$: Tamoxifen vs. Tamoxifen + RT (8/19)

Further information:

Hughes KS et al. 2013: N=636 eligible: WE+Tam RT vs WE + Tam med F/U 12.6 yrs. We would suggest that in this older population, comorbid conditions, not specific breast cancer treatments, dictate survival; the biology of the tumor dictates the rate of IBTR, not the length of life.

Reference:

**Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) – Partial Breast Irradiation (9/19)**

**Further information:**

The primary objective of this trial was Overall Survival. A reproducible benefit was observed with regard to Time to Ipsilateral Breast Tumour Recurrence as shown above. No significant benefit by boost irradiation was observed with regard to Time to First Recurrence neither in the entire study cohort nor in any of the age-defined subgroups (HR=0.94; 95%-C.I. 0.81-1.04; p=0.09). According to the publication, the endpoint “Time to First Recurrence” is the time from randomization to first relapse defined as a loco-regional or distant relapse, ipsilateral second cancer or death due to breast cancer. Young age and high-grade invasive ductal cancer were the most important risk factors for local relapse, in these patients the boost irradiation of 16 Gy significantly reduced the risk of relapse.

The first author of the EORTC Boost vs No Boost trial, H Bartelink, states in the conclusion of the publication: The extra radiation dose can be avoided in most patients older than age 60 years.

**Reference:**


References to the statements:
Radiotherapy (RT) after Breast Conserving Surgery (Invasive Cancer) - Partial Breast Irradiation -
Boost-RT (improves local control, no survival benefit) (LoE 1a A AGO+)


Boost-RT in pts <40 years (LoE 1b A AGO++)
Boost-RT in pts 40-60 years (LoE 1b B AGO+)


Boost-RT in pts >60 years, if G3 or >T1 (LoE 2b B AGO+/-)

Intraoperative irradiation (IORT/IOERT)
As boost-irradiation followed by WBI (LoE 2a B AGO+)


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+) (LoE 1b B AGO+/-)


>70 yrs LoE 1b B AGO+/-


Postoperative partial breast irradiation as sole radiotherapy modality (ABPI)
Interstitial brachytherapy (LoE 1b B AGO+/-)


Interstitial brachytherapy >70 yrs (LoE 1b B, AGO+)


Intracavity balloon technique (LoE 1b B AGO-)


IMRT (LoE 1b B AGO-*)


**Boost vs no Boost: EORTC 22881-10882 Trial (10-11/19)**

*Further information:*

Primary objective of this trial was Overall Survival. A reproducible benefit was observed with regard to Time to Ipsilateral Breast Tumour Recurrence as shown above. No significant benefit by boost irradiation was observed with regard to Time to First Recurrence neither in the entire study cohort nor in any of the age-defined subgroups (HR=0.94; 95%-C.I. 0.81-1.04; p=0.09). According to the publication, the endpoint “Time to First Recurrence” is the time from randomization to first relapse defined as a loco-regional or distant relapse, ipsilateral second cancer or death due to breast cancer.

*References:*


Postmastectomy Radiotherapy (PMRT)** to the Chest Wall (12/19)

Further information and references:

The interpretation of the current EBCTCG publication (2014) should take into account, that this meta-analysis is highly influenced by the Danish radiotherapy trials (Overgaard et al. 1997, 1999). Strong evidence on definition of low risk criteria with regard to the group of 1-3 tumor infiltrated axillary Lnn is lacking. Different definitions are discussed based on retrospective analyses eg.

Kyndi et al. 2013: Low risk of locoregional recurrence, if at least 3 out of 4 favourable criteria are present:
- Hormone receptor receptor status positive,
- Grad I,
- HER2 negative,
- Tumor <2 cm).

Truong et al. 2005: High risk of locoregional recurrence
- If younger age (<45 yrs; HR=3.44) and one of the following factors:
  - High proportion of positive nodes (>25%; HR=2.00),
  - Medial tumour location (HR=2.46) or
  - Negative ER-Status (HR=2.02) and,
- If age 45+ yrs and
  - high proportion of positive nodes (>25%).

Shen H et al. 2015: High risk of local recurrence (HR = multivariate hazard ratio)
- Younger age (<40 yrs): HR 3.77 (2.16, 6.56)
- HER2 positive: HR 2.28 (1.41, 5.63)
- Lymphovascular invasion: HR 5.96 (2.90, 12.26)

Also Grading (G3) and vessel invasion, are sometimes considered as criteria of high risk for locoregional recurrence.
However, from the current literature a unique definition cannot be concluded. Since EBCTCG overview demonstrates a broad benefit in patients with 1-3 tumor infiltrated axillary lymph nodes, the NCCN guidelines are stating: “Strongly consider radiation therapy to chest wall, infraclavicular region, supraclavicular area, internal mammary node, and any part of the axilla bed at risk.”


References according to the statements:

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with > 3 tumor infiltrated lymph nodes (Lnn.) (LoE1a A AGO++):

Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) high risk (LoE 1a A AGO+):


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with 1–3 tumor infiltrated lymph nodes (Lnn.) low risk (LoE 5 D AGO+/-):


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with T3 / T4 breast cancer (LoE 1a A AGO++):


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with pT3 pN0 R0 breast cancer (and no additional risk factors) LoE 2b B AGO+/-:


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in pts. with if R0 is impossible to reach (for invasive tumor) (LoE 1a A AGO++):


Postmastectomy Radiotherapy (PMRT) to the Chest Wall in young pts with high risk features (LoE 2b B AGO++):


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) (LoE 2a A AGO+):


4. Rusthoven CG\textsuperscript{1}, Rabinovitch RA\textsuperscript{1}, Jones BL\textsuperscript{1}, Koshy M\textsuperscript{2}, Amini A\textsuperscript{1}, Yeh N\textsuperscript{1}, Jackson MW\textsuperscript{1}, Fisher CM\textsuperscript{1}. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. Ann Oncol. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

Omission of Postmastectomy Radiotherapy (PMRT) to the Chest Wall after NACT in case of ypT0 ypN0 after NACT (LoE 2b B AGO+-):


4. Rusthoven CG\textsuperscript{1}, Rabinovitch RA\textsuperscript{1}, Jones BL\textsuperscript{1}, Koshy M\textsuperscript{2}, Amini A\textsuperscript{1}, Yeh N\textsuperscript{1}, Jackson MW\textsuperscript{1}, Fisher CM\textsuperscript{1}. The Impact of Postmastectomy and Regional Nodal Radiation after Neoadjuvant Chemotherapy for Clinically Lymph Node Positive Breast Cancer: A National Cancer Database (NCDB) Analysis. Ann Oncol. 2016 Feb 9. pii: mdw046. [Epub ahead of print]

Indications for Postmastectomy Radiotherapy (PMRT) to the Chest Wall and regional RT are independent of adjuvant systemic treatment (LoE 1a A)

Further references:

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.

Radiotherapy of the Axilla (13/19)

No further information

References:

References related to the statements:

Tumor residuals after axillary dissection (LoE 2b B, AGO ++)

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 (LoE 1b B, AGO --)


Axillary dissection not indicated e.g. cN0, SLN positive (see surgical chapter) (LoE 2a B, AGO -)


Extracapsular tumor spread (ECS) (LoE 2b B, AGO --)


Axillary micrometastases or isolated cells found in regional lymph nodes (LoE 3b B, AGO --)

Axillary Intervention in Patients with Positive Sentinel Lymph Nodes (14/19)

Further information:

The optimal management of patients with a positive axillary lymph node status (pSN1) remains unclear. Future studies (e.g. INSEMA) are urgently needed.

References related to the statements:

1-2 pos SLN: BCT: No further treatment to the axilla neither axillary dissection nor RT of the axilla (criteria according ACOSOG Z011) (LoE 1b B, AGO+/-)


1-2 pos SLN: BCT: Axillary dissection (LoE 1b B, AGO +/-)


1-2 pos SLN: BCT: radiotherapy of the axilla (LoE 1b B, AGO +/-)


1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, axillary dissection or radiotherapy of the axilla (LoE 1b B, AGO +)

1-2 pos SLN: Mastectomy: If RT of chestwall is indicated, no axillary treatment (criteria ACOSOG Z011) (LoE 5 D, AGO+/-)

EXPERT OPINION, extrapolated from:

1-2 pos SLN: Mastectomy: If RT of chestwall is not planned, axillary dissection or radiotherapy of the axilla (LoE 5 AGO++)

EXPERT OPINION, extrapolated from:
>=3 positive SLN: Axillary LN dissection (LoE 1b B, AGO ++)


>=3 positive SLN: Radiotherapy of the axilla (LoE 1b B, AGO +)


Radiotherapy (RT) of Other Locoregional Lymph Node Areas (SCG/ICG) (15/19)

Further information:

The definition of high risk and low risk pN1a is different with regard to that in PMRT and that in RT of supra- and infraclavicular lymphatic regions. A proposal by Yates et al. assigns patients as following:

- Low risk, if the following conditions are given:
  G1 with 1-3 positive LN; or G2 with 2 positive LN; or G3 plus 1 positive LN (10 years supraclavicular recurrence rate <10%).

- High risk if the following conditions are given:
  G3 plus 2-3 positive LN; or G2 plus 3 positive LN (10 years supraclavicular recurrence rate 21%).

References:

References related to the statements:

Supra-/infraclavicular lymphatic regions
RT to Supra-/infraclavicular lymphatic regions if ≥ pN2a (LoE 1b A; AGO++)


RT to Supra-/infraclavicular lymphatic regions if Level III involved (LoE 1b A; AGO ++)


RT to Supra-/infraclavicular lymphatic regions if pN1a high risk (LoE 2b B; AGO+)


RT to Supra-/infraclavicular lymphatic regions if pN1a low risk  (LoE 2b B; AGO+)


RT to Supra-/infraclavicular lymphatic regions if pN0 high risk, if radiotherapy of the internal mammaria inn. chain is indicated (see below) (LoE 2a B; AGO+/-)


RT to Supra-/infraclavicular lymphatic regions after NACT/NAT (indications as for PMRT) (LoE 2b B; AGO+/-


Radiotherapy (RT) of Other Locoregional Lymph Node Areas (IMN) - Slide 16/19

No further information

References:

Internal mammaria lymph node region (IMN)

RT to Internal mammaria lymph node region (IMC) if pN0 high risk with central/medial tumors LoE 1b


RT to Internal mammaria lymph node region (IMN) if pN1-pN2 and HR positive in patients who had systemic chemotherapy LoE 1b² B; AGO+


Multivariate Analysis of Overall Survival: Effect of Radiotherapy of the Internal Mammaria Lymph Nodes (17/19)

No further information

References:

Concomitant Use of Systemic Therapy with Radiotherapy (18/19)

No further information

References:

Trastuzumab* concurrent with radiotherapy (LoE2b B AGO+) (*in HER2 pos tumors parasternal RT should generally be avoided; no concurrent trastuzumab in parasternal RT)


Tamoxifen concurrent with radiotherapy (LoE 2b B AGO +)


AI (letrozole, anastrozole) concurrent with radiotherapy (LoE 2b B AGO +)


Other compounds (bevacizumab)

Interaction radiotherapy and smoking – Slide 19/19

No further information

References: